PROPHYLAXIS OF INFLUENZA IN THE ELDERY. IS THERE ANY ALTERNATIVE?

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The benefits of influenza vaccination in the elderly individuals are the subject of serious discussion. Existing estimates of the efficiency of vaccines come mainly from observational studies that may be biased because of difficulties in detecting and correcting confounding factors [1-5]. At the same time, the World Health Organization (WHO) considers an annual vaccination to be the most effective influenza prevention strategy, it is recommended for the elderly people in many developed countries [6].

The US Centers for Disease Control and Prevention (CDC) for the 2016-2017 season recommend a vaccination as the best way to prevent influenza in their recommendations for people aged 65 and older. These recommendations are based on the fact that this age group is subjected to an increased risk of serious complications from influenza if compared with young and healthy, as immune protection of an individual with age becomes weaker. Although influenza seasons may vary in grades of severity, most people over the age of 65 and older are the most susceptible to flu. Recently, for example, from 71% to 85% of seasonal deaths from flu occurred in people of this age, in addition, they accounted for 54-70% of hospital-related influenza (CDC, National Center for Immunization and Respiratory Diseases, 2017). Influenza in general is a significant component in an annual morbidity, and the persons aged ≥65 years belong to the groups with a high risk of complications [7-8].

Over the past decade, the influenza vaccine rates in the age group of 65+ have risen from about 15% in the 1960s up to 65% in the 1980s, while the mortality from an influenza infection among elderly people in response to an enhanced vaccination continued to increase. It was difficult to accept the fact that the vaccine does not protect the elderly, and in 2005 the National Institutes of Health of the United States intended to prove "once and forever" that concomitant or confounding factors should not block the essential benefit of the vaccine. Having studied all the data, they realized that the results confirm the growth of flu death since the routine vaccination of elderly Americans has become widespread [9].

Most estimates of the influenza vaccine effectiveness are based on trials using a variety of designs and results that have provided a wide range of seniors [10-11]. In addition, since most of these trials are observational, they are prone to bias. Confounding factors, such as either concomitant diseases or functional status, can affect the results, despite the proposed different methods of their correction [2, 12].

Evidence-based medicine can not boast of a large number of randomized clinical trials of the anti-influenza vaccine effectiveness in the elderly due to ethical issues [13]. Over the past 20 years, the only large randomized clinical trial was to investigate an inactivated anti-influenza vaccine in adults aged ≥60 years, which was performed during one season and limited to healthy subjects. This trial demonstrated a 58% reduction in the risk of serologically verified uncomplicated influenza infection in the patients aged 60-69, but no conclusive findings were made for the individuals aged ≥70 years, because the capacity of this study was insufficient to investigate the vaccination efficiency in this age group [13]. Moreover, an evidence of efficacy in healthy subjects aged 60-69 can not be related to the elderly at the age of 70, since elderly age and concomitant diseases are associated with an increased risk of complications and the immune system weakening [14-20]. With respect to the lack of an evidence, based on randomized clinical trials, we use the results of observational, usually retrospective cohort trials that may be biased [21-22].

Many observational trials compared the risk of death from pneumonia and overall mortality during hospitalization among the vaccinated and unvaccinated elderly people during an influenza season. At the same time for vaccinated subjects the mortality risk from all the causes was reduced by 50% and the one from pneumonia and influenza-related hospitalization, respectively was 27-33% decreased [23-38].

Some authors interpreted these results as an evidence that the influenza vaccine significantly reduced the risk of death and hospitalization in the elderly [11, 39-43].

At the same time, a survey published in 2007 by Lone Simonsen et al. states that the estimates of a risk reduction for the vaccinated and unvaccinated elderly individuals represent the data, which are not confirmed in laboratory, considered as a gold standard. Due to this finding, ≥50% mortality from all the causes for vaccinated elderly people during the flu season is unlikely, taking into account that the flu is at most 10% of all the deaths during its season [44], and therefore the vaccine against influenza can prevent 10% of deaths as much as possible, even if the vaccine efficiency is 100% in the elderly.

