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REVIEWS



# Towards better protection of older people against influenza and its complications. Polish recommendations for HD influenza vaccine

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**Summary** Annual vaccination is the most effective protection against influenza and its serious complications. It is especially important for people at high risk of severe course of the disease and serious complications: individuals with specific chronic medical conditions, pregnant women, children aged 6–59 months, older people, and healthcare workers. Despite a progressive increase in seasonal vaccine coverage, influenza-related morbidity, mortality, and hospitalization rates remain high and have continued to increase in people aged 65 years and over. Standard vaccines against influenza are less efficient in this group due to immunosenescence. Consequently, more effective vaccines are needed to prevent influenza and its complications in older adults.
**Key words:** immunosenescence, human influenza, vaccines, aged.

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## Background

Influenza constitutes a rapidly spreading acute viral respiratory illness, causing annual epidemics and sporadic pandemics. The transmission of influenza viruses occurs easily through airborne droplets from coughing and sneezing, as well as via contaminated surfaces and hands. Its prevalence peaks during winter in temperate zones and persists year-round in tropical regions, particularly in densely populated locales like schools, nursing homes, and public transport. Common symptoms of influenza encompass abrupt-onset fever, cough, headache, muscle pain, joint pain, weariness, sore throat, and a runny nose, which can persist for over 14 days. While many individuals recover in about a week without medical intervention, severe consequences such as hospitalization and even death can transpire, notably among older adults, infants, pregnant women, individuals with obesity, and those with chronic medical conditions [1–4].

While most assessments of the global impact of influenza tend to emphasize the respiratory symptoms, accumulating clinical evidence and epidemiological research reveal a concealed burden arising from the broader repercussions of the ailment. These encompass the worsening of pre-existing chronic conditions, heightened vulnerability to secondary infections, cardiovascular incidents, and a decline in functional capacity [5].

Influenza occurs all over the world and every year affects approx. 5–10% of adults and 20–30% of children [6]. According to World Health Organization (WHO) estimates, there are about a billion influenza cases per year with 3–5 million severe cases and 290–650 thousand deaths [2]. In Poland, in the 2022/23 season there were over 5 million confirmed and suspected influenza cases and 121 deaths [7, 8].

## Influenza in older people

Influenza has a major impact on morbidity and mortality among older people [9]. Adults aged 65+ years are more susceptible to infection and have higher risk of more severe illness, complications, and death. In the US, people aged over 65 years account for two-thirds of influenza-related hospitalizations and 90% of deaths [10]. Average annual influenza-associated excess respiratory mortality rates were estimated at 0.1–6.4 per 100,000 in people aged < 65 years, 2.9–44.0 per 100,000 in people aged 65–74 years, and 17.9–223.5 per 100,000 in people aged ≥ 75 years [11]. The pooled global influenza-associated hospitalisation rate was estimated at 40.5 per 100,000 persons, while for people aged > 65 years it was 96.8 per 100,000 [12]. Even if not hospitalized, older people can experience a persistent decline in function and prolonged recovery from influenza. In a Canadian study, 39.3% of older people who had influenza during the previous season reported that it took them longer than 2 weeks to recover, 21.5% reported reduced health and function during the recovery period, and 3.1% never fully recovered [13].

This higher susceptibility to a severe course of the disease is related to both immunosenescence, increasing prevalence of significant comorbidities that are themselves risk factors for influenza-related complications, and a vicious circle of frailty and infections [14–17].

Immunosenescence is the gradual deterioration of the immune system caused by advancing age. It is characterized by a decline of both innate and adaptive immunity, leaving the person more susceptible to disease [17, 18]. Age-related immunological changes include reduction in haemopoietic bone marrow and thymic involution, which reduces the production of various lymphoid precursors and their subsequent maturation. These changes lead to weaker response to aggression and to a state of chronic inflammation caused by increased release of pro-inflammatory cytokines [18]. Immunosenescence leads not only to higher susceptibility to disease, but also to lower efficacy of vaccines [19].

Elderly people suffer from significant comorbidities, many of which are themselves risk factors for severe course of influenza. These include chronic lung disease (e.g. COPD), heart disease (e.g. heart failure and coronary artery disease), endocrine disorders (e.g. diabetes), kidney and liver disorders, weakened immune system due to disease or medication (e.g. cancer therapy, chronic steroid use), and extreme obesity [17]. Multimorbidity, defined as 2 or more concurrent diseases occurring in the same individual, is not limited to elderly people, but its prevalence increases considerably with age [20]. A large study, including 1.7 million patients, demonstrated that in adults aged 45–64 years, 30.4% reported at least 2 chronic diseases, in adults aged 65–84 years multimorbidity was reported in 64.9% of cases, while in people aged over 85 years this proportion was as high as 80% [21]. Similar results were reported by Low et al., who demonstrated that by the age of 50 years, more than 50% of the population have at least one chronic condition, and by the age of 60 years more than 50% of the population have multimorbidity [22]. Various studies have shown the prevalence of multimorbidity ranging from 20% to 30% for the entire population and above 50% for people aged 60 years and over [20]. Aging and multimorbidity cause frailty, which, in turn, leads to higher risk of complications and poor outcomes [23].

