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## Effectiveness of influenza vaccine in patients on hemodialysis – a review

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The influenza virus is one of the most common causes of viral respiratory tract infections. Some chronic diseases predispose to a severe course of the disease and increase the risk of complications and death. To minimize the risk of infection and complications, care of patients with increased risk should include prophylactic measures such as the administration of a seasonal influenza vaccine. An influenza vaccine is the best and cheapest method of influenza prevention. It is indicated for patients with chronic kidney disease, both during conservative treatment and renal replacement therapy.





Many studies that have assessed the efficacy of an influenza vaccine in patients on hemodialysis have found that immune deficiency predisposes these patients to infection and a severe course of the disease. Because the immune response to a standard influenza vaccine in this population is weak, the studies covered many aspects of vaccination, including the need for a booster dose.

Unlike in a healthy population, the efficacy of an influenza vaccine in patients on hemodialysis might be insufficient; however, the vaccine is still able to induce immunity in a significant number of patients. Considering the latest data and the results of studies described above, the recommendation of a seasonal influenza vaccine should be obligatory in all hemodialysis patients.

This paper is based on original articles available from Medline database. The most recent and most significant literature on the influenza vaccine in patients on hemodialysis has been reviewed.

**Key words:** **influenza vaccination • chronic kidney disease • hemodialysis**

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## Background

The influenza virus is one of the most common causes of viral respiratory tract infections. In the 2012/2013 epidemic season in Poland, there were significantly more known or suspected influenza infections in comparison to previous epidemic seasons. A morbidity peak was observed at the beginning of the second half of January and reached almost 78 cases per 100 000 population daily. In total, more than 209 000 cases of confirmed or suspected infections were reported during that week [1]. In the 2012/2013 epidemic season, until May 31<sup>st</sup>, 2013, 2 714 882 cases of confirmed or suspected infections were reported in Poland. Morbidity was 7131 per 100 000 population, and 12 660 influenza-related hospitalizations and 129 deaths were reported in various age groups [1].

Influenza is a highly contagious acute viral disease typically occurring in epidemic outbreaks and pandemic outbreaks. Influenza complications are observed in the healthy population, but certain diseases predispose patients to a more severe course of the disease, and increase the risk of complications and death. Influenza complications include bronchitis and pneumonia, asthma exacerbation, otitis media (the most common complication), as well as transplant rejection (in transplant recipients), myocarditis or pericarditis, myositis, glomerulonephritis, and exacerbation of chronic disease, including chronic kidney disease and others [2]. To minimize the risk of infection and complications, care of patients with increased risk should include prophylactic measurements such as the administration of a seasonal influenza vaccine. An influenza vaccine is the best and cheapest method of influenza prevention [3,4]. Chronic kidney disease is listed as an indication for an influenza vaccine in the 2012/2013 recommendations [3]. Populations that should be vaccinated in the first instance are listed in Table 1.

For many decades infections have not been considered a major cause of mortality in the general population. Currently, the most common causes of death include cardiovascular diseases, neoplasms, accidents, and toxicoses. However, in the population of patients on hemodialysis, infections are still considered an important cause of death, which ranks second in terms of frequency [5]. Polish guidelines on the vaccination of patients on hemodialysis include not only a seasonal influenza vaccine, but also a hepatitis B vaccine (0, 1, and 6 months schedule, including booster doses to obtain anti-HBs antibody level of over 10 IU/l – the vaccine is currently complimentary for patients in both basic schedule and booster doses), non-conjugated, polysaccharide *Streptococcus pneumoniae* vaccine as well as *Haemophilus influenzae* type b (the latter is recommended for all immune deficient patients) [6].