None of the randomized trials evaluating the effectiveness of the trivalent vaccine have been addressed exclusively to the persons aged ≥65 years, and this is due to ethical issues. A single study for live attenuated influenza vaccine in adults of 60 years and older showed a significant overall efficiency (42%, 95% CI: 21-57), with efficiency lower in the subjects aged 60-69 (31%) and higher in the persons aged ≥70 years, i.e. 57% [45].

Cecilia Trucchi et al. (2015) in their report analyze the results obtained in four meta-analyzes, including both randomized and observational trials on the effectiveness of influenza vaccination in the elderly [41, 46-49].

Combined observational trials, all the meta-analyzes showed a significant reduction in mortality from all the causes, while the efficacy varied from 68% to 74%. The vaccination effect is expected to be higher when the genetic match between circulating and vaccine strains is improved [50]. And this is not always the case. For example, for the flu season 2014-2015, the vaccine's effectiveness was only 14% for people over 50 years [51].

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At the same time, Peter A. Gross et al. observed a significant improvement in vaccination even in those seasons where the strain mismatches were shown [41].

Tom Jefferson et al. (2010) noted the effectiveness of vaccine prophylaxis against hospitalization for either influenza or pneumonia, as well as mortality from all the causes, more pronounced in the seasons with a good strain match. While in the same Anna S. Dean et al. (2010) published a clustered randomized trial that showed that the anti-influenza vaccine could be effective in preventing those events, despite an incomplete vaccination [52].

Lamberto Manzoli et al. (2009), summarizing the results of the meta-analysis, noted that anti-influenza vaccines are effective to prevent influenza, hospitalization and death among elderly people, while Michael T. Osterholm et al. (2012) [47] also in reliance of the meta-analysis results, believe that "evidence for protection in adults aged 65 years or older is lacking".

In broad terms, Cecilia Trucchi et al. (2015) believe that most evidences suggest that anti-influenza vaccines provide an adequate protection against natural infection in the elderly, susceptible to a high risk of influenza and complications of the flu [53-55]. However, the assessment of benefits of vaccines still depends on significant methodological problems [56]. There is an evidence of bias in available experimental studies that assess the effectiveness of an influenza vaccine, as well as that the existing methods of correcting confounding factors are not able to adequately control them [57]. Some of the results that have been evaluated in a comprehensive review by Lamberto Manzoli et al. (2012) seem strange because of the incomprehensible mismatch between a significant impact on mortality from all the causes in the elderly, as opposed to a more moderate effect on cardiovascular events. Lamberto Manzoli et al. concluded that "although the discrepancies between the results of the meta-analysis of using the seasonal vaccines to the elderly were revealed, most of them showed statistically significant efficiency, the value of which, however, differed significantly" [58].

A solution could be the performance of the state-funded adequate randomized clinical trials for the elderly, but this would be a very costly and ethically challenging proposition, since the use of influenza vaccines is recommended throughout the world for several years [54, 55] and the issues of cost-effectiveness need to be properly reviewed during a recession [58].

The most significant (albeit not indisputable) achievement of recent years can be called entering the market of high-dose vaccine (containing 4 times more antigen than standard), which is specifically designed for people over 65 years. This is due to a stronger immune response after vaccination (higher antibody production). There are two high-dose vaccines: Fluad and Fluzone High-Dose.

The results of Fluzone High-Dose clinical trial involving more than 30,000 participants showed that the adults of 65 years and older who received a high-dose vaccine get sick with flu and flu-related illness by 24% less than those who received the standard influenza vaccine. A high dose vaccine has been approved to be used in the United States since 2009. The adjuvant flu vaccine Fluad is made using an adjuvant MF59, which is designed to create a stronger immune response to vaccination. .In the Canadian observational trial of 282 people aged 65 years and older, conducted during the 2011-2012 season, Fluad was 63% more effective than conventional non-adjuvant influenza vaccines. There were no randomized trials comparing Fluad with Fluzone High-Dose. For the first time, the Fluzone High-Dose vaccine was approved for the 2016-2017 season (CDC, 2017) and contained only 180 μg of hemagglutinin: A (H1N1) - 60 μg, A (H3N2) - 60 μg, B - 60 μg formaldehyde ≤100 μg octophenol ethoxylate ≤250 μg.