Frailty is defined as a clinically recognizable state characterized by increased vulnerability caused by age-associated declines in physiological reserve and function across multiple organ systems, such that the ability to cope with even subliminal stress is compromised [24]. It is highly prevalent in older age and is associated with increased risk of disability and mortality [16]. There is a lot of evidence that frail individuals are susceptible to infectious diseases and are more likely to experience severe course and long-term complications [16]. While frailty leads to more frequent infections, those infections in turn increase frailty, leading to accelerated functional decline and mortality [16]. There are several mechanisms through which inflammatory response to acute infections such as influenza affect the whole organism [16]. First, during infections, most of the anabolic mechanisms responsible for the turnover of damaged macromolecules and organelles are inhibited, mainly through the downregulation of the signalling of growth factors, leading to the progressive accumulation of unrepaired tissue damage [25]. Second, the inflammatory response and the immobilization accompanying acute infections may further lead to physical function deterioration and frailty [26]. Third, infections may indirectly promote frailty by triggering specific pathological conditions, as suggested by a meta-analysis in which recent respiratory infection was associated with increased myocardial infarction risk [27].

## Vaccinations against influenza

Given that influenza treatment is generally supportive and influenza-specific antiviral therapy is most effective at the beginning of the infection, vaccination remains the best defence against the disease and its complications [28, 29]. Vaccinations help to reduce the incidence of disease and diminish its severity in breakthrough cases, decreasing the risk of complications and death [30]. According to Centers for Disease Control and Prevention estimations, during the 2019/20 season influenza vaccination prevented approx. 7.09 million illnesses, 3.46 million medical visits, 100,000 hospitalizations, and 7100 deaths [31].

Vaccination against influenza may not only protect individuals but also increase herd immunity [28]. For example, it has been demonstrated that vaccination of children reduced the incidence of severe influenza virus infections in elderly individuals [32]. Hence, vaccination is often recommended not only to people in risk groups but to the whole population (excluding children up to 6 months old) [28].

The most common vaccines against influenza are administered intramuscularly inactivated influenza vaccines (IIV) licensed for use for children older than 6 months and for adults [28]. They have been used since 1944, first in a bivalent form and then in a trivalent formula in 1978 [33]. Trivalent inactivated influenza vaccines (IIV3) contain antigens of 2 influenza A viruses (H1N1 and H3N2) and one B virus strain, either Yamagata or Victoria line. Quadrivalent inactivated influenza vaccines (IIV4), introduced in the 2017/18 season, contain antigens of 2 A strains and 2 B strains [14, 34]. Another vaccine type is live attenuated influenza vaccine (LAIV) administered intranasally and licensed for children aged 2–17 years [28, 29].

Because influenza virus strains gradually change between seasons, the influenza vaccine composition is updated every year based on recommendations of the WHO, which monitors the global influenza virus occurrence [28, 30]. This and the short duration of immunity makes it necessary to repeat vaccination every year [9, 15].

Overall, influenza vaccines are safe and well tolerated [29]. The majority of solicited AEs were mild to moderate in severity and transient. The most common local AEs in adults were tenderness and erythema at the injection site, and the most common systemic AEs were irritability and sleepiness [35]. In an overview of systematic reviews including 47,740 participants, the safety of IIV4 was compared to that of IIV3. No differences between the 2 vaccines in terms of serious or systemic AEs were observed. IIV4 resulted in higher occurrence of injection site pain in both children and adults [36].

In older people, vaccines against influenza are also well tolerated and safe with rare serious and clinically important AEs [37, 38]. The proportion of local reactions in elderly people is lower than in children or young adults, with the most frequently reported reactions being pain, erythema, swelling, and indu-

ration [39]. The most common systemic reaction reported in people aged 65 years and over are malaise (7.2%), fever (5.7%), cough (6.6%), coryza (13.2%), and nausea (4.5%) [40].

IIV should not be administered in cases of confirmed anaphylaxis to egg white or other vaccine components, acute illness with fever, exacerbation of the course of the underlying disease, or Guillain-Barré syndrome diagnosed within 6 weeks of previous influenza vaccination. Each time, the decision to give an influenza vaccination is made by a vaccine eligibility healthcare professional, who determines whether the circumstances constitute an actual contraindication to vaccination. In many cases, a person at high risk of post-influenza complications may benefit from influenza vaccination despite the 'apparent' contraindications.