**Table 1.** Populations that should receive influenza vaccination in the first instance [3].

Influenza vaccine should be administered mainly to:

1. Transplant recipients
2. Pregnant women
3. Patients over 6 months of age with chronic diseases of heart, lungs, metabolic diseases, chronic kidney disease, chronic liver disease, chronic neurologic disorders and immune deficiency
4. The elderly
5. Nursing home patients
6. Children aged 6–59 months
7. Health care workers, including home caregivers of frail and elderly
8. Other risk groups indicated on the basis of national data and sources

## Immune system Abnormalities in Chronic Kidney Disease

Chronic kidney disease, especially in its most advanced stage, is strongly related to the activation of immune response (systemic inflammation) and immune deficiency [7]. These immunological conditions result in different consequences. Systemic inflammation is mainly responsible for the development of atherosclerosis, while immune deficiency results in a weakened immune response to infections and in consequence leads to a severe course of disease and increased complication and mortality rates. Immune deficiency is also responsible for a poor immune response to various vaccines.

The severity of immune deficiency increases parallel to uremia [8–10]. The immune system is affected on various levels, including deficiency in both innate and adaptive immunity. In innate immunity, the decreased phagocytic activity of monocytes, macrophages, and neutrophils is observed. It mainly negatively influences the elimination of microorganisms and infected and damaged cells. In consequence, the first line of defense is weakened and the healing process is hampered. Moreover, the population of dendritic cells is depleted and dysfunctional. As dendritic cells are involved in the first stage of adaptive response initiation and form a link between innate and adaptive immunity, their dysfunction results in an ineffective immune response to infections [8,11]. Adaptive response deficiency involves all types of T and B cells. In patients on hemodialysis, abnormal CD4+ T cells phenotype (mainly Th cells population) is observed. It involves the down-regulation of activation antigens (mainly CD28 and CD69) that may lead to a weakened response of T cells to microorganisms [12]. In uremic patients, the relationship between subpopulations of Th cells is also disturbed. The Th1 to Th2 ratio is increased, leading to increased secretion of IL-4 and IL-10, which inhibits cellular response [13]. End-stage renal failure is accompanied

by the aging of the T cell population, both CD4+ and CD8+. Lymphopenia, observed in many studies, is related mainly to the decreased number of naïve T cells caused by the decreased production of T cells in the thymus and increased apoptosis [7,8]. In the last stage of chronic kidney disease, the B cell population is also depleted, which leads to decreased efficacy of humoral immunity to infections [14].

Uremia is not the only cause of immune deficiency in these patients. Other factors involved in immune deficiency include concomitant systemic inflammation, hyperparathyroidism, iron accumulation, malnutrition, and hemodialysis itself [8,15]. Hemodialysis is an independent factor negatively influencing a number of dendritic cells, the number and phagocytic activity of granulocytes, and the number and suppressive activity of regulatory T cells [11,16,17]. In addition, age, which is significantly more advanced in patients with 5<sup>th</sup> stage of chronic kidney disease in comparison to the general population, is an independent factor related to poor immune response to infections [18,19].

### Parameters Used to Assess Influenza Vaccine Efficacy

In healthy patients over 65 years of age, inactivated influenza vaccine activity is assessed in 70–90%. Vaccinations significantly decrease hospitalization and mortality rates. In the elderly, the efficacy of the influenza vaccine is lower; nevertheless, vaccinations are able to decrease the number of complications and severity of influenza for 60% and mortality rate for 80% [20–22].

The assessment of humoral immunity to individual types/subtypes of influenza virus hemagglutinin subtypes H1 and H3 and type HB, is standardized according to international protocols and is based on anti-HA antibodies titre measurements.

According to the European Agency for the Evaluation of Medicinal Products (EMA) Committee for Propriety Medical Products (CPMP) and the Commission of the European Community's criteria on standardized procedures for influenza vaccinations, the assessment of serological response to influenza vaccine should include the following parameters [23]:

- mean increase in antibody level – increase in anti-hemagglutinin antibody titre index);
- protection rate – percentage of patients with antibody titre of at least 1:40;
- response rate – percentage of patients with at least a 4-fold increase in hemagglutinin antibody titre after vaccination.

These values depend on patient age and are shown in Table 2.