The Vaccine Adverse Event Reporting System (VAERS) caution you on the general effects of Fluzone High-Dose, which include high doses: pain at the injection site, muscle aches, malaise and headache (this is not a complete list).

Two clinical trials evaluated the safety of Fluzone High-Dose. Trial 1 (NCT00391053, at http://clinicaltrials.gov) was a multi-center, double-blind, pre-licensed, held in the United States. Post-administration and systemic adverse events were more commonly seen after Fluzone High-Dose vaccination if compared with Fluzone.

Within 6 months after vaccination, 156 (6.1%) in the recipients of Fluzone High-Dose 93 (7.4%) there were developed serious adverse events. Deaths were not recorded within 28 days of vaccination. There were reported 23 cases of death within 29-180 days of vaccination: 16 (0.6%) among Fluzone High-Dose and 7 (0.6%) among Fluzone recipients. Most of these participants had a history of cardiovascular, liver, neoplastic, renal and/or respiratory diseases. There was no cause-and-effect relationship between fatalities and Fluzone High-Dose vaccination.

Trial 2 (NCT01427309, http://clinicaltrials.gov) was a multi-center, double-blind, post-licensed study performed in the United States and Canada during two seasons of influenza. In this study, adults of 65 years age and older were randomized to receive Fluzone High-Dose or Fluzone (Stocks 2011-2012 and 2012-2013). The study compared the efficacy and safety of Fluzone High-Dose with Fluzone. The safety analysis set composed 15,992 recipients of Fluzone High-Dose and 15,991 recipients of Fluzone.

During the observation period (approximately 6-8 months after vaccination), in 1,323 (8.3%) recipients of Fluzone High-Dose and 1,442 (9.0%) of Flucone ones there were developed serious adverse events. Most of these participants suffered from one or more chronic concomitant diseases. Totally 167 deaths were reported during 6-8 months after vaccination: 83 (0.5%) among the Fluzone High-Dose and 84 (0.5%) among the Fluzone receipients. Within 30 days following the vaccination, 6 deaths were reported: 6 (0.04%) among Fluzone High-Dose recipients and 0 (0%) among Fluzone recipients. There was no cause-and-effect relationship between fatalities and Fluzone High-Dose vaccination.

Post-marketing data collection on Fluzone High-Dose is ongoing. Since these messages are not standardized, they pass spontaneously from an uncertain population, it is not always possible to reliably estimate

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their frequency or establish a causal relationship to the vaccine influence [51].

Fluad vaccine contains MF59 containing squalene. It causes an inflammatory reaction and acts mainly on the macrophages located at the injection site. MF59 increases the absorption of antigen by monocytes and promotes its migration to the lymph nodes, stimulating the production of antibodies and T-cell immune response [59].

The benefit of this stimulation to many researchers seems controversial, since the squalene can cause the chronic inflammation reactions in the body, including autoimmune diseases [60].

Is there an alternative to influenza vaccine in the elderly, which does not produce so many questions and concerns?

One of the most active advocates of an alternative vaccine prophylaxis in the world is Donald Miller Jr. is a cardiac surgeon and professor of surgery at Washington University in Seattle. He is a member of Doctors for Disaster Preparedness, Dr. John J. Cannell and his colleagues, Dr. Joseph Mercola. They actively propose the use of vitamin D to prevent influenza, the logical justification is as follows: the flu virus lives with a person all year round, and new strains are formed during the "dead season". In the southern and northern temperature zones the epidemic of influenza occurs in the cold season, from October to March and from April to September, respectively. Influenza epidemics also occur in the tropics during the rainy season.

The reasons why the flu epidemic occurs in winter, i.e., when it is cold, e.g. either the fact that people are inside the premises in a close contact with each other, or that the more dry air dries out the mucous membranes and does not allow the body to expel the virus, or that the virus remains longer on cold open surfaces, such as door handles, do not explain why epidemics occur in the tropics.

However, there is an explanation of why the epidemic of influenza occurs both in the warm and in cold climate. During the epidemic of influenza, wherever it is, the atmosphere blocks the ultraviolet radiation of the Sun. In temperature zones beyond 35 degrees of the north or south latitude, in winter the Sun is at a fairly low angle so that the ozone layer absorbs and blocks short (280-315 nanometers) ultraviolet waves. In the rainy tropics, heavy rain clouds also block ultraviolet rays during the rainy season.

