

Trawka Paulina, Wilczyński Michał, Porada Mateusz, Nawrocka Agnieszka, Flegiel Ewelina, Mlicki Paweł, Rymarska Olga, Osiak Joanna, Jabłońska Magdalena, Wszelaki Patrycja, Kędziora-Kornatowska Kornelia. The impact of influenza on elderly patients. *Journal of Education, Health and Sport*. 2019;9(7):303-312. eISSN 2391-8306. DOI <http://dx.doi.org/10.5281/zenodo.3337391>  
<http://ojs.ukw.edu.pl/index.php/johs/article/view/7146>

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).  
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

© The Authors 2019;

This article is published with open access at Licensee Open Journal Systems of Kazimierz Wielki University in Bydgoszcz, Poland  
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike.  
(<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 20.06.2019. Revised: 25.06.2019. Accepted: 16.07.2019.

## The impact of influenza on elderly patients

Paulina Trawka<sup>1</sup>, Michał Wilczyński<sup>1</sup>, Mateusz Porada<sup>1</sup>, Agnieszka Nawrocka<sup>1</sup>, Ewelina Flegiel<sup>1</sup>, Paweł Mlicki<sup>1</sup>, Olga Rymarska<sup>1</sup>, Joanna Osiak<sup>1</sup>, Magdalena Jabłońska<sup>1</sup>, Patrycja Wszelaki<sup>1</sup>, Kornelia Kędziora-Kornatowska<sup>1</sup>

1. Faculty of Health Sciences, Department and Clinic of Geriatrics, Nicolaus Copernicus University, Bydgoszcz

### Abstract

**Background:** Influenza is a disease affecting the human respiratory system. A common problem is to confuse colds with influenza, which results in problems with vaccination and complications related to influenza. Particular attention should be paid to the treatment of influenza, as it is a serious health risk if not treated in the elderly. Research conducted by scientists from Taiwan shows that currently the best way to protect against influenza is preventive vaccination. In addition to vaccination, antiviral drugs (Oseltamivir, Zanamivir, Amantadine, Rimantadine), antipyretics (aspirin, paracetamol) are used. Attention is paid to natural methods (ginseng extract, root lichen extract) and supplements (vitamin C, zinc).

**Material and Methods:** This article is based on a review of the current state of knowledge on influenza in the elderly. The most up-to-date literature with EBSCO, Google Scholar and PubMed has been reviewed. Key words such as influenza, influenza complications, vaccinations, influenza treatment.

**Results:** In the context of the above topics, particular attention is paid to the elderly, in whom a low level of immunity predisposes to getting sick. An increase in the incidence of disease causes an increase in the mortality of older people. Complications following the occurrence of influenza are closely related to the type of virus, where the influenza A virus classified as the heaviest in the course. It has been proven that the bird influenza virus is also a threat to humans. The classic symptoms of influenza are cough, fever, while complications associated with untreated influenza are primarily myocarditis or pneumonia.

**Conclusion:** Due to the decline in immunity, older people are particularly at risk of influenza virus. Scientists have demonstrated the high effectiveness of protective vaccination, but one should remember to repeat them every year. Vaccinations in the elderly have reduced effectiveness, which is why antiviral therapies, natural methods and supplements are used. In the rational treatment of influenza, it is noted that natural methods and supplements are an addition to classic antiviral therapy.

**Key words:** influenza in the elderly, complications from influenza, vaccinations, influenza treatment

### **Introduction**

Influenza is an acute illness caused by viruses (influenza virus) that attack the respiratory system [1]. Older people are particularly vulnerable to infections due to decreasing resistance with age. The incidence of influenza may be epidemic or seasonal [2].

Epidemiology in seniors is difficult to determine due to seasonal flu. Depending on the season, the incidence changes. Influenza viruses evolve all the time, obtaining immunity to the host's immune system [3]. They can act directly by destroying infected cells, damaging the respiratory epithelium or indirectly causing a number of symptoms.

The most characteristic symptoms of influenza include high fever, sore throat and muscle pain. Other common symptoms include joint pain and lack of appetite. Older people are often accompanied by pneumonia during influenza. According to the World Health Organization, every year 0.5-1 million people die from complications of influenza [4]. Among the elderly, complications of influenza and pneumonia are the fifth most common cause of mortality [5].