**Table 2.** Commission of the European Communities and Committee for Proprietary Medicinal Products requirements for influenza vaccine [24].

	Adults aged 18–60 years	Adults over 60 years of age
Conversion rate	>2.5	>2.0
Protection rate	>70%	>60%
Response rate	>40%	>30%

Brydak L.B., 1998

Vaccination efficacy criteria for patients over 60 years of age and for patients with immune deficiency are less stringent. American criteria of vaccination efficacy are similar to that described above [23,25].

Hemagglutination antibody inhibition (HAI) is a standard criterion of influenza vaccine response. HAI <1:10 means lack of protective antibodies (i.e., no immunity to infection). Efficacy of the influenza vaccine should be assessed separately for each viral strain used in the vaccine. To declare the vaccine efficient (according to current European criteria), at least 1 of the criteria listed in Table 2 must be fulfilled.

There are many studies assessing the efficacy of the influenza vaccine in patients on hemodialysis that consider immune deficiency predisposing these patients to infection and a severe course of the disease. Because the immune response to standard influenza vaccine in this population is weak, the studies covered many aspects of vaccination, including the need for a booster dose.

This paper is based on original articles available from Medline database. The most recent and most significant literature on influenza vaccine in patients on hemodialysis has been reviewed.

### Efficacy of Influenza Vaccine

The most commonly used trivalent inactivated influenza vaccine (TIV) contains 3 viral strains: A(H1N1) subtype, A(H3N2) subtype, and B type. Composition of the vaccine is modified with each epidemic season. Since the 2010/2011 season, A(H1N1) vaccine is composed of antigens of viral strain responsible for the 2009/2010 pandemic – A(H1N1)pdm09. Standard seasonal influenza vaccine contains 15 µg of hemagglutinin of each strain, with 45 µg/0.5 ml in total. The vaccine is intended for intramuscular or deep subcutaneous injection [26].

## Efficacy of a Single Dose of the Trivalent Vaccine

Ott et al. [27] showed that 2009/2010 seasonal influenza vaccine and monovalent adjuvanted vaccine against pandemic A(H1N1)pdm09 strain (Pandemrix®) are ineffective in patients on hemodialysis because of a low level of seroprotection. Seroprotection against pandemic A(H1N1)pdm09 strain was achieved in 35.1% of patients, against seasonal A(H3N2) strain in 36.8%, and seroprotection against both strains in only in 14% of the studied subjects. The effect was age-dependent; patients below 60 years of age responded significantly better, but response rate was still low (HAI  $\geq 1:40$  against A(H1N1) in 50% of patients, and was 45% against A(H3N2) in). Seroprotection was achieved in 27% and 32.4% of patients  $\geq 60$  years of age, respectively. Importantly, efficacy of the vaccine was analyzed 6 months after vaccination, which may explain the low results obtained in the study.

Other authors reported better results of TIV administration in patients on hemodialysis. Antonen et al. showed a relatively good response to TIV, the strongest against B strain and the weakest against A(H3N2) strain. The study was performed during the 1995/1996 season using Vaxigrip® [28]. A desirable seroconversion rate was not observed for any of the strains, but 60%, 36%, and 76% of patients achieved protective HAI against A(H1N1), A(H3N2), and B strains, respectively. Almost all patients were vaccinated against influenza during the previous epidemic season; this might result in the lack of seroconversion (the higher antibody titre before vaccination and the lower increase in antibody titre after vaccination) and a higher percentage of patients with protective antibody titers after vaccination [28,29].

During the 2009/2010 epidemic season, Mastalerz-Migas et al. showed that the influenza vaccine is effective in patients on hemodialysis; however, immune response was slightly weaker in comparison to healthy controls. Response rates against A(H1N1), A(H3N2), and B strains were 37% (65% in healthy controls), 66% (70% in healthy controls), and 68% (38% in healthy controls), respectively [30].

