REVIEW ARTICLE

Drugs 2000 Jul; 60 (1): 35-53
0012-6667/00/0007-0035/$25.00/0

Humoral Immune Response to Influenza Vaccination in Patients from High Risk Groups

Lidia B. Brydak and *Magdalena Machala*

National Influenza Center WHO, Department of Virology, National Institute of Hygiene, Warsaw, Poland

Contents

Abstract

Influenza is one of the most common respiratory diseases. Infections caused by this virus may be very serious and can lead to severe complications. So far, the most effective method of protection against influenza is annual vaccination. The Advisory Committee on Immunisation Practices recommends vaccination against influenza for some groups of people. Unfortunately, in spite of these clear indications, a large number of patients are not vaccinated.

This article reviews the current scientific literature on immunological response to influenza vaccination in patients who are at especially high risk for serious post-influenza complications and for whom immunisation against this virus is strongly recommended. Results of studies carried out in Poland and other countries in elderly people, in patients with pulmonary diseases, renal diseases, diabetes mellitus, cancer and haemophilia, and in those with HIV infection are presented. In this review, we focus on the immune response to haemagglutinin. There are some discrepancies between the results of studies carried out by different authors in high risk groups of patients. Some investigations indicated poorer humoral response to influenza vaccine in these groups, while others showed responses comparable to those in healthy individuals. These differences may be explained by differences in types and stages of the chronic diseases, in the treat-

ment and composition of influenza vaccines, and also patients' ages, vaccination history and prevaccination antibody titres. Influenza vaccines are well tolerated in high risk patients, and all adverse reactions are generally mild and similar to those observed in healthy people. Although, in some cases, immunological responses to influenza vaccination measured in the whole study group were poor, there were some individual patients who, after vaccination, developed antihaemaglutinin antibody titres which are considered to give protection against the infection or contribute to a milder course of the disease.

1. Vaccination Against Influenza: Recommendations, Coverage and Efficacy

Influenza is one of the most common respiratory diseases, affecting people of all age groups and influencing morbidity and mortality all over the world.[1-4] Infections caused by this virus may be very serious and can lead to severe post-influenza complications, including primary influenza pneumonia or secondary bacterial pneumonia.[2] Increased morbidity and mortality rates due to influenza and its complications are observed among elderly people and patients with underlying medical conditions. So far, the most effective method of protection against infection with the influenza virus is annual vaccination.[1,5]

Chemoprophylaxis, that is, use of amantadine or rimantadine, is not as well tolerated and effective as vaccination against influenza. These drugs only prevent infections with influenza A viruses, and not with influenza B. It is not known whether they prevent post-influenza complications. Moreover, their use can result in central nervous system and gastrointestinal adverse effects. Moreover, to effectively prevent infection, amantadine or rimantadine should be given each day during the peak of the influenza season and this results in significantly higher costs than vaccination.[1,6]

The Advisory Committee on Immunisation Practices (ACIP) recommends vaccination against influenza for all individuals over 65 years of age; residents of nursing homes with chronic medical conditions; people with chronic medical disorders of the pulmonary or cardiovascular systems; patients who have required regular medical follow-up or hospitalisation during the preceding year due to chronic metabolic diseases, renal dysfunction, haemoglobinopathies or immunosuppression; those who are receiving long term aspirin therapy; women who will be in the second or third trimester of pregnancy during the influenza epidemic season and also for those who can transmit influenza to other high risk patients.[6] Unfortunately, in spite of these clear indications and in spite of the national influenza vaccination policies, large numbers of patients are not vaccinated against influenza. This is true for healthy people as well as for those from high risk groups. For example, it has been assessed that only 1 to 7% of children from high risk groups are actually immunised against influenza.[7,8] This is the lowest administration rate of any vaccine for paediatric patients in spite of the fact that, besides the ACIP, the Committee on Infectious Diseases of the American Academy of Paediatrics recommends yearly immunisation against influenza for the selected high risk children.[9,10]

Many patients as well as physicians are not convinced of the efficacy of influenza vaccination. Some of them expect that the influenza vaccine will prevent all respiratory infections, while others are afraid of adverse reactions after vaccination. Moreover, the necessity for annual vaccination and its expense also discourage potential patients from getting immunised. This insufficient knowledge or the misconceptions about the dangerous consequences of influenza infections and the benefits of immunisation are the main reasons for the low influenza vaccination coverage. Nevertheless, there are many reports showing that influenza vaccination in high risk patients is as effective and safe as in healthy people because it prevents infections with the influenza virus or at least decreases the severity of the disease.[2,3,5,11,12]

The main protective effect of influenza vaccination is connected with the immune response to the haemagglutinin component. Antihaemagglutinin (HI) antibodies inhibit the attachment of influenza virus to target cell membrane receptors and neutralise virus infectivity. Depending on their concentration, they provide complete protection from acquisition of infection or provide prevention against serious illness. The most commonly used reference method for the assessment of HI antibody levels is the haemagglutinin inhibition test (HI test). This method uses the ability of influenza virus to agglutinate red blood cells. Agglutination can be inhibited by antibodies specific to the viral strain and also by the nonspecific inhibitors which can be found in sera. HI titres are read as the reciprocal of the highest serum dilution causing complete inhibition of agglutination.[13,14] Protection studies indicated that HI antibody titres of ≥1 : 40 can be considered as the protection threshold beyond which it is unlikely that development of serious illness will occur. Unlike antihaemagglutinin antibodies, antineuraminidase antibodies are not involved in neutralisation of virus infectivity. Their role in resistance to influenza virus infection lies in the inhibition of the release of mature viral particles from infected cells, which results in limitation of viral spread.[1,15] However, there are no estimated values of antineuraminidase antibody titres which could be considered to inhibit replication of the influenza virus. Therefore, in this review we focus on the immunological response to haemagglutinin which is assessed using the following serological parameters: geometric mean titre (GMT) of HI antibodies, mean-fold increase (MFI) of HI antibody titres after vaccination, protection rate, that is, the number of individuals with protective HI antibody titres ≥1 : 40, and response rate, that is, the number of individuals with at least a 4-fold increase of HI antibody titres after vaccination.[11]

According to the requirements of the Committee for Proprietary Medicinal Products and the Commission of the European Communities established for influenza vaccines, MFI of HI antibody titres in people aged 18 to 60 years vaccinated against influenza should amount to >2.5, protection rates should be at least 70% and response rates should amount to >40%, whereas in patients over 60 years of age, these values should be >2.0, >60% and >30%, respectively.[16,17]

This article reviews the current Polish and foreign scientific literature on immunological response to influenza vaccination in patients who are at especially high risk for serious post-influenza complications and for whom immunisation against this virus is strongly recommended. Recent studies which used similar methods and the same serological parameters were chosen from a search of the internet, MEDLINE and Influenza Bibliography (from the WHO Influenza Centre, National Institute for Medical Research, London). We hope that the data presented in this paper will contribute to an increase in awareness of the efficacy of immunisation against influenza among physicians and that they will promote the idea of influenza vaccination to their patients.

2. Immune Response in Patients from High Risk Groups

2.1 The Elderly

Patients aged 65 years are at increased risk for post-influenza complications and therefore vaccination against influenza is recommended for this age group.[6] It is known that 23% of individuals hospitalised because of respiratory diseases are 65 years or older and 60 to 70% or even 80 to 90% of influenza-associated deaths occur in patients from this age group.[11,18] A high incidence of infections in elderly people results from the impaired T and B cell response associated with aging.[11] This is also a reason for low influenza vaccination coverage in the elderly, which amounts approximately to 41 to 45%.[19] Because of the decreased number of B lymphocytes, the ability to achieve sufficient antibody levels for protection against viral and bacterial antigens may be reduced.[11] Therefore, many physicians and other healthcare workers are often not convinced about the benefits of influenza vaccination in the elderly people. Studies carried

out in the UK showed that lower than 20% of specialists in geriatric medicine offered immunisation against influenza to their elderly patients.[20] According to other authors' from the UK, 61% of elderly institutionalised patients had not been vaccinated against influenza, although 74% of them would have accepted influenza vaccination had it been offered.[21]

The results of many studies on immune response to influenza vaccination indicate that this form of prophylaxis is effective and the immune response is sometimes even similar to that observed in younger healthy individuals.[22,23] Available data show that during epidemics the rate of influenza infection is significantly lower in the vaccinated elderly compared with those who are not vaccinated.[22] In the studies of Nichol et al.,[18] influenza vaccination in the elderly was associated with a 17% reduction in pneumonia and influenza outpatient visits, a 6.4% reduction in all respiratory condition visits, a 51.2% reduction in pneumonia and influenza hospitalisations, a 28.6% reduction in congestive heart failure hospitalisations, a 30.7% reduction in hospitalisation costs for all respiratory conditions and congestive heart failure combined, and a 45% reduction in death from all causes.[18]

According to the requirements of the Committee for Proprietary Medicinal Products and the Commission of the European Communities established for people over 60 years of age, the protection rate should be >60%, the response rate ≥30% and the conversion rate should be at least 2.0 after influenza vaccination.[16,17] The results of many studies complied with the above requirements (table I).[2,11,23-26]

Many patients decide not to be vaccinated against influenza because of a fear of adverse reactions that may occur after the injection. However, there are findings suggesting that these adverse reactions are less frequent in the elderly than in children and younger adults.[22] Govaert et al.[27] observed local reactions (swelling, itching, warm feeling, pain when touched, constant pain, discomfort) in 17.5% of patients aged 60 years or older, while systemic reactions (fever, headache, malaise, other complaints) were noted in 11.0% of these elderly compared with 7.3% and 9.4%, respectively, in a placebo group.