The basic preventive measures against influenza include preventive vaccination. Neuraminidase inhibitors are very helpful in the treatment of influenza infection. It is worth remembering that over-the-counter drugs are used only to reduce the symptoms of influenza, they do not prevent its occurrence [6].

### **Why are aging people more vulnerable to influenza? - epidemiology and mortality.**

Influenza is a threat for elderly people due to physiological decreasing efficiency of immune system, which leaves the organism vulnerable to the development of infection. Unfortunately, in this age group, the flu is the leading cause of death with infectious aetiology [7]. Sadly, there still is the limited availability to determine the exact number of patients.

In fact, the incidence of influenza in elderly people from Eastern Europe is significant. In older adults the increasing of hospitalization and deaths were observed. [8] According to the global mortality estimates from 1999- 2015, 39% of people between 65-74 age and 32%

older than 75 age, died due to influenza – associated causes. In 75 age and older group, the one of highest mortality rates were estimated. The season's mortality is correlated with the type of virus and its circulation, climate, temperature and country. Moreover, to be sure, that influenza occurs and eventually it is the cause of death, the virologic tests should be performed. It is not often practise [9].

In 10 countries of Europe, in season 2016/17, 3959 number of cases were confirmed as an influenza, but 2827 had available age information. In group of 60-69 age, there was approximately 600 number of cases, similarly in group 80 and older. Around 800 patient between 70-79 was reported as having a influenza virus. In season 2016/17 the type A predominated.

In season 2017/18 7789 number of cases were confirmed as an influenza. In 4754 patient the information of age was available. Approximately 1200 patients were between 60-69 age, thereabout 1000 were between 70- 79 age. In age 80 and older, the number of confirmed cases was nearly 600. More cases was reported as a type B [10].

### **Cold or influenza? - characteristics.**

A usual cold is a mild and self-limiting viral disease that can be caused by more than 200 types of viruses, of which the most common are rhinovirus and coronavirus. Often, the duration of a cold does not exceed 1-2 weeks, and most patients feel better after the first week. In people with chronic diseases, the common cold may be life-threatening, but most patients undergo severe but clinically harmless cold symptoms. Many of these people, in particular children and the elderly, enjoy symptomatic treatment as well as antibiotic therapy, despite the absence of a bacterial pathogen. A very small proportion of cold cases do not resolve spontaneously. Complications are very rare and affect infants, the elderly, people with immunodeficiency and chronically ill [11,12].

Some aspects of the body's inflammatory response may protect against viral infections, as the number of cytokines and lung function increases during the infection. This suggests that we should not always try to reduce inflammation during viral upper respiratory tract infections [11].

Thanks to new knowledge about cytokines and their impact on our body, we understand some of the symptoms that occur in flu or cold, for example: fever, headache and muscle pain, runny nose, sneezing, chill or malaise [13]. These symptoms are much milder than those in the flu.

Influenza is a viral disease that, thanks to the continuous mutations that the influenza virus undergoes, causes annual epidemics, as well as occasional pandemics that occur at irregular intervals. For this reason, the flu is a disease that can not be eradicated. Influenza can lead to serious complications and even deaths, not counting economic losses. We distinguish two important types of influenza virus, which are the main cause of infection infecting humans - type A and type B. Frequent mutations of the influenza virus occur mainly in virus surface glycoproteins, but also can occur in each of the 8 gene segments in both type A and B virus. Molecular changes in the viral RNA segments arise through various mechanisms: 1) genetic reassortment (antigenic shift), 2) point mutations (antigen drift), 3) defective-interfering molecules, 4) RNA recombination. Thanks to these mechanisms, there is a constant evolution of influenza viruses. The influenza virus has a segmented genome, which also contributes to high variability of the genotype and phenotype [14].

A cold is quite often confused with influenza. This leads to the reporting of cold cases as a flu, and the ill person who has been vaccinated has unconsciously acquired a negative attitude to influenza vaccination. The result of a disrespectful approach to these vaccinations is the increased risk of multiorgan complications of influenza.