The skin contains a derivative of cholesterol, 7-dehydrocholesterol. In the skin under the influence of ultraviolet radiation, one of the carbon rings of this substance molecule is detached to form vitamin D.

The interest in vitamin D extraskeletal effects has rapidly grown over the last thirty years due to the identification of Vitamin D receptors (VDRs) in different systems, organs, and cell types [61, 62]. The biologically active form of vitamin D 1.25 (OH) 2D3 is produced by two hydroxylation reactions, the latter being mainly in the kidneys via 1α-hydroxylase (1α-ONAT). Binding of vitamin D active form to its receptor leads to the VDR heterodimerization with retinoid X receptors. The obtained complex binds to sensory elements in DNA and regulates the expression of several gene products involved into absorption and metabolism of calcium and phosphorus, the function of skeletal muscle, metabolism of bone tissue, function of parathyroid glands and regulation of inflammation [62].

The effects of 1.25 (OH) 2D3 on regulation of both inherent and adaptive immune systems are string and their evaluation has been just started. VDR was detected in activated CD4+ and CD8 + T cells, B cells, neutrophils, monocytes, macrophages, and dendritic cells [63]. Vitamin D binding to VDR in macrophages, neutrophils and monocytes results in the secretion of an antibacterial peptide, a catelcidine, which plays an important role in innate immune defense, due to its ability to lyze bacterial cells [64]. Serum levels of 25 (OH) D were associated with the expression and functionality of some TLR receptors (toll like receptors), especially those involved into viral responses [65]. The activation of congenital immune receptors, such as TLR2, enhances the expression of VDR, 1α-OHase and catelcidine, indicating the potential role of vitamin D in congenital immune responses against bacterial pathogens [66]. Vitamin D has also been shown to suppress the expansion of T cells and modulates the expression of cytokines with Th2 bias [67]. Vitamin D prevents the differentiation and proliferation of B-lymphocytes and secretion of immunoglobulins. Other immune effects that have been attributed to vitamin D include the maturation of dendritic cells, which lowers the regulation of expression of major histocompatibility complex class II, and enhances treatment and presentation of the antigen, resulting in the induction of more tolerant cytokines such as IL-10. This change in the priming environment affects the differentiation of Th cells into Th2.

Potential clinical manifestations of the VDR presence in immune cells compose a possible role in autoimmunity, infectious diseases and cancer. For example, the link between vitamin D deficiency and an increased incidence of autoimmune diseases, namely, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease in humans, as well as an increase in frequency of autoimmune disorders in animal models with vitamin D deficiency, have recently been published and discussed in the publication of Barbara Prietl et al., 2013. It has been shown that vitamin D inhibits the growth of *Mycobacterium tuberculosis* in human macrophages through the secretion of antibacterial peptides [68]. Recent studies have also shown that vitamin D has a beneficial effect on the survival of patients with non-small-cell lung cancer and can act as an agonist of VDR [69] and a therapeutic agent for mutant lung cancer [70].

Changed physiological functions, which lead to an impairment of the immune response to infectious diseases and to increased susceptibility, is a distinctive feature of aging [71]. This unregulated immune status is called as an immune loss [72-74]. During aging, there is a rise in colonization of epithelium and mucous surfaces with bacteria and fungi, reactivation of latent and chronic infections and increased susceptibility to infectious diseases [73, 75]. In addition, with aging the immunogenicity and effectiveness of prophylactic vaccines against bacterial and viral targets decrease [76, 77]. Laura A. Coleman et al., 2016 showed that the

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expression and function of the congenital immune receptors on macrophages and dendritic cells decreased with aging [78]. As well it has been shown that the reduced function of antigen-presenting cells promotes an immune dysfunction during aging, which can be reversed either by joint stimulation during vaccination or during the development of adjuvant vaccines [79-82].