Vaccine effectiveness (VE) varies across seasons, populations, age groups, and products [41]. For example, in a study including 27,180 outpatients aged ≥ 6 months and covering seasons between 2011 and 2016, VE was 47% in 2011/12, 49% in 2012/13, 54% in 2013/14, 19% in 2014/15, and 48% in 2015/16 [42]. In another study covering 3 influenza seasons (2010/11, 2011/12, and 2012/13), VE ranged from 34.2% in 2011/12 to 69.7% in 2012/13 [30]. In a meta-analysis of test-negative design studies published between 2004 and 2015, it was demonstrated that VE is higher for A(H1N1) and B strains than for the A(H3N2) strain [41]. Pooled VE against A(H1N1)pdm09 was 67% with low heterogeneity between seasons, pooled VE against type B was 54% with low heterogeneity, while pooled VE against A(H3N2) was 33% with high heterogeneity across populations and seasons [43]. In another study including 9311 US participants in the 2014/15 season, VE for influenza B/Yamagata was 55%, while VE for A(H3N2) it was 6% [44]. This low VE for A(H3N2) was explained by a mismatch between the vaccine and circulating viruses [44]. Indeed, the match between strains included in the vaccine and those circulating in a given season is the most important factor affecting VE [45]. It has been calculated that VE increases by > 25% when there is a match between the vaccine and the most prevalent circulating strains [45]. For example, a meta-analysis on VE in people aged 15–64 years yielded a pooled VE on laboratory-confirmed influenza of 55.4% when there was a match between the vaccine and circulating strains vs. 39.3% otherwise [45].

At the same time, lower VE for older adults has been consistently reported. Across 5 seasons between 2011 and 2016 in the US, the VE for adults aged 18–64 and for those aged 65 years and older was similar for A(H1N1) and B strains, but it was lower for older people for A(H3N2) [46]. For seasons between 2011 and 2017 in the UK, the vaccine was found to be inefficient against A(H3N2) for adults aged 65 years and over, while the efficacy was moderate for other strains until the age of 75 years [47]. According to a systematic review and meta-analysis, influenza vaccine caused a 51% reduction in influenza-related hospitalizations in the population of 18–65-year-olds and only 37% reduction in people aged over 65 years [48]. This lower VE in older adults can be explained by the weaker antibody response of this group as compared to the general population. A quantitative review of 31 studies published between 1986 and 2002 demonstrated that people aged 65 years and over had significantly lower antibody response to influenza vaccination compared with younger adults. After adjusting for vaccine- and patient-related factors, response to vaccine in older people was approximately 1/4 as rigorous for H1 and B antigens and about 1/2 as rigorous for H3 antigens when compared to the response in younger people [49].

## Moving towards implementation of new, improved influenza vaccines

Because antibody response and VE in older people are reduced and suboptimal protection against seasonal influenza in this group has been demonstrated [17, 50–53], some newer, enhanced vaccines have been developed, aimed at boosting the immune response in this population. New products include MF59® adjuvanted, cell-based, recombinant haemagglutinin and high-dose (HD) influenza vaccines [17, 54]. According to a recent systematic review, MF59® adjuvanted and cell-based influenza vaccines are more effective than no vaccination in protecting against laboratory-confirmed influenza, but their effectiveness compared with traditional vaccines is uncertain and based on limited data [54]. Recombinant haemagglutinin vaccine has been shown to offer better protection than no vaccination or standard influenza vaccines with some possible cross protection to drift variants [54]. HD influenza vaccine, containing 4 times more antigen than standard-dose (SD) products (i.e. 60 mg hemagglutinin per strain), has consistently shown improved protection against both influenza and its serious complications in people aged 65+ years. When compared to SD vaccine, the relative VE (rVE – fraction of people protected by HD vaccine among those that were unprotected by SD vaccine) of the HD product was 24.2% for laboratory-confirmed influenza [55], 14.3% for influenza-like illnesses [56], 11.2% for influenza-related hospitalizations [56], 39.8% for serious pneumonia [57], 17.7% for cardio-respiratory events possibly related to influenza [57], 14.7% for respiratory-related hospitalizations [56], and 12.8% for cardiovascular-related hospitalizations [56]. Furthermore, it has been demonstrated that older people who received HD vaccine had a 22% reduction in influenza-coded hospital admissions and emergency department visits compared with those who received SD vaccine [58]. The effect on mortality seems to depend on the season: in one study the HD vaccine reduced post-influenza deaths by 36% as compared to SD vaccine in the 2012/13 season, but no differences were observed in the subsequent season [59]. In another study, HD and SD vaccines provided similar levels of protection against post-influenza death in the 2016/17 season, but a 17–20% reduction in mortality appeared in the next 2 seasons for the HD vaccine [60]. The authors explained these differences by the degree of match between the vaccine and the circulating viruses – in seasons with a poor match, the HD vaccine offers better protection than the SD vaccine [60].