Typically, post-influenza complications result from the fact that the influenza virus, entering the respiratory system, damages the epithelium, thus opening the way for bacteria and viruses. The most common complication of flu is pneumonia and it is in the sixth place of the cause of death, and in the 5th position in the case of the elderly. Not only the complications of influenza are the direct cause of increased mortality during the flu epidemic. Exacerbation of already existing diseases of the respiratory system, circulatory system and other chronic diseases in people with flu contributes to the increase in mortality [15].

### **Influenza treatment and its efficiency.**

Untreated flu, especially in elderly people can lead to many complications such as difficult to treat upper respiratory tract infection, pneumonia or myocarditis. Currently, vaccination is the most important way to protect against flu. Unfortunately, in addition to the fact that vaccinations need to be repeated each year, their effectiveness is also lower in the elderly. For the above reasons, in addition to, natural methods, supplements and symptomatic therapy, it is very important to use antiviral drugs such as neuraminidase inhibitor – Oseltamivir and Zanamivir or M2 protein inhibitors - Amantadine and Rimantadine.

Oseltamivir and Zanamivir are newer generation antiviral drugs. These are neuraminidase inhibitor that inhibit the replication of both influenza A and B viruses [16]. Oseltamivir commercial product is Tamiflu. It was the main drug used during the 2009 influenza epidemic. Zanamivir is taken by inhalation. Its commercial product is Relenza. Zanamivir has a very low tendency to select for resistance, which is why it is a frequently used medicine [17]. Both drugs show the highest efficacy when therapies begin within 24-48 hours of the onset of fever. They accelerate the time to return to full activity, reduce the severity of symptoms and the risk of serious complications. These drugs are well tolerated by elderly patients and those with other associated diseases.

Amantadine and Rimantadine are the first medicines that have been registered as preparations for the treatment of influenza. They are inhibitors of the M2 protein, which occurs only in the influenza A virus. Similarly to the neuraminidase inhibitors, their activity is also the highest for the first 48 hours after the onset of symptoms [18]. When using these drugs, gastrointestinal symptoms are often observed. Rimantidine may also cause central nervous system disorders [19]. Therefore, special care should be taken when using these medications, especially in elderly patients.

John H Beigel, Yajing Bao, Joy Beeler published an article about the study that examined the efficacy of combination therapy with oseltamivir, amantidine and ribavirin compared to oseltamivir monotherapy for the treatment of influenza. The clinical effects of monotherapy and combination therapy were very similar. During the study one of the patient died from cardiovascular causes. This was not related to participation in the experiment [20]. However, it should be remembered that the elderly often take many medications that can interact with each other. Therefore, if monotherapy gives similar clinical effects in the treatment of influenza, it should be more preferred than the treatment of several antiviral drugs at the same time.

Another group of drugs used in the treatment of influenza are antipyretic drugs such as aspirin and paracetamol. These are medicines that can reduce the severity of some flu symptoms. However, they can prolong the duration of the disease, because fever is one of the most important defense mechanisms of the body [21]. Additionally, Aspirin as a non-steroidal anti-inflammatory drug may increase the risk of gastrointestinal bleeding, which may be particularly vulnerable to elderly patients [22].

Extremely important in the treatment of influenza are also supplements and natural methods. Some of them were already known in antiquity. These include medicinal preparations of plant origin such as ginseng extract or root lichen extract, which can be used in both prophylaxis and treatment. It is also worth using supplements like vitamin C and zinc, which can reduce the duration of colds and flu. However, it should be remembered that natural methods and supplements should be only an addition to antiviral therapy [23].

### **Complications of influenza - why is it so dangerous?**

Influenza viruses can cause symptoms of particularly high severity. They are most often possible to be self-cured, but unfortunately in many cases, complications can also lead to death. Children, elderly people, as well as people suffering from chronic respiratory and circulatory system disorders and others who have an adverse effect on immunity are particularly vulnerable to this disease [24,25].