Can injections (or pills) of vitamin D prevent flu better than vaccines? There is good reason to believe that it cans [83]. Adrian R. Martineau et al. analyzed twenty five randomized controlled trials (11,321 participants aged from 0 to 95 years). Adding vitamin D reduced the risk of acute respiratory infections among all the participants (0.88 corrected odds ratio, 95% 0.81-0.96 confidence interval, P for heterogeneity <0.001). In the analysis of subgroups, it was shown that protective effects were observed in those who received daily or weekly vitamin D without additional bolus doses (corrected odds ratio of 0.81, 0.72-0.91), but not for those who received one or several bolus doses (corrected odds ratio of 0.97, 0.86-1.10, P for interaction = 0.05). Among those receiving either daily or weekly vitamin D, the protective effects were more pronounced in the patients with an initial level of 25-hydroxy vitamin D <25 nmol/l (corrected odds ratio of 0.30, 0.17-0.53) than in those with an initial level of 25-hydroxy vitamin D ≥25 nmol/l (corrected odds ratio of 0.75, 0.60-0.95, P for interaction = 0.006). Vitamin D did not affect a part of participants who experience at least one serious adverse event (corrected odds ratio of 0.98, 0.80-1.20, P = 0.83). The evidence supporting these analyzes has been assessed as being of high quality. It was finally concluded that the vitamin D supplement was safe and generally protected against acute respiratory infections. Patients with vitamin D deficiency and those who did not receive bolus doses received the most benefit [83].

To summarize, all that is lacking is the words of Professor Donald Miller: "A large multi-center randomized trial conducted over multiple flu seasons comparing vitamin D to a flu shot can show conclusively which is better and safer. But given the financial stakes underpinning the flu shots, and unpatentable vitamin D, who will fund it?" [84].

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PROPHYLAXIS OF INFLUENZA IN THE ELDERY. IS THERE ANY ALTERNATIVE?

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The benefits of influenza vaccination in the elderly individuals are the subject of serious discussion. Evidence-based medicine can not boast of a large number of randomized clinical trials of the anti-influenza vaccine effectiveness in the elderly due to ethical issues. Over the past 20 years, the only large randomized clinical trial was to investigate an inactivated anti-influenza vaccine in adults aged ≥60 years, which was performed during one season and limited to healthy subjects. This trial demonstrated a 58% reduction in the risk of serologically verified uncomplicated influenza infection in the patients aged 60-69, but no conclusive findings were made for the individuals aged ≥70 years, because the capacity of this study was insufficient to investigate the vaccination efficiency in this age group. Moreover, an evidence of efficacy in healthy subjects aged 60-69 can not be related to the elderly at the age of 70, since elderly age and concomitant diseases are associated with an increased risk of complications and the immune system weakening. With respect to the lack of an evidence, based on randomized clinical trials, we use the results of observational, usually retrospective cohort trials that may be biased. We analyzed the results of randomized multicenter vaccine trials including Fluzone High-Dose Vaccine, meta-analysis data, and concluded that evidence for protection in adults aged 65 years or older is lacking. As an alternative, the results of clinical trials and a meta-analysis of the effectiveness of vitamin D3 for the prevention of influenza / influenza-like illnesses are considered. The extraskeletal effects of vitamin D are analyzed. The interest in vitamin D extraskeletal effects has rapidly grown over the last thirty years due to the identification of Vitamin D receptors (VDRs) in different systems, organs, and cell types. The effects of 1.25 (OH) 2D3 on regulation of both inherent and adaptive immune systems are string and their evaluation has been just started. VDR was detected in activated CD4+ and CD8 + T cells, B cells, neutrophils, monocytes, macrophages, and dendritic cells. The results of the meta-analysis twenty five randomized controlled trials (11,321 participants aged from 0 to 95 years) published by Adrian R. Martineau et al. were presented. The meta-analysis has found that adding vitamin D reduced the risk of acute respiratory infections among all the participants (0.88 corrected odds ratio, 95% 0.81-0.96 confidence interval, P for heterogeneity <0.001). Vitamin D did not affect a part of participants who experience at least one serious adverse event (corrected odds ratio of 0.98, 0.80-1.20, P=0.83). It was finally concluded that the vitamin D supplement was safe and generally protected against acute respiratory infections. A conclusion was drawn on the need for a large clinical trial comparing the efficacy and safety of a flu vaccine and vitamin D3.

Key words: influenza, flu-related illness, flu vaccine, elderly, vitamin D3, extraskeletal effects.

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