When considering different types of influenza vaccines, that is, split and whole virus vaccines, there are some suggestions that in the elderly with T cell dysfunction, a whole virus vaccine may be more effective than a split vaccine in stimulating helper T cells. This is because B cell response is dependent on T cell help for the production of most antigen-specific antibodies, and immunisation in healthy elderly people with whole virus vaccine effectively increases interleukin (IL)-2 production by helper T cells to normal levels.[28,29] However, it should be noted that, at present, most of the available influenza vaccines are subunit or split.

2.2 Patients with Pulmonary Diseases

2.2.1 Bronchopulmonary Dysplasia

Respiratory tract infections, especially the most common infections with influenza virus and respiratory syncytial virus, may lead to exacerbations of chronic respiratory disease in patients with bronchopulmonary dysplasia (BPD), and are the major cause of rehospitalisation and increased morbidity and mortality in this group.[30,31] For these reasons, immunisation against influenza should be given to each patient with BPD according to their chronological and not gestational age.[31] Reactogenicity of the influenza vaccines in BPD patients is low and only mild adverse reactions are observed.[8,32]

Many studies confirmed that children with BPD are able to achieve a successful seroconversion after vaccination against influenza. Li et al.[33] immunised 42 preterm children with chronic lung disease with two 0.25ml doses of split influenza vaccine. After vaccination protection rate, that is, the number of patients with HI antibody titre ≥1 : 32, ranged from 73 to 96% in preterm sick children, while in the healthy control group these values were between 76 and 98%. Response rates ranged from 65 to 86% in children with chronic lung disease, while in the controls it was between 71 and 93%.[33] In the studies carried out by Daubeney et al.[32] in 51 children with chronic respiratory disease, congenital heart disease or both, post-vaccination protection rates were

Table I. Humoral response to influenza vaccination in the elderly as measured by the haemagglutinin inhibition test

Epidemic season, vaccine and antigens	Patients (no.)	Protection rate (%)		Response rate (%)	MFI of HI titers	Comments	Ref.
		before	after vaccination	after vaccination	after vaccination		
1991/92, trivalent, split	Ave. age 80y (58)		21-28 days	21-28 days	21-28 days	55 patients previously vaccinated in 1990; protective titres ≥1:40	11
A/Singapore/6/86 (H1N1)		52	96	78	7.6		
A/Beijing/353/89 (H3N2)		43	100	62	8.4		
B/Yamagata/16/88		55	96	83	7.7		
1994/95, trivalent, ?	Healthy elderly, ave. age 75y (79)	24-58	28 days		28 days	Protection assumed to be associated with HI titre ≥1:40	24
A/Texas/36/91 (H1N1)			24-58		1.7-2.2		
			54-86				
A/Shangdong/9/93 (H3N2)	Infirm elderly, ave. age 82y (19)	21-28	42-50		1.5-2.3		
B/Panama/45/90							
1989/90, trivalent, subunit, split	Elderly with heart disease, lung disease or diabetes; aged 61 to 83y (60) vaccinated with subunit vaccine and aged 60 to 77y (24) received split vaccine		30-45 days			Protection assumed to be associated with HI titre ≥1:40	23
A/Singapore/6/86 (H1N1)							
A/Shanghai/11/87 (H3N2)							
B/Yamagata/16/88		3-37	3-52				
		8-33	42-71				
1991/92, tetravalent, split	Elderly aged 60-91y (927)		21 days		21 days	Protective titres ≥100 for A strains and ≥200 for B strains; titres expressed as the reciprocal of the last dilution showing 50% inhibition of hemagglutination after addition of 3 units of haemagglutinin from the antigen	25
A/Singapore/6/86 (H1N1)		3	43		9.1		
A/Beijing/353/89 (H3N2)		2	68		24.1		
B/Panama/45/90		8	47		9.7		
B/Beijing/1/87		10	45		8.5		
	Placebo group aged 60 to 91y (911)		21 days		21 days		
A/Singapore/6/86 (H1N1)		3	2		1.6		
A/Beijing/353/89 (H3N2)		3	3		1.2		
B/Panama/45/90		7	2		<1.0		
B/Beijing/1/87		10	2		<1.0		

Landscape table I to be placed here.

between 55 and 71% compared with 2 to 25% before vaccination, and response rates ranged from 55 to 71%. Strong immunological response in children with either bronchopulmonary dysplasia or congenital disease was recorded by Levandovski et al.[34] After vaccination with split vaccine, 100% of patients showed at least a 4-fold increase in HI antibody titres to 1 of 3 antigens included in the vaccine.[34] In other studies carried out in children aged 6 to 18 months with BPD or congenital heart disease, the protection rate (number of patients with HI antibody titres ≥1 : 32) and response rate values measured for A(H3N2) antigens after the second dose of vaccine ranged from 31 to 100% and 38 to 93%, respectively. In the case of A(H1N1) strains, protection rates were 45 to 48% and response rates were 48 to 54%, and for B strains these values ranged from 29 to 62% and 45 to 77%, respectively.[8]

The same authors recorded convincing results in their later studies where the immunogenicity and safety of 3 different doses of new influenza haemagglutinin antigen vaccine and the standard dose of split influenza vaccine in preterm children with chronic pulmonary disease were assessed.[35] Six weeks after the first dose of the vaccine response rates in children receiving standard vaccine were 50% for antigen H1N1, 75% for H3N2 and 17% for B, while in children receiving HA antigen (67.5μg HA per 0.25ml dose) these values were 67, 56 and 44%, respectively. Four months after the first dose of the vaccine there was a decline in antibody levels. In children receiving standard vaccine, the percentage of patients with a 4-fold titre increase was 33% for H1N1, 42% for H3N2 and 33% for B, while in children receiving HA antigen these values were 22, 44 and 44%, respectively.[35]

The results of our investigations showed that preterm children with BPD vaccinated in two consecutive seasons achieved high post-vaccination antibody titres, despite their chronic disease and prematurity (unpublished observations). All MFIs were much higher than 10.0, reaching the highest values of 70.5. Despite the small number of 6 patients included in our study, protection rate and response rate values were calculated and were at least

Table I. Contd

Epidemic season, vaccine and antigens	Patients (no.)	Protection rate (%)		Response rate (%)	MFI of HI titers	Comments	Ref.
		before	after vaccination	after vaccination	after vaccination		
1993/94, trivalent, subunit	Elderly with chronic medical diseases aged 65-94y (80)		21 days	21 days	21 days	Protection assumed to be associated with HI titre ≥1:40	26
A/Texas/36/91 (H1N1)		2	31	27	4.4		
A/Beijing/32/92 (H3N2)		30	90	67	6.1		
B/Panama/45/90		79	99	45	3.8		
1994/95, trivalent, split	Elderly aged 65-100y with cardiovascular disease, bronchopulmonary disease or cancer (457)		28 days	28 days	28 days	Protection assumed to be associated with HI titre ≥1:40	2
A/Singapore/6/86 (H1N1)		10-25	50-64	52.5-75	4.7-5.4		
A/Shangdong/32/92 (H3N2)		13-25	50-78	50-72	4.4-8.3		
B/Panama/45/90		50-63	89-100	50-59	3.1-4.5		

MFI = mean-fold increase.