Existing types of influenza viruses determine the occurrence of various complications, of which the A virus is responsible for the most severe in the course - is the cause of epidemics and pandemics, including even entire continents [24,25,27]. According to statistics, as a result of a pandemic in 1918, there were 20 million deaths [24,26]. Infection with influenza virus also causes degeneration of bronchial epithelium. In person's deprived of diseases of individual body systems, it is regenerated and functions are restored. This process, however, is undefined in time, and the long-lasting one causes increased cough and excessive reactivity of the bronchi. People with respiratory problems, such as asthma, have worsening symptoms and symptoms of influenza [24].

As the research shows, the types of virus A and B also affect the efficiency of human cognitive functions. They cause increased drowsiness, social isolation and emotional sphere disorders. It is supposed that this is due to the increased immune response from the nervous system, which in turn leads to weakening of cognitive processes. According to another hypothesis - infection of the nervous system caused by the influenza virus carries with it the multiplication of it in the CNS, which in turn leads to the leveling of nerve cells responsible for brain efficiency. For this reason, the influenza virus may show some mental illnesses or cause neurodegeneration [27].

Since 1997, the influenza virus (HPAI) causing the so-called bird flu has become pathogenic to humans. It caused havoc on farms, also reaching the human community. According to statistics conducted by WHO over the period 1997-2014, 394 people died due to avian influenza [26].

The most common consequence of influenza is pneumonia with a viral nature, in which the symptoms are observed, and sometimes hemoptysis. Other symptoms are dyspnoea and cyanosis, as well as changes in the bronchial tree causing respiratory failure. This applies mainly to people already burdened with cardiovascular and respiratory diseases who have

reduced immunity. There is a risk of developing this disease also in young people. Pneumonia can also occur in a bacterial form when the viral form has not developed. Symptoms that accompany a sick person include fever, cough containing purulent secretion and disturbances in the functioning of defense mechanisms. Another complication is bronchiolitis obliterans, the rarest form of the consequences of influenza, but not impossible. It involves inflammation of the walls of the bronchi and bronchioles and tissues that surround them. It is a form that can develop mainly in young children [24].

The consequences of influenza also include the cardiovascular system, leading to the onset of heart attacks, strokes and strokes belonging to the group of cerebrovascular diseases. They can also cause a disturbance in the functioning of the mitral valve, which prevents blood from going back from the left atrium to the left ventricle. Such disorders cause an increase in pressure in the left atrium, which determines the increase of its capacity, and thus the irregularity in its contraction [24, 27].

### **Vaccination as the most effective way to avoid influenza.**

One of the proofs that vaccines are the most effective way to avoid influenza in various clinical conditions is the study of scientists in Taiwan. They noticed the connection between protective effect of influenza vaccination on outcomes in geriatric stroke patients. As it turned out stroke patients with influenza vaccination (IV) showed better outcome than non-vaccinated patients. They also showed fewer complications and lower mortality compared with non-IV patients. These findings suggest the urgent need to promote IV for this susceptible population of stroke patients [28].

Vaccines are also an invaluable weapon in the fight against weakness of immune system after an operation of the body. Vaccinated elderly patients who underwent surgery had a lower risk of pneumonia and in-hospital mortality. Their results were compared with non-vaccinated patients who had undergone similar serious surgery [29]. As older patients are more often exposed to various types of surgical procedures, vaccination of geriatric patients is particularly important as they are also often exposed to more serious complications and worse final effects associated with them.

In other studies, we can observe how enormous benefits are brought not only by the vaccination of a particularly vulnerable person, but also people in their environment. A study in the US investigated the effect of vaccinating hospital workers on patients' influenza incidence. The results shows that increased rates of vaccination by HCW (health care workers) were associated with a reduction in the proportion of hospital flu infections in immunocompromised patients [30].

In another of the published studies, this time carried out in Japan, we can read that influenza vaccine has shown good preventive action against hospitalization associated with influenza in the elderly [31]. This is just an example of one of the many studies conducted on this subject, which proves that vaccines are the best means to reduce the incidence of flu and hospitalization related to it worldwide.

In addition, researchers in the US have noticed that in addition to anti-flu, this vaccine may have other benefits. As it turns out, this vaccine may have immune-modifying effects. This effect may be associated with an immune response to certain vaccine antigens. This is just the beginning of research on this issue, but it certainly will not end in this one study.