On the other hand, the results of these 3 studies suggest a lack of response to A(H1N1) vaccine with a relatively good response to other viral strains present in TIV. Vogtländer et al. demonstrated protective HAI against A(H1N1) in only 46% of hemodialysed patients, and in 77% and 87% against A(H3N2) and B strains, respectively [31]. Moreover, this study showed that the seroprotection rate in this case is similar to rates observed among nursing home patients and significantly lower in comparison to the control group that was significantly younger than the population of patients on hemodialysis (mean age 31 vs. 70 years). The study was performed during the 1998/99 epidemic season and employed Inluvac® vaccine [31].

Eiselt et al. observed a reduced efficacy of A(H1N1) vaccine and a relatively good response to other viral strains contained in the vaccine product Inluvac® [32]. The study group (all patients over 60 years of age) responded well to A(H3N2) and B strains (all vaccine efficacy criteria were met, including seroconversion and seroprotection rates, as well as GMT increase). Protective HAI titre against A(H1N1) was observed only in 27.5% of patients. The study was performed during the 2008/2009 epidemic season. Results of immune response analysis were similar to those obtained for the control group consisting of nursing home patients [32].

Even better results, especially in terms of anti-A(H1N1) response, were observed by 2 research groups. Cavdar et al. demonstrated the efficacy of the vaccine against all influenza virus strains contained in the trivalent vaccine Vaxigrip® as measured with percentage of patients who achieved protective HAI titre [15]. Seroprotection against A(H1N1), A(H3N2), and B strains was observed in 67%, 73%, and 86% of vaccinated patients on hemodialysis, respectively. Similarly to previously described results, the weakest response was observed against A(H1N1); however, in this study the vaccine efficacy criteria were met. On the other hand, seroconversion rate against all studied strains was below efficacy criteria. The seroconversion rate was between 7% and 21% and was the lowest for B strain. It was related to the highest number of patients with a protective antibody titre before vaccination. Vaccination efficacy was lower in comparison to healthy controls; however, patients on hemodialysis were statistically older (mean age was 47 vs. 37.6 years), which might also influence the immune response [15].

Tanzi et al. demonstrated the efficacy of the influenza vaccine against all studied viral strains as measured using a geometric mean antibody titre increase [33]. The study was performed during the 2003/2004 epidemic season and used Flud® (Chiron Corp.) vaccine. In patients below 60 years of age, HAI titre  $\geq 1:40$  against A(H1N1), A(H3N2), and B strains were achieved in 94.7%, 84.2%, and 36.8% of patients, respectively, and in the elderly it was 66.7%, 56.4%, and 43.6%, respectively. The results suggest a slightly weaker response against B strain. The study was performed using a standard dose of hemagglutinin (15  $\mu$ g each) with MF59 adjuvant, which might explain the good immune response [33].

The majority of the described studies confirm that trivalent influenza vaccine is effective in patients on hemodialysis, but usually to a lesser extent than in the control group.

## Efficacy of a Single Dose of the Monovalent Vaccine

Chang et al. demonstrated that pandemic strain A(H1N1)pdm09 vaccine (AdimFlu-S®) is ineffective in patients on hemodialysis

(low seroconversion and seroprotection rates, low increase in GMT) [34]. The seroprotection rate was only 40% in the studied patients on hemodialysis, in comparison to 88.4% seroprotection rate in healthy controls. The seroconversion rate was also low (23.4% in patients below 60 years of age and 25.4% in patients >60 years of age) and was significantly lower in comparison to healthy controls (86.7%). A significant imparity between both groups was also observed for GMT increases: 1.8 in hemodialysed patients in comparison to 23.4 in healthy controls [34].

Lertdumrongluk et al. reported slightly better results [35]. They showed that 4 weeks after administration of non-adjuvanted monovalent influenza vaccine in hemodialysed patients, seroconversion and seroprotection rates were lower in comparison to healthy controls (38.6% vs. 63.1% and 50% vs. 67.1% respectively) (with almost identical percentage of patients with protective IgG titers before vaccination); however, after age-adjustment, the differences were statistically insignificant (i.e., the rates were similar in both groups). GMT increases after vaccination were also similar in both groups [35]. Despite a similar response to vaccine in patients on hemodialysis and healthy controls in terms of GMT increase, it did not confirm efficacy of the vaccine.