80 and 60%, respectively (unpublished observations). The results of our study did not confirm the observations made by Li et al.,[33] who found a significant increase in serological response in the second year of vaccination. Post-vaccination antibody titres recorded in our study were almost at the same levels as in the epidemic seasons 1995/96 and 1996/97. In previously immunised patients, lower post-vaccination antibody titres had been expected after the second vaccination.[36-38] However, Li et al.[33] suggested that in preterm children, humoral response to influenza vaccine increases with age and repeated immunisation or combination of these two factors may influence this response.

Interesting results were obtained by Groothius et al.,[39] who studied immune response to split influenza vaccine in previously unimmunised healthy full term children, in previously unimmunised sick preterm children, previously immunised preterm children with active BPD, and in previously immunised healthy preterm children who had resolved BPD. Six weeks after the first vaccination, ELISA-measured antibody levels were significantly higher in the unimmunised healthy full term children than in the sick preterm group. Since patients were similar in age, it was supposed that their health status was responsible for these differences. In contrast, no difference was found between sick and healthy preterm children who had been previously immunised. The commonly used but less sensitive HI test showed that all patients developed antibodies in titres ≥1 : 32, regardless of their health status, history of prematurity or previous immunisation status.[39]

It is worth adding that, unlike preterm children, full term infants may benefit from the passive acquisition of antibodies from their vaccinated mothers. Studies by Englund et al.[40] showed that maternal immunisation results in transplacental transfer of immunoglobulin (Ig)G antibodies to the fetus. The levels of these specific anti-influenza antibodies in infants are theoretically sufficient to provide protection for the first months of life.

2.2.2 Asthma

In patients with asthma, influenza infections may cause asthma exacerbations where increased airway responsiveness and airflow obstruction are observed, and a higher mortality rate is noted. Therefore, the ACIP and the WHO recommend vaccination against influenza for patients with asthma.[6,41,42] However, there are some reports suggesting that influenza vaccines cause exacerbations in patients with asthma.[43] Another reason for low influenza vaccination coverage in patients with asthma is misunderstanding of the recommendations of The Committee of Infectious Diseases of the American Academy of Paediatrics.[44] According to these recommendations, influenza immunisation should be deferred in patients receiving high dose corticosteroids, equivalent to prednisone at either 2 mg/kg or a total of 20 mg/day, and it is known that asthma exacerbations are often treated with prednisone.[44] Although the above recommendation does not mean that patients asthma should not be vaccinated against influenza at all, this delay often results in missed immunisation.

Adverse effects of influenza vaccination in patients with asthma are mostly mild and they include decreased peak flow, increased medication requirements or increased airway irritability measured by histamine or methacholine challenge within 48 hours after vaccination.[43,45,46] Hassan et al.[43] found that severe asthma attacks and respiratory failure requiring mechanical ventilation were extremely rare. Furthermore, a casual relationship between asthma exacerbations and influenza vaccination is difficult to assess because the vaccine is administered during the season with a high incidence of asthma exacerbations which are often caused by a cold.[46,47] Reid et al.[48] did not find any evidence of increased airway responsiveness or airway obstruction in 22 patients with stable asthma vaccinated with subunit influenza vaccine. No patients showed any exacerbation of asthma symptoms or increase in medication use after vaccination. Eight of 22 immunised patients (36.4%) developed local or systemic post-vaccination adverse reactions, but all of them were mild and did

not last longer than 48 hours.[48] Similar results were obtained by Ghirga et al.[49] who studied 95 children with asthma vaccinated with subunit influenza vaccine. No child had fever within 48 hours after immunisation and no child showed worsening of asthma. The only local adverse effect observed in three patients was pain, which probably caused restricted movement of the limb for 8 to 12 hours. Convincing results were also obtained by Bell et al.[50] They showed that in children with chronic asthma, immunisation against influenza caused a significant reduction in hospitalisation for influenza-like illness and for influenza-like illness accompanied by asthma, whereas hospitalisation for asthma alone was not affected.[50]

The results of studies on safety and immunogenicity of subunit influenza vaccine in children with acute asthma exacerbation and concurrent prednisone therapy showed that 2 weeks after vaccination, humoral response to A(H1N1) and A(H3N2) influenza antigens was similar to that observed in the control group without asthma, and the response to B strain was better in the patients with asthma. There were also no significant differences in adverse reactions recorded in these 2 study groups of children.[51] Similar results were observed by McIntosh et al.[52] who vaccinated children with asthma, high risk children without asthma and healthy children with 2 doses of bivalent influenza vaccine.[52] Post-vaccination HI antibody levels for 1 of 2 antigens included into the vaccine were different in these 3 study groups, however, without any determined trend. In the case of the second vaccine antigen, HI titres measured after the first dose of vaccine were significantly lower in patients with asthma compared with 2 other groups, whereas after the second dose they were similar to those in normal children and higher than those in the high risk group without asthma. As for adverse reactions, their indexes determined after the first dose of vaccine were greater in children with asthma than in those from high risk group without asthma or normal children.[52]

Most of the studies on the effects of influenza vaccination in patients with asthma do not take into consideration colds, which, as we described before, may cause asthma exacerbations and therefore may be wrongly considered as vaccine-related adverse reactions. In the studies of Nicholson et al.,[47] colds were taken into consideration and the results indicated that among 255 participants, 11 showed a fall in peak expiratory flow (PEF) of more than 20% after influenza vaccination compared with 3 patients from placebo group. In 8 patients, a fall in PEF of more than 30% was recorded after immunisation compared with none from the placebo group. When patients with colds were excluded there were no significant differences in PEF falls of more than 20% between the vaccine and placebo group. However when analysing PEF decrease of more than 30% these differences were significant, but they concerned patients who were vaccinated for the first time.[47]

Thus, the results of the above studies show that pulmonary complications may occur after influenza vaccination, but the risk of their occurrence is small compared with the benefits of vaccination, including significantly reduced morbidity from subsequent influenza infection observed in the vaccinated patients. Unfortunately, there are no studies on immune response to influenza vaccination carried out in patients with asthma in Poland, but we plan to examine the response of this group in the near future.

2.3 Patients with Diabetes Mellitus

It is recommended that adults and children with diabetes mellitus be vaccinated against influenza before every epidemic season.[6] Viral and bacterial diseases are associated with the increased morbidity and mortality in patients with diabetes, however, this problem seems to be underestimated. Influenza infection and its complications may cause loss of metabolic control leading to an increase of glycosylated serum proteins, ketoacidosis which may result in an increased hospitalisation rate and mortality rate, and prolonged complications.[53,54]

There are suggestions that influenza vaccination is ineffective in this group of patients. Nevertheless, many studies show that majority of patients

with diabetes are able to achieve sufficient humoral and cellular immunity and be successfully protected against the infection.[55] Usually more than 70% patients with type 1 (insulin-dependent) diabetes produce a satisfactory response to influenza vaccination, whereas in patients with type 2 (noninsulin-dependent) diabetes, response is similar to healthy people.[56]

In the studies of Diepersloot et al.,[57] 159 patients with type 1 or 2 diabetes were vaccinated with whole virus influenza vaccine. The humoral response was lower in patients with diabetes compared with healthy vaccinated controls, however the differences in MFI values were not statistically significant between these 2 groups. The protection rates measured after vaccination ranged from 57 to 85% in patients with diabetes and 50 to 90% in the controls. Response rates were between 44 and 78% in patients with type 1 diabetes and between 65 and 87% in patients with type 2, while in the control group these values were from 67 to 100%.[57] The above values almost entirely comply with the requirements of the Committee for Proprietary Medicinal Products and the Commission of the European Communities.[16,17]

Similar results were obtained by El-Madhun et al.[53] Although their studies were carried out on only 5 juvenile patients with diabetes, after vaccination all patients and the healthy controls achieved protective HI antibody titres and all showed a 4-fold or higher increase in HI antibody levels. The assessment of influenza-specific antibody-secreting cells (ASC) of all antibody classes indicated that by day 7 after vaccination, the ASC number significantly increased to all vaccine strains in both the patients with diabetes and the control group, suggesting a normal B cell proliferation in patients with diabetes.[53] As with patients with asthma, studies on immune response to influenza vaccination in patients with diabetes have not been carried out in Poland yet, but they are planned in the near future.