After numerous tests, it may turn out in the future that the vaccine against influenza is not enough that it is the best way to prevent this disease, it also has other, additional properties that positively affect our immune system [32].

## **Discussion**

The aim of this article is to show how serious is the problem of influenza among older people, as well as the consequences resulting from complications and treatment methods and prophylaxis.

Older people, according to statistics, belong to the group with a particularly high risk of developing influenza [10]. This is due to a number of reasons among which one should mention the already not-so-efficient immune system, as well as numerous comorbidities that burden the body. More importantly, the history of influenza infection in the elderly is a risk factor for these complications in the form of pneumonia, the leading cause of death [33]. Unfortunately, in the case of virostatic drugs that inhibit the influenza virus, such as amantadine, therapeutic efficacy can only be expected if treatment is undertaken within the first 48 hours after the onset of symptoms, and the time of treatment is often delayed due to difficulty in varying the flu from the common cold. However, symptomatic treatment in the case of older people may prove to be additional or insufficient. The inconvenience of treatment, as well as the growing population of older people, necessitates the development of strategies allowing effective prevention. The most effective are the vaccines. According to the recommendations of the Advisory Committee on Immunization Practices (ACIP), vaccination against influenza should apply to all people over 6 months of age in the absence of contraindications [36]. At the same time, according to the WHO, vaccinations are particularly recommended, among others, for people aged 65 and older. As part of preventive programs, they are available free of charge in countries such as Canada, Australia or Great Britain [35].

In addition, it should be noted that vaccination carries a small risk of side effects. A meta-analysis of 29 studies on 3 classes of adjuvanted vaccine: AS01 / AS02, AS03 and MF59 showed no significant adverse effects compared to control vaccines. It should be noted, however, that adjuvanted vaccines are more reactive and are associated with a higher incidence of irritability, drowsiness or loss of appetite. Similarly, in the case of high-dose vaccines, the risk of adverse reactions is comparable to the risk associated with the use of standard vaccines in older people - there is no increased risk of side effects [35].

Although influenza vaccination is the most effective form of prophylaxis, one should take into account their reduced effectiveness in the elderly population. This is due to the weakened immune response, which is directly submitted to, lower than in younger people, effectiveness of vaccination. The disproportion between the population of older and younger people is visible in every type of influenza virus. The effectiveness of vaccination for people at working age is estimated at 51%, with an efficacy of 37% for older people [37]. In order to increase the effectiveness of vaccination among the elderly, it seems necessary to optimize the antigenic fit between the vaccine and the dominant strain of influenza in the environment [35].

Attention should also be paid to medical personnel dealing with elderly people. These people should undergo yearly vaccinations against influenza as well, because during flu seasons their direct contact with patients carries a high risk of transferring the virus to their charges to people in their care [34].

## Conclusions

Influenza is a common viral disease which can have very dangerous consequences, including death. It causes neurological, respiratory, gastrointestinal and musculoskeletal symptoms. It has seasonal activity and may lead to epidemic.

Elderly people should be really careful as they are more vulnerable to the disease. The immune system is less effective with age and is often not able to manage the fight with attacking viruses. In one season in Europe there are thousands of influenza cases among elderly. It is one of the most common reason of death in this group, especially in patients with chronic diseases of cardiovascular or respiratory system.

Many people do not see the significant difference between cold and influenza. It is important to distinct them. Cold is usually caused by rhinoviruses or coronaviruses and lasts about a week. Its symptoms like fever or muscle pain are milder than flu, there is also a runny nose and cough. Serious complications are rare, usually in patients with immunodeficiency. Influenza is caused by virus type A and B, but A is more dangerous. Viruses have an ability to mutate its glycoproteins and RNA thanks to various mechanisms and this is why they are so difficult to eradicate. Influenza has more negative effect on organism than cold and is harder to treat.

Influenza treatment involves antiviral drugs – neuraminidase inhibitors such as Oseltamiwir and Zanamiwir. They are effective and safe. There are also M2 inhibitors – Amantadine and Rimantadine but they are used only against type A virus and may cause side effects affecting central nervous system. Monotherapy appears to be better than combination therapy of these drugs. Aspirin and paracetamol are also used to reduce uncomfortable symptoms, they may weaken natural organism defense though. Elderly often use natural methods and supplements to strengthen their immune system, but their efficiency is controversial.

