

Vaccination Practices in Pediatric Dialysis Patients Across Europe. A European Pediatric Dialysis Working Group and European Society for Pediatric Nephrology Dialysis Working Group Study

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Keywords

Vaccination · Children · Dialysis · Immunization

Abstract

Background: Data on the immunization practices in pediatric chronic kidney disease (CKD) patients are scarce. The purpose of this study was to evaluate current vaccination prac-

tices for children on dialysis across European pediatric nephrology centers. **Methods:** A total of 18 tertiary pediatric nephrology centers from 12 European countries were included in the study. The data on universal national immunization programs and immunization practices for children with chronic disease or risk were recorded from European Center for Disease Prevention and Control and the World Health Organization. The immunization practices and center protocols for monitoring antibody titers after vaccination in dialysis patients were obtained through a questionnaire. **Results:** All centers included in the study recommended immunization against hepatitis B virus (HBV), diphtheria, tetanus, pertussis, *Hemophilus influenzae* type b (Hib), poliomyelitis, measles, mumps, rubella (MMR), and streptococcus pneumonia in dialysis patients. In 16 centers, dialysis patients were vaccinated against influenza virus annually. HBV protective antibody titers were measured in 17 centers (during dialysis period in 14 centers, during pre-renal transplantation preparations in 14 centers or in both times in 11 centers). Hepatitis A virus (HAV) was reported to be followed in 13 centers, in 8 centers during dialysis period, and in 11 centers during pre-RTx preparations. MMR and varicella-zoster virus (VZV) protective antibody titers were measured during the dialysis period or before renal transplantation (RTx) in 12 and 15 centers, respectively, and in 6 centers both titers were checked both times. **Conclusion:** There are variations in vaccination practice across Europe. Children with CKD, those undergoing dialysis, and transplant candidates should receive age-appropriate vaccinations before RTx as well as before the transition to adult nephrology clinics and antibody levels should be monitored to evaluate the immunization status before and after RTx.

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Introduction

Immunization is among the most efficient strategies to decrease mortality and morbidity due to infections. There are national differences in the recommended immunization schedule for healthy children in Europe, depending on the epidemiology of diseases [1]. Immunization against diphtheria, tetanus, pertussis, *Hemophilus influenzae* type b (Hib), poliomyelitis, measles, mumps, and rubella (MMR) is recommended for all healthy children, while vaccination against hepatitis A and B viruses (HAV and HAB, respectively), varicella-zoster virus (VZV), human papillomavirus, rotavirus, *Mycobacterium tuberculosis*, influenza virus, and pneumococcus may vary significantly among European countries [1, 2]. While epide-

miological patterns of disease are slower to change, worldwide travel and immigration patterns can put immunocompromised children at greater risk.

Along with the achievements in technology and treatment of chronic diseases, today the number of children surviving with chronic diseases has increased. Children on dialysis, with chronic kidney disease (CKD) stages 2–5 and those with renal transplants (RTx) are at increased risk for vaccine-preventable infections, which are significant causes of morbidity and mortality [3–6]. These patients are vulnerable to infections because of the alterations in humoral and cellular immune response, which are adversely affected by uremic toxins, malnutrition, and immunosuppressive medications [7, 8]. Children with CKD should receive all the recommended childhood immunizations according to the standard schedule whenever possible [3]. The completion of the vaccination schedule before RTx is of particular importance [3, 7, 9]. Studies suggest that children with CKD and RTx candidates should also be protected against varicella, influenza, hepatitis B, and *Streptococcus pneumoniae*, if not included in their national universal immunization schedule [3, 4, 9]. Although vaccination in children with CKD is safe, vaccination coverage among children with CKD remains low due to safety concerns and doubts about vaccine immunogenicity and efficacy [4, 5]. In addition, data on the immunization practices in pediatric CKD and dialysis patients are scarce. Available guideline recommendations for children with CKD are derived from small or single center studies, or represent the opinion of a group of experts. Therefore, immunization recommendations vary between countries and even between different health authorities [4].

In this study, we aimed to evaluate current vaccination practices for children with CKD and those on dialysis across European pediatric nephrology centers.

Patients and Methods

A survey was sent to all members of the European Society for Pediatric Nephrology dialysis working group in 2015. A total of 18 tertiary pediatric nephrology centers from 12 European countries (Belgium, Czech Republic, Finland, France, Germany, Greece-2 centers, Italy-3 centers, Lithuania, Poland, Spain, Turkey-4 centers, and United Kingdom) responded to the survey. There were 357 prevalent dialysis patients (205 peritoneal dialysis [PD] and 152 hemodialysis [HD] patients) in these centers in 2014.