2.4 Patients with Renal Diseases

Influenza infections are known to be more severe in patients with chronic renal diseases, therefore the ACIP recommends annual immunisation against influenza for this group.[6,58] However, there are some discrepancies between the results of studies on immune response to influenza vaccination in patients with renal diseases. Some of these studies confirmed a good seroresponse in this group of patients, while others indicated significantly lower antibody levels compared with healthy people. In patients with renal diseases the number of lymphocytes as well as levels of IgG, IgM and IgA are generally close to the normal ranges, but the specific humoral response is impaired.[59,60] Immunological disorders observed in patients with chronic renal failure may be connected with many various factors including uraemic toxins, chronic hypoproteinaemia, and hypoglycaemia caused by intensified catabolism or a chronic deficiency of microelements. In the case of patients on haemodialysis, an additional cause is direct contact of immunological cells with dialysing membranes and the use of heparin.[58]

Because of mild or severe immunological disorders observed in patients with renal disorders, a poorer immune response would normally be expected in this group, and this is compounded by the administration of corticosteroids to these patients which inhibits antibody production and synthesis of interferon.[59,61] For example, it is known that prednisone in doses of 2 mg/kg every 48 hours have an evident immunosuppressive effect.[61] However, 22 children with nephrotic syndrome achieved very high protection rates (81 to 95%) and response rates (68 to 86%) after influenza vaccination, comparable to those in healthy people, despite the fact that the majority of them were receiving prednisone.[62] It seems that impaired humoral response observed in patients with renal diseases is associated in some disorders with the stimulation of B lymphocytes by T cells, although a defect in B lymphocytes may be also a possible explanation.[59,60]

There are reports showing that the response to influenza vaccination may be impaired especially in those patients with renal diseases who require dialysis and who had never been vaccinated previously, whereas other studies indicate that about 50% patients undergoing haemodialysis responded to the influenza vaccine and MFIs were the same in uraemic patients as in healthy controls.[63-68] The results of studies carried out by Furth et al.[69] on children with chronic renal failure, end-stage renal disease requiring dialysis and in patients after renal transplantation showed that these patients benefit from vaccination against influenza, regardless of the severity of renal disease. This was confirmed by the protection rate values which, 4 weeks after vaccination, ranged from 66 to 80% in children with chronic renal failure, 80 to 100% in dialysed patients, 71 to 88% in post transplantation patients, and 71 to 86% in the healthy control group. Convincing results were also obtained by Grekas et al.,[70] where the percentage of patients on haemodialysis (age 20 to 60 years) showing at least a 4-fold increase of HI antibody titres ranged from 31.5 to 47% one month after vaccination and 87.5 to 100% two months after vaccination in 19 patients. The above data indicated that the examined patients with renal diseases, including those who were on haemodialysis, were able to achieve post-vaccination protection rate and response rate levels which are required for healthy people.[16,17]

Nevertheless, the results of our studies carried out in children with end-stage renal disease, where 12 patients were on continuous ambulatory peritoneal dialysis (CAPD) and 8 were on haemodialysis, and in those with chronic renal failure (CRF) are contradictory to the above findings (unpublished observations).[71] They showed that humoral immune response to influenza vaccination was better in patients on CAPD and those with CRF than in the children on haemodialysis. Three and 6 months after vaccination, the number of patients with HI antibody titres $\geq 1:40$ ranged from 67 to 83% in children with CRF, 42 to 67% in those on CAPD and only 25 to 37% in children on haemodialysis. Response rate values ranged from 67 to 83% in children with CRF, 42 to 67% in those on CAPD and only 13 to 25% in patients on haemodialysis (unpublished observations).[71] However, we are not alone with these kinds of observations, because similar results were obtained by other authors.[58,72,73] These differences in antibody response to influenza vaccination between patients nondialysed and those on peritoneal dialysis or haemodialysis may be partly explained by the abnormally low production of IL-2 and interferon (IFN)-γ which influence the proliferation of CD4+ T cells. In patients on maintenance haemodialysis, expression of the IL-2 gene and IFNγ gene is strongly decreased compared with patients treated by peritoneal dialysis where IL-2 production is normal but IFNγ synthesis is even more strongly induced.[59,74] In patients on haemodialysis, a higher plasma level of soluble IL-2 receptors can be observed at the same time as the defect of IL-2 secretion. This decreases bioavailability of IL-2 and contributes to impaired antibody response in these patients.[59,74]

2.5 Patients with Cancer

An increased incidence of influenza and a high morbidity rate due to infections with this virus are observed in patients with proliferative diseases. Although the symptoms of influenza may not be severe in this group, the duration of the illness often tends to be prolonged in these patients.[75,76] Kempe et al.[76] found that the incidence of influenza in children with cancer is significantly higher than in the control group. Virus isolation or serological tests confirmed influenza A infection in 32% of patients with cancer compared with 14% of children in a control group.[76] Considering the above reasons the ACIP recommends vaccination against influenza for all immunosuppressed patients, including those with cancer.[6]

Because of impaired humoral and cellular immunity observed in patients with cancer, they are more susceptible to infection with different infectious agents and their immunological response is expected to be significantly less effective than in healthy people. On the one hand these immunological disorders are directly associated with the dis-

ease process, and on the other hand they result from immunosuppressive chemotherapy and radiotherapy used in majority of cancer patients, which may adversely affect the immunological response to viral infections and inhibit an immune response to vaccines.

Similarly to other high risk groups of patients, the results of studies on immune response to influenza vaccination in cancer patients are variable. In a study involving 41 patients, Steinhertz et al.[77] reported that those who have not been treated with chemotherapy for at least 30 or more days responded to bivalent split influenza A vaccine in the same way as normal patients.[77] Similar results were obtained by Brown et al.[78] in 10 children with cancer who were not receiving chemotherapy. They received three 0.5ml doses of trivalent split vaccine and showed antihaemagglutinin antibody titres ≥1 : 32 with the same frequency as did normal children.

The results of our studies carried out in 49 children with acute lymphoblastic leukaemia from 6 months to 3 years after chemotherapy and immunised with subunit vaccine showed that 6 months after vaccination the number of patients with protective HI antibody titres ≥1 : 40 ranged, depending on the antigen, from 45 to 88%, while the percentage of patients with at least a 4-fold increase in HI antibody levels ranged from 39 to 47%.[79] Our other study on the immunogenicity of subunit influenza vaccine in 2 groups of children (group A consisted of 25 patients who had previously been vaccinated, and group B consisted of 20 children who were vaccinated against influenza for the first time) with acute lymphoblastic leukaemia gave similar, even slightly better results.[80] The proportion of patients with HI antibody titres of ≥1 : 40 ranged from 52 to 92% three weeks after vaccination and from 68 to 100% six months after vaccination. It can be supposed that these better results may be associated with the fact that in the majority of patients included in this study chemotherapy had been completed at least 1 month to 17 years before immunisation, thus, a much longer time had been elapsed from the completion of chemotherapy when compared with our previously described study.[79,80] The other possible explanation is that these high values recorded 6 months after vaccination may have resulted from the contact of patients with the influenza virus during the study and this intensified the immunological response.[80]

There are also studies showing that a significant humoral response to influenza vaccine can be achieved in children with acute lymphoblastic leukaemia regardless of the amount of time that had elapsed from the end of chemotherapy treatment.[81]

The findings presented above are contradictory to the results of Bucalossi et al.[82] They studied humoral response to trivalent influenza vaccine in patients with B cell chronic lymphocytic leukaemia who were not treated with chemotherapy or steroids for at least 4 weeks prior to vaccination. Sixteen of 30 patients (53%) achieved post-vaccination HI antibody titres >1 : 10 and this was considered to be a protective level.[82] However, it is necessary to stress that at present HI antibodies in titres at least 1 : 40 are commonly considered to give a protective effect against influenza infection, while earlier studies suggested that even antibody levels ≥1 : 10 may protect against the infection or disease.[83]

There are some discrepancies between the antibody responses recorded by different authors in cancer patients immunised with influenza vaccine during chemotherapy. Some investigations indicated poorer humoral immune response to influenza vaccine in this group, whereas others showed responses comparable to those in healthy controls.[76,84-89] Smithson et al.[85] immunised 27 children with different types of cancer with bivalent split vaccine. After one dose of vaccine 18% of patients had HI antibody titres ≥1 : 20 and 11% had HI antibody titres ≥1 : 40, whereas after 2 doses 70% of children had HI antibody titres ≥1 : 20 and 40% had HI antibody titres ≥1 : 40.[85] The results also showed that the third dose of vaccine did not significantly increase the number of patients with HI antibody titres ≥1 : 32.[78] Other authors recorded a seroconversion rate for HI antibodies in patients with leukaemia in complete remission and receiving maintenance chemotherapy that was 2

times lower 4 weeks after vaccination with monovalent vaccine than in the control group. However, despite of the fact that long term combination chemotherapy depressed response in these patients the incidence of influenza and influenza-like illness was 10%, while in the nonvaccinated children with leukaemia it was 45.5% and in normal children 25.5%.[86] The results of studies carried out in a group of 20 patients with proliferative diseases of the haematopoietic or lymphatic system, and treated with various combinations of cytostatic drugs, showed that 10 days after vaccination 5, 15 and 30% of patients can be protected against influenza A(H1N1), A(H3N2) and B, respectively, while 28 days after vaccination these values were 10, 35 and 70% compared with 0% individuals protected before immunisation.[90] The number of patients who showed a significant response (at least a 4-fold increase of HI antibody levels) reached similar values as those of protection rate. Thus, the requirements of the Committee for Proprietary Medicinal Products and the Commission of the European Communities were complied with only 28 days after vaccination for antigen B.[90] Similar observations were made by Sumaya and Williams[87] who vaccinated 38 children with cancer receiving chemotherapy with bivalent split or whole vaccine. Two weeks after immunisation the number of patients with HI antibody titres ≥1 : 20 was 68% for A(H1N1) and 94% for A(H3N2), while 12 months after vaccination these values were 29% and 76%, respectively.[87] Unfortunately, it is not known how many patients achieved HI antibody levels ≥1 : 40.