Special attention should be paid to complications caused by influenza as they may be a huge threat. Virus A is the most problematic and may lead to pandemic and millions of deaths. Asthmatic patients are more vulnerable to respiratory consequences such as bronchitis or pneumonia. The disease can affect the nervous system causing degeneration of cells. Elderly with chronic heart disease should take care of themselves thoroughly because their condition might worsen.

It is essential to tell the patients about the importance of influenza vaccination every year. Studies showed that vaccinated stroke patients may avoid serious complications of influenza. Also those non-vaccinated who were after surgery had higher chance of pneumonia than those vaccinated. It is known that vaccine has a great effect on immune system and may reduce hospitalization and mortality rate.

Influenza is underestimated but dangerous disease that may lead to life-threatening situations, especially in geriatric patients. The virus is very insidious because of its frequent mutations. Therefore, it should be examined all the time and various new ways of protecting people from it should be investigated.



## References

1. Ciebiada, M., Barylski, M., Górską-Ciebiada, M. (2010). Zachorowania na grypę u osób w podeszłym wieku w świetle najnowszych danych epidemiologicznych i zaleceń terapeutycznych. *Geriatrics*, 2, 191-198.
2. Taubenberger, J. K., Kash, J. C. (2010). Influenza virus evolution, host adaptation, and pandemic formation. *Cell host & microbe*, 7(6), 440-451.
3. Simonsen, L., Viboud, C., Taylor, R. J., Miller, M. A. (2011). The epidemiology of influenza and its control. *Influenza vaccines for the future*, 27-54.
4. Lerch, D., Mastalerz-Migas, A. (2013). Ocena wiedzy na temat grypy i jej powikłań na podstawie badań ankietowych. *Family Medicine & Primary Care Review*, 3, 342-343.
5. Brydalk, L. (2011). Grypa chorobą rodziny. *Family Medicine & Primary Care Review*, 2, 281-286.
6. Brydak, L. (2012). Można i należy walczyć z grypą. *Family Medicine & Primary Care Review*, 2, 235-241.
7. Pop-Vicas, A., Gravenstein, S. (2010). Influenza in the Elderly – A Mini-Review. *Gerontology*, 57, 397-404.
8. Kovács, G., Kaló, Z., Jahnz-Rozyk, K., et al. (2013). Medical and economic burden of influenza in the elderly population in central and eastern European countries. *Human vaccines & immunotherapeutics*, 10(2), 428-440.
9. Iuliano, A. D., Roguski, K. M., Chang, H. H., et al. (2017). Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*, 391(10127), 1285-1300.
10. Adlhoch, C., Snacken, R., Melidou, A., Ionescu, S., Penttinen, P., The European Influenza Surveillance Network. (2018). Dominant influenza A(H3N2) and B/Yamagata virus circulation in EU/EEA, 2016/17 and 2017/18 seasons, respectively. *Euro surveill.*, 23(13), 18-00146.
11. Luca, D., Schildgen, O. (2018). Healthier without healthcare? The paradox of the common cold. *Respiratory Research*, 19, 260.
12. Worrall, G. (2007). Common cold. *Can Fam Physician.*, 53(10), 1735-1736.
13. Eccles, R. (2005). Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis.*, 5(11), 718-725.
14. Brydak, L.B. (2011). Influenza – the passion of my academic research life. *Przewodnik Lekarza/Guide for GPs*, 14(1), 19-24.
15. Brydak, L.B. (2012). Influenza – a danger for everyone regardless of age. *Przewodnik Lekarza/Guide for GPs*, 15(1), 65-70.
16. Sander, B., Gyldmark, M., Aultman, R., Aoki F.Y., (2004). Impact on health outcome and costs of influenza treatment with oseltamivir in elderly and high-risk patients. *Journal of Medical Economics*, 7, 67-83.
17. Hurt, A.C. (2019). Antiviral Therapy for the Next Influenza Pandemic. *Tropical Medicine and Infectious Disease*, 4(67), 1-7.
18. Mossad S.B. (2001). Prophylactic and symptomatic treatment of influenza. *Postgraduate Medicine*, 109(1), 97-105.
19. Hall, M., Brown, M.D. (2005). Are Amantadine and Rimantadine Effective In Healthy Adults With Acute Influenza?. *Annals of Emergency Medicine*, 46(3), 292-293.
20. Beigel, J.H., Bao, Y., Beeler, J., et al. (2017). Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: a multicentre, double-blind, randomised phase 2 trial. *The Lancet Infectious Disease*, 17(12), 1255-1265.