Assuming that the SD vaccine has an absolute efficacy of 50%, the efficacy of the HD vaccine in older adults has been estimated at 62% – a similar level of protection to that observed for SD vaccines in younger adults [50, 61]. This is consistent with an immunogenicity study in which immune responses induced by the HD vaccine in adults aged 65+ years were similar to those observed with the SD vaccine in younger adults [62].

The HD vaccine is in general safe and well-tolerated, with no major safety concerns [63]. Most studies report higher rates of local and systemic AEs for the HD vaccine when compared to the SD vaccine [55, 63–65]. The most frequently reported AEs are as follows: injection-site pain [63, 66, 67], injection site erythema [67], injection site swelling [67], injection site induration [67], myalgia [63, 66], headache [63, 66], malaise [66], and shivering [63, 66, 67]. Most reactions were mild and resolved quickly [63, 66].

The trivalent formulation of the HD vaccine (HD-IIV3), available only in the US, was approved in 2009 and used until the end of the 2019/20 season. Then, it was replaced by the quadrivalent version (HD-IIV4) approved in 2019 and licensed in many European countries since 2020 [14, 63]. The HD vaccine approved in Europe contains an A(H1N1)-like strain, an A(H3N2)-like strain, a B-like strain (Victoria lineage), and a B-like strain (Yamagata lineage) [68, 69].

The HD vaccine (60 mg hemagglutinin per strain) should be administered as a single 0.7-ml injection by the intramuscular route in adults aged 60 years and over [69]. If it needs to be given at the same time as another injectable vaccine, immunization should be carried out on separate limbs. Adverse reactions may be intensified by any co-administration. Co-administration of the HD vaccine with a booster 100 mcg dose of COVID-19 mRNA vac-

cine has been evaluated, and it yielded no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay, as well as similar responses to COVID-19 mRNA vaccine, as assessed by an anti-spike IgG assay [69].

## International recommendations regarding improved influenza vaccination for older adults

Due to more efficient prevention of influenza and its complications, the HD vaccine can provide cost savings when compared to the SD vaccine in older adults [14, 17]. The HD vaccine is currently recommended for elderly people in several countries. The US Advisory Committee on Immunization Practices recommended that adults aged ≥ 65 years preferentially receive enhanced vaccines such as HD, recombinant, or adjuvanted influenza vaccines instead of SD vaccines [70]. Also, Canada's National Advisory Committee on Immunization recommended the HD over the SD vaccine for adults aged 65 years and older [71]. In Canada, the HD vaccine is reimbursed for adults aged 65 years and older in Ontario and for long-term care residents aged 65 years and older in Saskatchewan, Manitoba, and Prince Edward Island [72]. In Europe, HD-IIV4 is recommended for immunization against influenza in people aged 60+ years [14]. In Belgium, the HD vaccine is recommended for people aged 65+ years who live in long-term healthcare facilities [14], and it is reimbursed for all people aged over 75 years. In Germany, the HD vaccine has been preferentially recommended and reimbursed for all people aged 60+ years since 2021 [73]. In the Czech Republic, it is recommended that people aged 65 years and over receive HD-IIV4 if possible, otherwise they should be given IIV4 [74]. Also, in the UK, HD-IIV4 is recommended for patients aged 65 years and over together with adjuvanted IIV4 and quadrivalent recombinant influenza vaccine [75].

In Poland there are no general recommendations regarding influenza vaccination for people aged 60 years and over. The Polish Society of Family Medicine recommends influenza vaccines to all people aged 6 months and over without contraindications to be vaccinated, with particular emphasis on risk groups [76]. The Polish Diabetes Association also recommends yearly influenza vaccination of children aged 6 months and over as well as adults (C-level recommendation) [77]. The Polish Cardiac Society recommends yearly influenza vaccination for patients with cardiovascular disease (class IIa, B-level recommendation) [78]. The preventive vaccination plan recommends influenza vaccination for clinical reasons to transplant recipients, children and adults with chronic diseases, children in risk groups and with heart disease, immunodeficient patients, and pregnant women. For epidemiological reasons the influenza vaccination is recommended to healthy children aged over 6 months, adults aged over 55 years, and residents of care centres [79].

## Vaccination coverage rate among patients aged 65+ years

Influenza vaccination coverage in Poland is one of the lowest in European countries. In the 2022/23 season, 5.5% of the general population were vaccinated, a decrease after 2 COVID-19 pandemic seasons, when slightly higher values were observed (6.01% in 2020/21 and 7% in 2021/22) [80]. Among people aged 65+ years, vaccination coverage in 2021 in Poland was 10%, higher than in Latvia and Bulgaria (7.7% and 8.9%, respectively) but significantly lower than in some other European countries (Spain 67.7%, Netherlands 72.6%, Denmark 75%, Ireland 75.4%, UK 80.9%) [81]. The vaccination rate for people aged 65+ years in Poland was also significantly lower than the WHO-recommended coverage (75%). However, despite this low value, elderly people constitute the group most willing to receive an annual flu vaccination.