There are some investigations where authors did not observe any significant differences in immune response to influenza vaccines between patients with cancer receiving chemotherapy, and the healthy control group and patients off chemotherapy.[88,89,91] For example, in the studies carried out by Lange et al.,[89] 22 children with acute lymphoblastic leukaemia in remission who were receiving maintenance chemotherapy and 16 children who had discontinued chemotherapy for a mean of 15 months were vaccinated against influenza with two 0.5ml doses of split bivalent vaccine. Four weeks after the first vaccination children off therapy showed significantly higher titres to one of the strains included in the vaccine than children receiving therapy. Four weeks after the second immunisation, children off therapy had higher titres of antibodies to both antigens than children who were receiving therapy, while one year after vaccination there were no significant differences between these 2 groups. It is interesting that children off therapy achieved abnormally high antibody titres to both influenza antigens. This phenomenon was also observed by Borella and Webster.[86] They suggested several theories to explain this unexpected increase in antibody levels after the completion of therapy: (i) that once immunosuppression is stopped, antigen that remains in the reticuloendothelial system becomes accessible to an expanding lymphoid cell population; (ii) that a discrete population of long-lived memory cells regenerate once chemotherapy is stopped; (iii) that memory cells are capable of interaction with an expanding, antibody-producing cell population; or (iv) that suppressor T cells fail to regenerate normally after years of chemotherapy and therefore fail to modulate the B cell response to viral antigen.[86]

All these discrepancies in the different authors' results may be explained by differences in types and stages of proliferative diseases, in the treatment and composition of influenza vaccines, and in patients' ages, vaccination history and prevaccination antibody titres.[36,38,92] Nevertheless, there is some clinical evidence that immunisation provides some protection against influenza infections.[75] The results of many studies show that no cancer patients had symptoms of influenza virus infection after influenza vaccination. However, given that different respiratory pathogens cause similar symptoms of disease, every case of respiratory infection should be confirmed by laboratory diagnosis. Influenza vaccines are well tolerated in patients with cancer and all adverse reactions are generally mild and similar to those observed in healthy controls.[88,91]

2.6 Patients with HIV Infection

The ACIP recommends influenza vaccination for all patients infected with the human immunodeficiency virus.[6] However, in spite of these clear recommendations, many physicians and patients are not convinced that immunisation against influenza is actually effective, legitimate and well tolerated in this group. On the one hand there are opinions that the incidence of influenza and mortality due to influenza is low in adult patients with HIV infection, whereas it is known that the risk of serious post-influenza complications, including primary pneumonia or secondary bacterial pneumonia, is significantly higher.[6,93-95] The second factor which discourages medical practitioners to offer influenza vaccines to their patients with HIV infection is that according to many authors' findings, good serological response after vaccination may be expected only in those patients who have minimal AIDS-related symptoms and high CD4+ T lymphocyte counts.[6,96,97] The last issue in question is that influenza vaccine, as well as tetanus toxoid and pneumococcal vaccine, probably increase the replication of HIV in the plasma or peripheral blood mononuclear cells and increase the susceptibility of uninfected cells to HIV infection.[6,98,99] However, this is not generally confirmed. There are some reports showing that this increased risk of a rise in HIV-1 RNA after vaccination occurs in patients not taking antiretroviral therapy. Therefore, it has been suggested that antiretroviral treatment should be maximised at the time of planned immunisation. This would only be in order to limit increases of HIV replication because postvaccination antibody titres appear to be similar in patients with HIV infection treated with antiviral drugs and those not receiving these drugs.[100] Although immunisation against influenza may enhance HIV replication and reduce CD4+ count, influenza infection might have an even more marked impact and result in serious consequences for a patient's health.[98]

In the majority of studies that we reviewed, humoral immune response to influenza vaccination in patients with HIV infection was generally poorer than that in healthy people.[100,101] Certainly, it must be stressed that this response depends on many factors, including influenza vaccine antigens. In our studies carried out in 34 patients with HIV infection in different stages of the disease, protection rate indexes determined one month after vaccination with subunit vaccine was only 17.6% for antigen A(H1N1) and 41.2% for antigen B, while for antigen A(H3N2) it was 79.4%.[101] Better results were obtained by Huengsberg et al.[102] who recorded that after vaccination 50% of asymptomatic patients with HIV infection were protected against all 4 tested antigens compared with 63% in the control group. The response rate was 73% for at least one of the antigens included in the vaccine compared with 93.5% in the healthy vaccinated control group.[102] In our studies, response rate values remained at similar levels during the whole study and ranged only from 9.4 to 14.7%.[101]

Significantly worse results were obtained by Schneider et al.[100] who studied humoral response to subunit influenza vaccine in patients with HIV infection and different CD4+ counts. In these studies the percentage of patients with protective HI antibody titres ranged only from 7 to 26% compared with 42 to 74% in the vaccinated control group (table II).[100]

It is worth adding that our studies, as well as those of Schneider et al. and Huengsberg et al., did not confirm significant differences in humoral response between patients with different CD4+ counts, nor between patients with AIDS and those without AIDS.[100-102]

Although the humoral response to influenza vaccination, characterised by protection rate and response rate indexes, is generally poor in patients with HIV infection, this finding does not mean that vaccinations against influenza should be stopped in this group. It is necessary to take into account the benefits of vaccination for individual patients since some of them are able to develop HI antibodies in titres which are considered to give a protection against infection and its complications or at least to contribute to a milder course of the disease.

Table II. Antibody response to influenza vaccination in patients with HIV infection as measured by the haemagglutinin inhibition test

Epidemic season, vaccine and antigens	Patients (no.)	Protection rate after vaccination (%)		MFI of HI antibody titres		Comments	Ref
1991/92, tetravalent, subunit [A/Singapore/6/86 (H1N1); A/Beijing/353/89(H3N2); B/Panama/45/90; B/Beijing/1/87]		After 3 weeks		After 3 weeks	At the end of the influenza season	Protection assumed to be associated with HI titre ≥100 for A strains and ≥200 for B strains	100
	Total HIV patients aged 24-64y (54)	7-26		3.8-8.5	1.7-3.9		
	CD4+ count ≤200 (29)	3.4-13.8					
	CD4+ count = 201-499 (15)	13.3-40					
	CD4+ count ≥500 (10)	0-40					
	Control aged 24-42y (19)	42-74		25.5-33.2	17.2-53.4		
1992/93, trivalent, subunit [A/Singapore/6/86(H1N1); A/Beijing/353/89(H3N2); B/Yamagata/16/88]	Total HIV patients aged 17-54y (44)	50% of patients had protective HI titres to all tested antigens		After 15-110 days		Protection assumed to be associated with HI titre ≥1 : 40	102
	CD4+ count <200 (6)			2.0-4.0			
	CD4+ count 200-500 (23)			2.0-4.0			
	CD4+ count >500 (15)			2.0-4.0			
	Control aged 20-51y (16)	63% of controls had protective HI titres to all tested antigens		4.0 - 16.0			
1997/98, trivalent, subunit [A/Bayern/7/95(H1N1); A/Wuhan/359/95(H3N2); B/Harbin/7/94]		After 1 month	After 6 months	After 1 month	After 6 months	Protection assumed to be associated with HI titre ≥1:40	101
	Total HIV patients aged 18 to 55y (34)	17.6-79.4	20.6-82.4	1.5-5.5	1.5-9.1		
	CD4+ count <200 (6)	16.7-66.7	16.7-66.7	2.1-8.2	2.1-12.0		
	CD4+ count 200-499 (19)	11.1-77.8	16.7-77.8	1.97-5.8	1.97 - 12.9		
	CD4+ count >500 (9)	25-87.5	25-87.5	1.6-6.5	1.6-8.7		

CD4+ = CD4+ T lymphocytes expressed as cells/μl; **MFI** = mean-fold increase.