Moderate efficacy of monovalent influenza vaccine containing 3.75 µg of antigen and squalene as an adjuvant (Pandemrix®) was reported by Labriola et al. [36]. They showed that in a group of patients on hemodialysis and healthy controls with similar GMT before vaccination (mean age 71 years vs. 47 years, respectively), administration of influenza vaccine induced ≥4-fold increase in GMT in 64% and 94% of subjects, respectively. The study revealed a large disparity in response between the studied groups; however, it also showed a positive response to vaccine in the majority of patients [36]. Temiz et al. studied a vaccine containing 7.5 µg hemagglutinin and squalene as an adjuvant (Focetria®). They observed a positive response to the vaccine in 97.14% of patients on hemodialysis and 95% of healthy controls (in a sero-neutralization assay). Level of anti- A(H1N1)pdm09 IgG in hemodialysed patients after vaccination was higher than in the control group. According to the authors, these surprising results might be explained by the seasonal vaccination of hemodialysed patients but not healthy controls, which suggests the presence of cross-reactive antibodies against seasonal and pandemic A(H1N1) strains [37].

## Persistence of Vaccine-Induced Immune Response

In the majority of studies, immune protection was assessed at approximately 1 month after the administration of the

vaccine. However, influenza season in Europe lasts more than 4.5 months and longer protection is desirable [37]. Some authors assessed vaccine efficacy 6 months after vaccination. Ott et al. observed a low efficacy of influenza vaccine (Pandemrix®) 6 months after administration, as demonstrated in a low seroprotection rate (35.1 against pandemic A(H1N1)pdm09 strain and 36.8% against A(H3N2) strain). However, since the study lacked serological assessment before vaccination and shortly after vaccination, in addition to the fact that there was no control group, the results are hard to interpret [26]. Lertdumrongluk and colleagues demonstrated a decrease in seroconversion (38.6% vs. 27.3%) and seroprotection rates (50% vs. 38.6%) in patients on hemodialysis between 4 and 24 weeks after vaccination; however, the results were statistically insignificant [35]. These studies confirm that even 6 months after vaccination, more or less, one-third of the patients on hemodialysis are protected against influenza virus infection.

## Efficacy of a Booster Dose

Considering the encouraging results of a booster dose of hepatitis B vaccine in patients on hemodialysis [39], a similar approach was employed to increase efficacy of the influenza vaccine in this population. However, the results of these trials were negative. Tanzi et al. demonstrated that a booster dose of adjuvanted trivalent vaccine in patients on hemodialysis only resulted in a marginal, statistically insignificant increase in seroprotection and seroconversion, and an increase in GMT against all viral strains contained in the vaccine [33]. Versluis et al. showed a slight, statistically insignificant increase in seroconversion rate after the booster dose (25% vs. 31%, 66% vs. 76%, and 27% vs. 38% against A(H1N1), A(H3N2), and B strains, respectively) [40]. In contrast, Vogtländer et al. observed a statistically significant increase in seroprotection rate after the booster dose only against A(H3N2), but not against the other strains [29].

To conclude, contrary to the healthy population, efficacy of an influenza vaccine in patients on hemodialysis might be insufficient (i.e., lower response rate in comparison to the healthy population); however, the vaccine is still able to induce immunity in a significant number of patients. Despite a weak response to an influenza vaccine, studies performed in the U.S. showed that vaccination significantly reduces all-cause hospitalization risk and mortality rate in comparison to the unvaccinated population of patients on hemodialysis [41]. Analysis performed by Wang et al. in Taiwan revealed that an influenza vaccine reduces mortality of patients on hemodialysis [42]. Considering the latest data and the results of the studies described above, recommendation of a seasonal influenza vaccine should be obligatory in all hemodialysed patients.

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