21. Plaisance, K.I, Kudaravalli, S., Wasserman, S.S., et al. (2000). Effect of Antipyretic Therapy on the Duration of Illness in Experimental Influenza A, *Shigella sonnei*, and *Rickettsia rickettsii* Infections. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 20, 1417-1422.
22. Gostout, J.Ch. (2000). Gastrointestinal Bleeding in the Elderly Patient. *American Journal of Gastroenterology*, 95(3), 590-595.
23. Mousa, H.A. (2016). Prevention and Treatment of Influenza, Influenza-Like Illness, and Common Cold by Herbal, Complementary, and Natural Therapies. *Journal of Evidence-Based Complementary & Alternative Medicin*, 22(1), 166-174.
24. Piotrowski, W., Górski, P. (2002). Pulmonary complications of influenza. *Alergia Astma Immunologia*, 7(1), 27-31.
25. Brydak, L. (2012). You can and should fight the flu. *Family Medicine&Primary Care Review*, 14(2), 235-241.
26. Brydak, L. (2014). Flu known for centuries – still dangerous. *Family Medicine&Primary Care Review*, 16(2), 181-184.
27. Talarowska, M., Florkowski, A., Macander, M., Gałecki, P. (2010). The influenza infection and cognitive functions. *Neuropsychiatria i Neuropsychologia*, 5, 3-4.
28. Lam, F., Chen, T.L., Shih, Ch.Ch., et al. (2019). Protective effect of influenza vaccination on outcomes in geriatric stroke patients: A nationwide matched cohort study, *Atherosclerosis*, 282, 85-90.
29. Liu, W.Chi., Lin, Ch. S., Yeh, Ch. Ch. et al. (2018). Effect of Influenza Vaccination Against Postoperative Pneumonia and Mortality for Geriatric Patients Receiving Major Surgery: A Nationwide Matched Study. *The Journal of Infectious Diseases*, 217(5), 816–826.
30. Frenzel, E., Chemaly, R.F., Ariza-Heredia. E. (2016). Association of increased influenza vaccination in health care workers with a reduction in nosocomial influenza infections in cancer patients; *American Journal of Infection Control*, 44(9), 1016-1021.
31. Seki, Y., Onose, A., Murayama, T. et al. (2018). Influenza vaccine showed a good preventive effect against influenza-associated hospitalization among elderly patients, during the 2016/17 season in Japan. *J Infect Chemother.*, 24(11), 873-880.
32. Keshtkar-Jahromi, M., Ouyang, M., Keshtkarjahromi, M. (2016). Effect of Influenza Vaccine on Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TWEAK) in Older Population. *Open Forum Infectious Diseases*, 3(1), 716.
33. Heo, J.Y, Song, J.Y, Noh, J.Y. et al. (2017). Effects of influenza immunization on pneumonia in the elderly, *Hum Vaccin Immunother.* 14(3):744–749.
34. Thomas, R.E., Jefferson, T., Demicheli, V., Rivetti, D. (2006). Influenza vaccination for healthcare workers who work with the elderly, 19(3).
35. Sullivan, S.G., Price, O.H., Regan, A.K. (2019). Burden, effectiveness and safety of influenza vaccines in elderly, paediatric and pregnant populations. *Ther Adv Vaccines Immunother.*
36. Grohskopf , L.A., Sokolow, L.Z., Broder, K.R. et al. (2017). Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, *Influenza Season. MMWR Recomm Rep.* 66(2).
37. Rondy, M., Omeiri, N., Thompson, M.G., Levêque, A., Moren, A., Sullivan, S.G. (2017) Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. *J Infect.* 75(5):381-394.