2.7 Patients with Haemophilia

In patients with haemophilia, immunological disorders of cellular as well as humoral response can be observed.[103-106] They are probably connected with transfusion of blood product preparations and may be a reason for impaired response to influenza vaccination and consequently a lack of protective effect against influenza infection.[103-106]

Therefore, patients with haemophilia can be considered to be at increased risk and should be immunised against influenza every year, despite the fact that the ACIP does not clearly recommend influenza vaccination for this group.[6]

The results of studies carried out in Poland in patients with haemophilia indicated a significant seroconversion to influenza vaccine in this group. In the 1993/94 epidemic season, 51 children with haemophilia A or B were vaccinated with subunit influenza vaccine.[107,108] Three weeks after vaccination MFI of HI antibody titres ranged from 2.7 to 5.3 in children with haemophilia and 1.1 to 1.3 in the healthy nonvaccinated control group. Six months after immunisation, MFI values were between 1.6 and 5.8 in the vaccinated group, while in the control these values were below 1.0.[107,108] The number of patients protected ranged from 71 to 90% three weeks after vaccination and 75 to 94% six months after vaccination, while in the control group these values were between 0 to 93% and 2 to 47%, respectively. The number of patients showing at least a 4-fold increase of HI antibody titres ranged from 43 to 63% three weeks after vaccination and 22 to 61% six months after vaccination. In the control group response rate values were between 2 to 5% and 0 to 22%, respectively. Three weeks after vaccination there were several seronegative patients, while 6 months after vaccination all vaccinated patients were seropositive.[107,108]

In the epidemic season 1996/97, influenza vaccine was administered to 38 children with haemophilia who had been immunised for the first time in 1993/94.[109] Three weeks after immunisation, HI antibody levels were 3.9 to 10.9 times higher than before vaccination, while 6 months after vaccination they ranged from 8.4 to 28.6. Before vaccination, only 2.6 to 7.9% of the study group had HI antibody titres equal to or higher than 1 : 40. The highest proportion of individuals protected was observed 6 months after immunisation and ranged from 76.3 to 97.4% compared with 52.6 to 60.5% three weeks after vaccination. Similar values were obtained for response rate and ranged from 71.1 to 86.8% six months after vaccination compared with 39.5 to 42.1% three weeks after immunisation.[109]

We also carried out studies on humoral response to subunit influenza vaccine in 26 children with severe haemophilia (group A) and 12 patients with mild haemophilia (group B).[110] Three weeks after vaccination, HI antibody titres increased from 2.2 to 5.2 times in group A and 2.8 to 6.0 times in group B. Six months after vaccination a further increase of HI antibodies was observed for antigens H1N1 and H3N2. The highest percentage of individuals protected were observed 6 months after vaccination and they ranged from 65.4 to 96.2% in group A and 83.3 to 100% in group B. The number of patients with at least a 4-fold increase of HI antibody titres 3 weeks after vaccination ranged from 38.5 to 61.5% in group A, 41.7 to 66.7% in group B, and 0 to 4.3% in the healthy nonvaccinated control group. No statistically significant differences were found in HI antibody titres between patients with severe haemophilia and those with mild haemophilia.[110]

It must be stressed that in the most cases, influenza vaccines used in the described studies induced a production of HI antibodies in titres which are sufficient to protect against infections caused by the influenza virus. Moreover, these antibody titres remained at the high levels even 6 months after vaccination. Moreover, no vaccinated patients with haemophilia were infected with the influenza virus and no serious adverse reactions were observed after administration of the vaccine.[107-110]

3. Conclusions

This article has looked at the results of studies carried out in high risk patients vaccinated against influenza. Data recorded by different authors are

variable and it is difficult to find one clear conclusion. In the same high risk group some investigations indicated poorer humoral immune response to influenza vaccine, whereas others showed responses comparable to those in healthy individuals.

It is known that humoral immune response levels depend on many factors, including a patient's age, their medical condition, the type of treatment they are receiving, their vaccination history and prevaccination antibody titres. Moreover, the composition of influenza vaccines and the immunogenicity of vaccine strains must also be taken into consideration. At least one strain is different from those used in the previous epidemic season and this may vary from year to year, which influences humoral response. Another problem is a selection of appropriate control groups. In the majority of studies the control group consisted of healthy vaccinated or nonvaccinated people. However, because of ethical reasons it is very difficult to obtain a control group consisting of nonvaccinated high risk patients. Moreover, the number of patients included in the study is also an important factor which influences the results. Although in some cases immunological responses to influenza vaccination measured in the whole study group were poor, there were some individual patients who, after vaccination, developed HI antibodies in titres which are considered to give a protection against infection or contribute to a milder course of the disease.

Nevertheless, the question of what level of immune response actually protects against influenza infection in high risk patients remains. For example, Kempe et al.[76] found that HI antibody levels ≥1 : 32 correlated highly with protection against influenza in healthy patients but not in patients with cancer. This may be explained by the impaired antibody production in these patients and/or deficiencies in cell-mediated immunity, possibly in the function of cytotoxic T cells or T helper cells. In addition, the disruption of mucosal barriers by chemotherapy may facilitate the infection despite antibody titres which are high enough to give protection in healthy people.[76] Thus, another unresolved question is whether HI antibody levels are a good marker for the assessment of efficacy influenza vaccines in high risk groups of patients. It is necessary to take into account that not only humoral response but also cellular immunity play an important role in protecting against influenza infections and reduction of the disease severity, and that cellular and humoral response both to vaccine and wild disease are not always parallel.[111]

References

1. Brydak LB. Influenza and its prophylaxis. Springer PWN: Warsaw, 1998
2. Van Hoecke Ch, Prikazsky V, Ütö I. Immunogenicity of an inactivated split influenza vaccine in institutionalized elderly patients. Gerontology 1996; 42: 190-8
3. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995; 333: 889-93
4. Brydak LB, Bialek J, Rudnicka H, et al. Seroconversion assessment in a billeted military medical university student group after antiinfluenza vaccinations in 1993/1994 in Poland. Antiinfect Drugs Chemother 1997; 15 (1): 13-6
5. Nicholson KG. Socioeconomics of influenza and influenza vaccination in Europe. PharmacoEconomics 1996; 9 (3): 75-8
6. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999; 48: RR-4
7. Hall CB. Influenza: a shot or not? Pediatrics 1987; 79: 564-6
8. Groothius JR, Levin MJ, Rabalais GP, et al. Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. Pediatrics 1991; 87 (6): 823-8
9. Serwint J. Pediatrician-dependent barriers in influenza vaccine administration. Pediatric Infect Dis J 1993; 12 (11): 956-8
10. Committee on Infectious Diseases, American Academy of Pediatrics. Immunization in special clinical circumstances. In: Report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1991; 22: 46-66
11. Glathe H, Bigl S, Grosche A. Comparison of humoral immune responses to trivalent influenza split vaccine in young, middle-aged and elderly people. Vaccine 1993; 11 (7): 702-5
12. Ghendon Y. The immune response to influenza vaccines. Acta Virol 1990, 34: 295-304
13. Center for Disease Control. Concepts and procedures for laboratory-based influenza surveillance. Atlanta (GA): Center for Disease Control, 1982
14. Manuguerra JC, Hannoun C. Influenza and other viral respiratory diseases. Surveillance and laboratory diagnosis. Paris: Institute Pasteur, 1999: 188-90
15. Ada GL, Jones PD. The immune response to influenza infection. Curr Topics Microbiol Immunol 1986; 128: 1-54
16. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines (revision). 1997 Mar 12: CPMP/BWP/214/96
17. Commission of the European Communities. The rules governing medicinal products in the european community. Brussels: Commission of the European Communities, 1992; 3, 2: 93-8
18. Nichol KL, Margolis KL, Wouremna J, et al. Effectiveness of influenza vaccine in the elderly. Gerontology 1996; 42: 274-9