## Summary: why HD influenza vaccine in older people is needed

While influenza is mainly recognized as a respiratory infection associated with a notable number of respiratory-related deaths, there is evidence indicating that it imposes an extra burden due to complications affecting several organs. Consequently, cardiovascular events, the worsening of pre-existing chronic conditions, heightened vulnerability to secondary bacterial infections, and a decline in functional well-being can appear. All these factors collectively contribute to an elevated risk of hospitalization and mortality.

Due to population ageing, the proportion of older people in the entire population is gradually increasing. In Poland, people aged 60 years and over constituted 1/4 of the population in 2020 and – according to predictions – will constitute as much as 40.4% in 2050 [82]. The elderly population experience notable comorbidities, many of which are risk factors for a severe course of influenza. In Poland, the prevalence of chronic diseases and medical problems is high in people aged 55 years and over, reaching 70.9% in people aged 55–59 years, 88.4% in those aged 65–79 years, and 93.9% in those aged 80 years and over [83]. Better protection against influenza and its complications is important for this vulnerable population and can bring tangible benefits to both patients and the healthcare system.

Even though the vaccination rate among elderly individuals in Poland is currently low, this age group exhibits the highest motivation to receive an annual flu vaccination.

**Polish experts recommendations for patients aged 60 years and over**

- HD-IIV (60 mg hemagglutinin per strain) is strongly recommended as vaccine of first choice for people aged 60 years and over.
- If HD-IIV (60 mg hemagglutinin per strain) is unavailable or not accepted, individuals aged 60 years and over can be vaccinated with SD-IIV.

Seasonal flu vaccine should be offered as soon as possible after it becomes available in the autumn because the onset of the flu season is difficult to predict and seasonal flu activity may begin as early as in November in the Northern Hemisphere.

While we strongly recommend getting vaccinated before the start of the flu season, the vaccine can be administered until the end of the season. Although its effectiveness may be reduced if exposure to influenza has already occurred, every opportunity to administer influenza vaccine to at-risk individuals who have not yet been immunized in the current season should be used, even after the flu season begins.