19. Influenza vaccination coverage levels in selected sites: United States, 1989. MMWR Morb Mortal Wkly Rep 1990; 39: 159-67
20. Lennox IM, Macphee GJ, McAlpine CH, et al. Use of influenza vaccine in long-stay geriatric units. Age Ageing 1990; 19: 169-72
21. Morgan R, King D, Turnbull CJ. Influenza vaccination: do the aged reap the benefit? Postgrad Med J 1995; 71: 22-3
22. Ikematsu H, Kashiwagi S. Efficacy and adverse reactions of influenza vaccine in the elderly. Nippon Rinsho 1997 Oct; 55 (10): 2751-7
23. Zei T, Neri M, Iorio AM. Immunogenicity of trivalent subunit and split influenza vaccines (1989-90 winter season) in volunteers of different groups of age. Vaccine 1991 Sep; 9: 613-7
24. Gross PA, Russo C, Teplitzky M, et al. Time to peak serum antibody response to influenza vaccine in the elderly. Clin Diagn Lab Immunol 1996 May; 3 (3): 361-2
25. Govaert ThME, Sprenger MJW, Dinant GJ, et al. Immune response to influenza vaccination of elderly people. A randomized double-blind placebo-controlled trial. Vaccine 1994; 12 (13): 1185-9
26. Brydak LB, Ordyñska E, Wasilewski B, et al. Immunogenicity of trivalent subunit influenza vaccine in elderly people with chronic medical conditions vaccinated in 1993 in Poland. Antiinfect Drugs Chemother 1997; 15 (1): 9-12
27. Govaert ThME, Dinant GJ, Aretz K, et al. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ 1993; 307: 988-90
28. McElhaney JE, Meneilly GS, Beattie BL, et al. The effect of influenza vaccination on Il2 production in healthy elderly: implications for current vaccination practices. J Gerontol 1992; 47: M3-M8
29. McElhaney JE, Meneilly GS, Lechelt KE, et al. Antibody response to whole-virus and split-virus influenza vaccines in successful ageing. Vaccine 1993; 11 (10): 1055-60
30. Cunningham CK, McMillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks gestation. Pediatrics 1991; 88: 527-32
31. Abman SH, Groothius JR. Pathophysiology and treatment of bronchopulmonary dysplasia. Pediatric Clin North Am 1994; 41 (2): 277-310
32. Daubeney P, Taylor CJ, McGaw J, et al. Immunogenicity and tolerability of a trivalent influenza subunit vaccine (Influvac) in high-risk children aged 6 months to 4 years. BJCP 1997; 51 (2): 87-90
33. Li M, Groothuis JR, Lehr MV, et al. Maturation of antibody response to influenza vaccine in premature infants. Immunol Infect Dis 1995; 5: 211-7
34. Levandovski RA, Regnery HL, Staton E, et al. Antibody responses to influenza B viruses in immunologically unprimed children. Pediatrics 1991; 88; 5: 1031-6
35. Groothuis JR, Lehr MV, Levin MJ. Safety and immunogenicity of a purified haemagglutinin antigen in very young high-risk children. Vaccine 1994; 12 (2): 139-41
36. Künzel W, Glathe H, Engelmann H, et al. Kinetics of humoral antibody response to trivalent inactivated split influenza vaccine in subjects previously vaccinated or vaccinated for the first time. Vaccine 1996; 14, 12: 1108-10
37. Pyhälä R, Kumpulainen V, Alanko S, et al. HI antibody kinetics in adult volunteers immunized repeatedly with inactivated trivalent influenza vaccine in 1990-1992. Vaccine 1994; 12 (10): 947-52
38. Beyer WEP, Palache AM, Sprenger MJW, et al. Effects of repeated annual influenza vaccination on vaccine sero-response in young and elderly adults. Vaccine 1996; 14 (14): 1331-9
39. Groothius JR, Levin MJ, Lehr MV, et al. Immune response to split-product influenza vaccine in preterm and full-term young children. Vaccine 1992; 10 (4): 221-5
40. Englund JA, Mbawuike I, Hammill H, et al. Maternal immunization with influenza or tetanus toxoid vaccine for passive protection in young infants. J Infect Dis 1993; 168: 647-56
41. Little JW, Hall WJ, Douglas RG, et al. Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. A Rev Respir Dis 1978; 118: 295-303
42. Quarles van Ufford WJ, Savelberg PJ. Asiatic influenza in allergic patients with bronchial asthma. Int Arch Allergy Appl Immunol 1959; 15: 189-92
43. Hassan WU, Henderson AF, Keaney NP. Influenza vaccination in asthma. Lancet 1992; 339: 194
44. Committee of Infectious Diseases. Influenza. In: 1994 Red Book. Elk Grove Village (IL): American Academy of Pediatrics, 1994: 275-83
45. Banks J, Bevan C, Fennerty A, et al. Association between rise in antibodies and increase in airway sensitivity after intramuscular injection of killed influenza virus in asthmatic patients. Eur J Respir Dis 1985; 66: 268-72
46. Oullette JJ, Reed CE. Increased response of asthmatic subjects to methacholine after influenza vaccine. J Allergy 1965; 36: 558-63
47. Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, et al. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. Lancet 1998 Jan 31; 351: 326-31
48. Reid DW, Bromly CL, Stenton SC, et al. A double-blind placebo-controlled study of the effect of influenza vaccination on airway responsiveness in asthma. Respir Med 1998; 92: 1010-1
49. Ghirga G, Ghirga P, Rodino P, et al. Safety of the subunit influenza vaccine in asthmatic children. Vaccine 1991; 9 (12): 913-4
50. Bell TD, Chai H, Berlow B, et al. Immunization with killed influenza virus in children with chronic asthma. Chest 1978; 73 (2): 140-5
51. Park CL, Frank AL, Sullivan M, et al. Influenza vaccination of children during acute asthma exacerbation and concurrent prednisone therapy. Pediatrics 1996; 98 (2): 196-200
52. McIntosh K, Foy HM, Modlin JF, et al. Multicenter two-dose trials of bivalent influenza a vaccines in asthmatic children aged six to 18 years. J Infect Dis 1977; 136 Suppl.: S645-S7
53. El-Madhun AS, Cox RJ, Seime A, et al. Systemic and local immune responses after parenteral influenza vaccination in juvenile diabetic patients and healthy controls: results from a pilot study. Vaccine 1998; 16 (2/3): 156-60
54. Eickhoff TC, Sherman JL, Serfling RE. Observations on excess mortality associated with epidemic influenza. JAMA 1961; 176: 776-82
55. Erkelens DW. Vaccinate against flu. Diabetes Rev Int 1994; 3 (4): 1
56. Haaheim LR. Diabetics and influenza immunization: missed opportunities. ESWI Influenza Bull 1995; 2: 5
57. Diepersloot RJA, Bouter KP, Beyer WEP, et al. Humoral immune resopnse and delayed hypersensitivity to influenza vaccine in patients with diabetes mellitus. Diabetologia 1987; 30: 397-401
58. Steele RW. Current status of vaccines and immune globulins for children with renal disease. Pediatr Nephrol 1994; 8: 7-10
59. Descamps-Latscha B, Chatenoud L. T cells and B cells in chronic renal failure. Semin Nephrol 1996; 16: 183-91