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## References


1. Paules CI, Fauci AS. Influenza vaccines: good, but we can do better. *J Infect Dis* 2019; 219(Suppl. 1): S1–S4.
2. WHO. Influenza (Seasonal) 2023 [cited 03.10.2023]. Available from URL: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal).
3. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir Med* 2014; 2(6): 445–454.
4. GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2019; 7: 69–89, doi: 10.1016s2213-260030496-x.
5. Macias AE, McElhaney JE, Chaves SS, et al. The disease burden of influenza beyond respiratory illness. *Vaccine* 2021; 39(Suppl. 1): A6–A14, doi: 10.1016/j.vaccine.2020.09.048.
6. WHO. Influenza [cited 28.05.2009]. Available from URL: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccines-quality/influenza.
7. Sezon grypowy 2022/2023: liczba zachorowań na grypę i zgonów. Puls Medycyny 2023 [cited 31.05.2023]. Available from URL: https://pulsmedycyny.pl/sezon-grypowy-2022-2023-liczba-zachorowan-na-grype-i-zgonow-1173692 (in Polish).
8. Meldunki epidemiologiczne "Zachorowania i podejrzenia zachorowań na grypę w Polsce" [cited 03.07.2023]. Available from URL: http://wwwold.pzh.gov.pl/oldpage/epimeld/grypa/index.htm (in Polish).
9. Buchy P, Badur S. Who and when to vaccinate against influenza. *Int J Infect Dis* 2020; 93: 375–387, doi: 10.1016/j.ijid.2020.02.040.
10. McElhaney JE, Verschoor CP, Andrew MK, et al. The immune response to influenza in older humans: beyond immune senescence. *Immun Ageing* 2020; 17: 10, doi: 10.1186/s12979-020-00181-1.
11. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018; 391(10127): 1285–300, doi: 10.1016/s0140-6736(17)33293-2.
12. Paget J, Staadegaard L, Wang X, et al. Global and national influenza-associated hospitalisation rates: Estimates for 40 countries and administrative regions. *J Glob Health* 2023; 13: 04003, doi: 10.7189/jogh.13.04003.
13. Andrew MK, Gilca V, Waite N, et al. Examining the knowledge, Attitudes and experiences of Canadian seniors Towards influenza (the EXACT survey). *BMC Geriatrics* 2019; 19: 1–9.
14. Alvarez FP, Chevalier P, Borms M, et al. Cost-effectiveness of influenza vaccination with a high dose quadrivalent vaccine of the elderly population in Belgium, Finland, and Portugal. *J Med Econ* 2023; 26(1): 710–719, doi: 10.1080/13696998.2023.2194193.
15. Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. *Nat Rev Dis Primers* 2018; 4(1): 3, doi: 10.1038/s41572-018-0002-y.
16. Vetrano DL, Triolo F, Maggi S, et al. Fostering healthy aging: The interdependency of infections, immunity and frailty. *Ageing Res Rev* 2021; 69: 101351, doi: 10.1016/j.arr.2021.101351.
17. Wilhelm M. Influenza in older patients: a call to action and recent updates for vaccinations. *Am J Manag Care* 2018; 24(2 Suppl): S15–S24.
18. Villar-Álvarez F, de la Rosa-Carrillo D, Fariñas-Guerrero F, et al. Immunosenescence, Immune Fitness and Vaccination Schedule in the Adult Respiratory Patient. *Open Respir Arch* 2022; 4(3): 100181, doi: 10.1016/j.opresp.2022.100181.
19. Jabłońska MK. Immunoaging – impact of aging on the components of the immune system. *Gerontol Pol* 2013; 4: 143–147.
20. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011; 10(4): 430–439, doi: 10.1016/j.arr.2011.03.003.
21. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380: 37–43.
22. Low LL, Kwan YH, Ko MSM, et al. Epidemiologic Characteristics of Multimorbidity and Sociodemographic Factors Associated With Multimorbidity in a Rapidly Aging Asian Country. *JAMA Netw Open* 2019; 2(11): e1915245, doi: 10.1001/jamanetworkopen.2019.15245. Erratum in: *JAMA Netw Open* 2021; 4(2): e211476.
23. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J* 2014; 44(4): 1055–1068, doi: 10.1183/09031936.00059814.
24. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014; 9: 433–441, doi: 10.2147/CIA.S45300.
25. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15: 505–522.
26. Welch C, Hassan-Smith ZK, Greig CA, et al. Acute sarcopenia secondary to hospitalisation – an emerging condition affecting older adults. *Aging Dis* 2018; 9: 151–164.
27. Barnes M, Heywood AE, Mahimbo A, et al. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart* 2015; 101: 1738–1747.
28. Peteranderl C, Herold S, Schmoldt C. Human Influenza Virus Infections. *Semin Respir Crit Care Med* 2016; 37(4): 487–500, doi: 10.1055/s-0036-1584801.
29. Trombetta CM, Gianchecchi E, Montomoli E. Influenza vaccines: Evaluation of the safety profile. *Hum Vaccin Immunother* 2018; 14(3): 657–670, doi: 10.1080/21645515.2017.1423153.
30. Torner N, Martínez A, Basile L, et al. Program Of Catalonia TP. Influenza vaccine effectiveness assessment through sentinel virological data in three post-pandemic seasons. *Hum Vaccin Immunother* 2015; 11(1): 225–230, doi: 10.4161/hv.36155.
31. CDC Estimated Influenza Illnesses, Medical visits, and Hospitalizations Prevented by Vaccination in the United States – 2019–2020 Influenza Season. 2022 [cited 29.12.2023]. Available from URL: https://www.cdc.gov/flu/about/burden-averted/2019-2020.htm.
32. Cohen SA, Chui KK, Naumova EN. Influenza vaccination in young children reduces influenza-associated hospitalizations in older adults, 2002–2006. *J Am Geriatr Soc* 2011; 59: 327–332.
33. Hannoun C. The evolving history of influenza viruses and influenza vaccines. *Expert Rev Vaccines* 2013; 12(9): 1085–1094, doi: 10.1586/14760584.2013.824709.
34. Clements ML, Murphy BR. Development and persistence of local and systemic antibody responses in adults given live attenuated or inactivated influenza A virus vaccine. *J Clin Microbiol* 1986; 23(1): 66–72.
35. Moa AM, Chughtai AA, Muscatello DJ, et al. Immunogenicity and safety of inactivated quadrivalent influenza vaccine in adults: A systematic review and meta-analysis of randomised controlled trials. *Vaccine* 2016; 34(35): 4092–4102, doi: 10.1016/j.vaccine.2016.06.064.

36. Carregaro RL, Roscani ANCP, Raimundo ACS, et al. Immunogenicity and safety of inactivated quadrivalent influenza vaccine compared with the trivalent vaccine for influenza infection: an overview of systematic reviews. *BMC Infect Dis* 2023; 23(1): 563, doi: 10.1186/s12879-023-08541-0.
37. Demurtas J, Celotto S, Beaudart C, et al. The efficacy and safety of influenza vaccination in older people: An umbrella review of evidence from meta-analyses of both observational and randomized controlled studies. *Ageing Res Rev* 2020; 62: 101118, doi: 10.1016/j.arr.2020.101118.
38. Smetana J, Chlibek R, Shaw J, et al. Influenza vaccination in the elderly. *Hum Vaccin Immunother* 2018; 14(3): 540–549, doi: 10.1080/21645515.2017.1343226.
39. Barry DW, Mayner RE, Hochstein HD, et al. Comparative trial of influenza vaccines. II. Adverse reactions in children and adults. *Am J Epidemiol* 1976; 104(1): 47–59, doi: 10.1093/oxfordjournals.aje.a112273.
40. Rowhani-Rahbar A, Klein NP, Baxter R. Assessing the safety of influenza vaccination in specific populations children and the elderly. *Expert Rev Vaccines* 2012; 11(8): 973–984.
41. McLean HQ, Belongia EA. Influenza Vaccine Effectiveness: New Insights and Challenges. *Cold Spring Harb Perspect Med* 2021; 11(6): a038315, doi: 10.1101/cshperspect.a038315.
42. Balasubramani GK, Nowalk MP, Sax TM, et al. Influenza vaccine effectiveness among outpatients in the US Influenza Vaccine Effectiveness Network by study site 2011-2016. *Influenza Other Respir Viruses* 2020; 14(4): 380–390, doi: 10.1111/irv.12741.
43. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* 2016; 16(8): 942–951, doi: 10.1016/S1473-3099(16)00129-8.
44. Zimmerman RK, Nowalk MP, Chung J, et al. US Flu VE Investigators; U.S. Flu VE Investigators. 2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. *Clin Infect Dis* 2016; 63(12): 1564–1573, doi: 10.1093/cid/ciw635.
45. Martins JP, Santos M, Martins A, et al. Seasonal Influenza Vaccine Effectiveness in Persons Aged 15–64 Years: A Systematic Review and Meta-Analysis. *Vaccines* (Basel) 2023; 11(8): 1322, doi: 10.3390/vaccines11081322.
46. Russell K, Chung JR, Monto AS, et al. Influenza vaccine effectiveness in older adults compared with younger adults over five seasons. *Vaccine* 2018; 36: 1272–1278.
47. Pebody RG, Warburton F, Andrews N, et al. Uptake and effectiveness of influenza vaccine in those aged 65 years and older in the United Kingdom, influenza seasons 2010/11 to 2016/17. *Euro Surveill* 2018; 23(39), doi: 10.2807/1560-7917.ES.2018.23.39.1800092.
48. Rondy M, El Omeiri N, Thompson MG, et al. 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* 2017; 75: 381–394.
49. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine* 2006; 24(8): 1159–1169, doi: 10.1016/j.vaccine.2005.08.105.
50. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12(1): 36–44.
51. Praditsuwan R, Assantachai P, Wasi C, et al. The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community. *J Med Assoc Thai* 2005; 88: 256–264.
52. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. *JAMA* 1994; 272: 1661–1665.
53. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med* 1995; 123: 518–527.
54. Seasonal influenza vaccines. ECDC 2023 [cited 27.10.2023]. Available from URL: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/seasonal-influenza-vaccines.
55. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; 371: 635–645.
56. Lee JKH, Lam GKL, Yin JK, et al. High-dose influenza vaccine in older adults by age and seasonal characteristics: Systematic review and meta-analysis update. *Vaccine X* 2023; 14: 100327, doi: 10.1016/j.jvacx.2023.100327.
57. DiazGranados CA, Robertson CA, Talbot HK, et al. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. *Vaccine* 2015; 33(38): 4988–4993.
58. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis [published correction appears in *Lancet Infect Dis* 2015; 15: 263]. *Lancet Infect Dis* 2015; 15: 293–300.
59. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing post-influenza deaths during 2012–2013 and 2013–2014. *J Infect Dis* 2017; 215: 510–517.
60. Chaves SS, Naeger S, Lounaci K, et al. High-Dose Influenza Vaccine Is Associated With Reduced Mortality Among Older Adults With Breakthrough Influenza Even When There Is Poor Vaccine-Strain Match. *Clin Infect Dis* 2023; 77(7): 1032–1042, doi: 10.1093/cid/ciad322.
61. DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. *Vaccine* 2012; 31: 49–57.
62. Tsang P, Gorse GJ, Strout CB, et al. Immunogenicity and safety of Fluzone(®) intradermal and high-dose influenza vaccines in older adults ≥ 65 years of age: a randomized, controlled, phase II trial. *Vaccine* 2014; 32(21): 2507–2517, doi: 10.1016/j.vaccine.2013.09.074.
63. Pepin S, Nicolas JF, Szymanski H, et al. QHD00011 study team. Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized Phase III trial. *Hum Vaccin Immunother* 2021; 17(12): 5475–5486, doi: 10.1080/21645515.2021.1983387.
64. Falsey AR, Treanor JJ, Tornieporth N, et al. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* 2009; 200: 172–180.
65. Comber L, O Murchu E, Jordan K, et al. Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥ 18 years of age. *Rev Med Virol* 2023; 33(3): e2330, doi: 10.1002/rmv.2330.
66. Chang LJ, Meng Y, Janosczyk H, et al. QHD00013 Study Group. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥ 65 years of age: A phase 3 randomized clinical trial. *Vaccine* 2019; 37(39): 5825–5834, doi: 10.1016/j.vaccine.2019.08.016.