60. Köhler H, Girndt M, Dumann H, et al. Immunodefekt bei Niereninsuffizienz. Teil II. Mechanismen des uremischen Immunodefekts. Dtsch Med Wochenschr 1993b; 118: 790-5
61. Grzesiowski P. Vaccinations in children with renal diseases [in Polish]. Terapia i Leki 1996; XXIV, XLVI, 7-8: 241-7
62. Brydak LB, Rajkowski T, Machala M, et al. Humoral antibody response following influenza vaccination in patients with nephrotic syndrome. Antiinfect Drugs Chemother 1998; 16 (2): 151-5
63. Suga T, Niki H, Niikura M, et al. Influenza antibody titers after vaccination of chronic renal failure patients, before and during hemodialysis, or on chronic ambulatory peritoneal dialysis. Tokai I Exp Clin Med 1990; 15: 245-51
64. Versluis DJ, Beyer WEP, Masurel N, et al. Intact humoral immune response in patients on continuous ambulatory peritoneal dialysis. Nephron 1988; 49: 16-9
65. Cappel R, Van Beers D, Liensnard C. Impaired humoral and cell-mediated immune response in dialysed patients after influenza vaccination. Nephron 1983; 33: 21-5
66. Versluis DJ, Beyer WEP, Masurel N. Value of booster immunization with influenza vaccine in patients undergoing haemodialysis. BMJ 1987; 294: 348-50
67. Grekas D, Alivanis P, Kotzadamis N, et al. Influenza vaccination in chronic hemodialysis patients. The effect of zinc supplementation. Ren Fail 1992; 14 (4): 575-8
68. Nikoskelainen J, Vaananen P, Forsstrom J, et al. Influenza vaccination in patients with chronic renal failure. Scand J Infect Dis 1982; 14 (4): 245-51
69. Furth SL, Neu AM, McColley SA, et al. Immune response to influenza vaccination in children with renal disease. Pediatr Nephrol 1995; 9: 566-8
70. Grekas D, Alivanis P, Kiriazopoulou V, et al. Influenza vaccination on renal transplant patients is safe and seerologically effective. Int J Clin Pharmacol Ther Toxicol 1993; 31 (11): 553-6
71. Brydak LB, Roszkowska-Blaim M, Leszczyñska B, et al. HI antibody kinetics in children with renal failure immunized with inactivated trivalent influenza vaccine. Central European Conference on Modern Vaccinology 'Vaccines and Immunization'. Poland: Pulawy 1997 May 6-9
72. Schnaper HW. The immune system in minimal change nephrotic syndrome. Pediatr Nephrol 1989; 3: 101-10
73. Giacchino F, Quarello F, Pellerey M, et al. Continuous ambulatory peritoneal dialysis improves immunodeficiency in uremic patients. Nephron 1983; 35: 209-10
74. Koziol-Montewka M, Ksiazek A, Majdan M, et al. Influence of some immune factors on the IL-6 and soluble IL-2 receptor in haemodialized patients. Int Urol Nephrol 1997; 29, 3: 369-75
75. Ridgway D, Wolff LJ. Active immunization of children with leukemia and other malignancies. Leuk Lymphoma 1993; 9: 177-92
76. Kempe A, Hall CB, MacDonald NE, et al. Influenza in children with cancer. J Pediatr 1989; 115 (1): 33-9
77. Steinhertz PG, Brown AE, Gross PA, et al. Influenza immunization of children with neoplastic diseases. Cancer 1980; 45: 750-6
78. Brown AE, Steinhertz PG, Miller DR, et al. Immunization against influenza in children with cancer: results of a three-dose trial. J Infect Dis 1982; 145 (1): 126
79. Brydak LB, Rokicka-Milewska R, Jackowska T, et al. Kinetics of humoral response in children with acute lymphoblastic leukemia immunized with influenza vaccine in 1993 in Poland. Leuk Lymphoma 1997; 26: 163-9
80. Brydak LB, Rokicka-Milewska R, Machala M, et al. Immunogenicity of subunit trivalent influenza vaccine in children with acute lymphoblastic leukemia. Pediatr Infect Dis J 1998; 17: 125-9
81. Brydak LB, Rokicka-Milewska R, Machala M, et al. Studies on the humoral immune response to hemagglutinin of influenza vaccine in children with acute lymphoblastic leukemia after chemotherapy treatment. Int J Pediatr Hematol Oncol. In press
82. Bucalossi A, Marotta G, Galieni P, et al. Immunological response to influenza virus vaccine in B-cell chronic lymphocytic leukaemia patients. Acta Haematol 1995; 93: 56
83. Kilbourne ED, Chanock RM, Choppin PW, et al. Influenza vaccines: summary of influenza workshop V. J Infect Dis 1974; 129: 750
84. Schafer AI, Chirchill WH, Ames P, et al. The influence of chemotherapy on response of patients with haematologic malignancies to influenza vaccine. Cancer 1979; 43: 25-30
85. Smithson WA, Siem RA, Ritts RA, et al. Response to influenza virus vaccine in children receiving chemotherapy for malignancy. J Pediatr 1978: 632-3
86. Borella L, Webster RG. The immunosuppressive effects of long-term combination chemotherapy in children with acute leukemia in remission. Cancer Res 1971; 31: 420-6
87. Sumaya CV, Williams TE. Persistance of antibody after the administration of influenza vaccine to children with cancer. Pediatrics 1982; 69 (2): 226-9
88. Sumaya CV, Williams TE, Brunell PA. Bivalent influenza vaccine in children with cancer. J Infect Dis 1977; 136: S656-60
89. Lange B, Shapiro SA, Waldman MTG, et al. Antibody response to influenza immunization of children with acute lymphoblastic leukemia. J Infect Dis 1979; 140 (3): 402-6
90. Brydak LB, Calbecka M. Immunogenicity against influenza in patients with blood cancer disease. Leuk Lymphoma 1999; 32 (3-4): 369-74
91. Brunell PA. Immunologic response of immunosuppressed children to influenza vaccine. MMWR 1977 Feb 18: 54
92. Hirota Y, Kaji M, Ide S, et al. The hemagglutination inhibition antibody responses to an inactivated influenza vaccine among healthy adults: with special reference to the prevaccination antibody and its interaction with age. Vaccine 1996; 14 (17/18): 1597-602
93. Cohen JP, Macauley. Susceptibility to influenza A in HIV-positive patients. JAMA 1989; 261: 245
94. Cohn D. Bacterial pneumonia in the HIV-infected patients. Infect Dis Clin North Am 1991; 5: 485-507
95. Thurn JR, Henry K. Influenza A pneumonitis in a patient infected with the human immunodeficiency virus (HIV). Chest 1989; 95: 807-10
96. Nelson KE, Clements ML, Miotti P, et al. The influence human immunodeficiency virus (HIV) infection on antibody responses to influenza vaccines. Ann Intern Med 1988; 109: 383-8
97. Kroon FP, Van Dissel JT, De Jong JC, et al. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD+ lymphocytes. AIDS 1994; 8: 469-76
98. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. Vaccine 1998; 16 (9/10): 1039-42
99. Glesby MJ, Hoover DR, Farzadegan H, et al. The effect of influenza vaccination on human immunofdeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. J Infect Dis 1996; 174: 1332-6
100. Schneider MME, Sprenger MJW, Hoepelman IM, et al. Antibody response to tetravalent influenza subunit vaccine in pa-

tients infected with human immunodeficiency virus type 1. Int J Antimicrob Agents 1996; 6 (4): 195-200
101. Brydak LB, Hryniewicz HJ, Machala M, et al. Humoral response to influenza vaccination in HIV-infected patients. Clin Drug Invest 1999; 17 (6): 435-43
102. Huengsberg M, Chakraverty MP, Cooper G, et al. Response to influenza immunization in asymptomatic HIV infected men. Genitourin Med 1995; 71: 355-7
103. Boguslawska-Jaworska J, Dobaczewski G. Immunological disorders in children with hemophilia. In: Rokicka-Milewska R. Pediatria [in Polish]. Warszawa: PWN, 1992
104. Gazengel C, Rothschild C. Immunologic abnormalities in French non-HIV infected hemophiliac children [abstract book no. 430]. International Congress of the WFH: Oct 12-17; Athens, 1992
105. Madhok R, Gracie A, Lowe GDO, et al. Impaired cell mediated immunity in hemophilia in the absence of infection with human immunodeficiency virus. BMJ 1986; 293: 978-81
106. Cuthbert RJG, Ludlam CA, Steel CM, et al. Immunologic studies in HIV seronegative haemophiliacs: relationship to blood product therapy. Br J Haematol 1992; 80: 364-9
107. Brydak LB, Rokicka-Milewska R, Klukowska A, et al. Antibody kinetics in children with hemophilia immunized with influenza vaccine in 1993 in Poland. Int J Pediatric Hematol Oncol 1998; 5 (1): 13-9
108. Klukowska A, Brydak L, Rokicka-Milewska R, et al. Influenza vaccinations of haemophilic children [in Polish]. Acta Haematol Polonica 1995; 26 (3): 305-10
109. Brydak LB, Rokicka-Milewska R, Machala M, et al. Efficacy of subunit influenza vaccine in previously vaccinated children suffering from hemophilia. Clin Microbiol Infect 1998; 4 (10): 589-93
110. Rokicka-Milewska R, Brydak L, Machala M, et al. Antibody response to influenza vaccine in children with severe and mild hemophilia. Int J Pediatr Hematol Oncol. In press
111. McMichael AF, Gotch FM, Noble GR, et al. Cytotoxic T-cell immunity to influenza. N Engl J Med 1983; 309: 13-7

Correspondence and offprints: Professor *Lidia B. Brydak*, National Influenza Center WHO, Department of Virology, National Institute of Hygiene, ul. Chocimska 24, 00-791 Warsaw, Poland.
E-mail: nic@pzh.gov.pl