67. Sanchez L, Nakama T, Nagai H, et al. QHD00010 Study Group. Superior immunogenicity of high-dose quadrivalent inactivated influenza vaccine versus Standard-Dose vaccine in Japanese Adults ≥ 60 years of age: Results from a phase III, randomized clinical trial. *Vaccine* 2023; 41(15): 2553–2561, doi: 10.1016/j.vaccine.2023.02.071.
68. EMEA-002359-PIP01-18-M05 – paediatric investigation plan [cited 29.06.2023]. Available from URL: https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/emea-002359-pip01-18-m05.
69. Summary of product characteristics Efluelda. Available from URL: http://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2131-015-001_23082023123426.pdf.
70. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices – United States, 2023–24 Influenza Season. *MMWR Recomm Rep* 2023; 72(2): 1–25, doi: http://dx.doi.org/10.15585/mmwr.rr7202a1.
71. Influenza vaccines: Canadian Immunization Guide [cited 18.12.2023]. Available from URL: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-10-influenza-vaccine.html#a6.4.
72. Dalcin D, Kwong JC. High-dose influenza vaccination. *CMAJ* 2019; 191(11): E313, doi: 10.1503/cmaj.181477.
73. Pahmeier K, Speckemeier C, Neusser S, et al. Vaccinating the German Population Aged 60 Years and Over with a Quadrivalent High-Dose Inactivated Influenza Vaccine Compared to Standard-Dose Vaccines: A Transmission and Budget Impact Model. *Pharmacoeconomics* 2023; 41(11): 1539–1550, doi: 10.1007/s40273-023-01299-y.
74. Doporučení české vakcinologické společnosti ČLS JEP k očkování proti chřipce. 2023 [cited 28.06.2023]. Available from URL: https://www.vakcinace.eu/doporuceni-a-stanoviska/doporuceni-ceske-vakcinologicke-spolecnosti-cls-jep-k-ockovani-proti-chripce-3 (in Czech).
75. Joint Committee on Vaccination and Immunisation Advice on influenza vaccines for 2022/23. 2021. Available from URL: https://www.nitag-resource.org/sites/default/files/2021-10/JCVI%20Statement%20on%20Influenza%20Vaccines%202022-23.pdf.
76. Mastalerz-Migas A, Kuchar E, Nitsch-Osuch A, et al. Recommendations for preventing, diagnosing, and treating influenza in adults for general practitioners: FLU COMPASS GP – ADULTS. Expert recommendations from the Polish Society of Family Medicine, Polish Vaccinology Society and from the Polish National Program against Influenza. *Fam Med Prim Care Rev* 2020; 22(1): 81–96.
77. Zalecenia kliniczne dotyczące postępowania u osób z cukrzycą 2023 Stanowisko Polskiego Towarzystwa Diabetologicznego Zalecenia kliniczne dla osób z cukrzycą. Available from URL: https://ptdiab.pl/zalecenia-ptd/zalecania-aktywni-czlonkowie-2023 (in Polish).
78. Wytyczne ESC 2021 dotyczące diagnostyki i leczenia ostrej i przewlekłej niewydolności serca. Available from URL: https://ptkardio.pl/wytyczne/44-wytyczne_esc_2021_dotyczace_diagnostyki_i_leczenia_ostrej_i_przewleklej_niewydolnosci_serca (in Polish).
79. Komunikat Głównego Inspektora Sanitarnego z dnia 28 października 2022 r. w sprawie Programu Szczepień Ochronnych na rok 2023. Available from URL: https://dziennikmz.mz.gov.pl/DUM_MZ/2022/113/oryginal/akt.pdf (in Polish).
80. Ogólnopolski Program Zwalczania Chorób Infekcyjnych. Raport epidemiologiczny – HPV, grypa, Covid-19, pneumokoki 2023_PRESS. Available from URL: www.opzci.pl (in Polish).
81. OECD (2023), Influenza vaccination rates (indicator), doi: 10.1787/e452582e-en [cited 23.10.2023]. Available from URL: https://data.oecd.org/healthcare/influenza-vaccination-rates.htm.
82. The situation of older people in Poland in 2020. Gus 2021. Available from URL: https://stat.gov.pl/files/gfx/portalinformacyjny/en/defaultaktualnosci/3618/1/3/1/the_situation_of_older_people_in_poland_in_2020.pdf.
83. Piotrowicz K, Pac A, Skalska A, et al. Patterns of multimorbidity in 4588 older adults: implications for a nongeriatrician specialist. *Pol Arch Intern Med* 2021; 131(12): 16128, doi: 10.20452/pamw.16128.

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