Universal national immunization programs and immunization practices for children with chronic diseases or risk were recorded from European Center for Disease Prevention and Control and the World Health Organization [1, 2]. The immunization practices for

pediatric dialysis patients were obtained from each center through a questionnaire completed by pediatric nephrologists. Center protocols for monitoring protective antibody titers after vaccination were also noted. Local Ethical Committee approval was obtained.

Results

Of the above mentioned centers, 7 of the pediatric nephrology centers were in children's hospitals and 11 were located in general hospitals. Also, 14 centers had PD and HD nurses, 3 centers had only PD nurses, and 1 had only HD nurse.

The vaccinations of dialysis patients were recorded by pediatric nephrologists in 13 centers, by both pediatric nephrologist and dialysis nurse in 3 centers, and by health care center in the remaining 2 centers. The national universal vaccination recommendations and national recommendations for children with chronic disease or risk according to the European Center for Disease Prevention and Control and World Health Organization are summarized in Table 1.

All vaccines included in the universal vaccination programs were also recommended for children with CKD, except those who are already on immunosuppression or have an underlying immune deficiency. However, in several countries, some vaccines not included in the national universal program were recommended for children with chronic diseases, namely in this case for children with CKD/dialysis including vaccines against Bacille Calmette Guérin (BCG), Hepatitis A and B, influenza, varicella, and meningococcus. All countries recommended pneumococcal conjugated vaccine for CKD patients, if not vaccinated before. Following completion of pneumococcal conjugated vaccine series, dialysis patients were routinely given the pneumococcal polysaccharide vaccine in 9 out of 18 centers (7 countries). Pneumococcal vaccines were paid by social security in all countries for children at risk.

Hepatitis B booster was recommended when titers fall below protective levels in 17 centers in which protective antibody titers were measured. Double dosage of hepatitis B vaccine is routinely used in children on dialysis in those centers except Polish center. In 16 of 18 centers, dialysis patients were vaccinated against influenza virus annually, a double dose was used in 3 countries (Table 1, 2). Center-based reports revealed that purified protein derivative (PPD) skin test or Quantiferon test was applied in 12 of 18 centers during pre-RTx preparations (Table 2).

Rejection of vaccination by parents was reported from 4 centers (Germany, Italy, and Lithuania) related to parental beliefs about possible adverse reactions of vaccines or for ideological reasons including the impression that the whole vaccination campaign is driven by pharmaceutical companies and lack of knowledge about underlying diseases and potential consequences of vaccine preventable diseases in these cases.

Centers' policy for screening antibody titers for HBV, HAV, MMR, and VZV at regular intervals or after completion of vaccination or during pre-RTx preparation are displayed in Table 3. In 17 out of 18 centers, protective antibody titers were measured for HBV and in 13 centers, for HAV, either during dialysis period or during pre-RTx preparation or both. A total of 11 of 18 centers reported HBV antibody measurement both during the dialysis period and before RTx. HAV antibody titers were reported to be monitored in 8 of 18 centers during dialysis period and in 11 of 18 centers before RTx. Only in 6 of 18 centers, hepatitis A and B antibody titers were checked during dialysis and before transplantation. Also, 12 centers reported checking MMR antibodies during dialysis or pre-RTx preparations. VZV antibodies were followed in 10 of 18 centers during dialysis period and in 12 of 18 centers before RTx. MMR and VZV antibody measurements were applied during both periods in 6 centers and 8 centers, respectively.

Discussion

Recently, widespread vaccination in the pediatric population has significantly reduced the spread of vaccine-preventable infections, which also reduces the risk of infections in children with CKD. Nevertheless, children with CKD are looked upon as a risk population for severe infections due to their defective immune status. Children with CKD generally produce protective antibodies following primary vaccinations; however, some children on dialysis and after RTx may not respond optimally due to reduced titer or duration of antibodies after immunization and may require repeated vaccination [3, 4, 9]. Furthermore vaccination coverage among these children may be suboptimal due to frequent hospitalizations and long hospital stays, relatively high cost of vaccines which are not provided by the national health system in some countries, limited knowledge among families, and health-care providers about the importance of vaccination and concerns about the safety, immunogenicity, and efficacy of vaccines [5, 10]. In our survey, all centers had dialysis

Table 1. National universal vaccination recommendations and recommendations for children with chronic disease or risk (ECDC, WHO) in 12 European Countries

Recommendation Vaccine	Included in national universal immunization programme	Recommended for children with chronic disease/risk	No recommendation
BCG	GR, LT, PL, TR, UK ¹	CZ, FI, FR,	BE, DE, ES, IT ²
DTaP/DTwP	All countries ³	All countries	–
Hib	All countries	All countries	–
IPV	All countries	All countries	–
OPV*	TR	–	BE, CZ, DE, ES, FI, FR, GR, IT, LT, PL, UK
Hepatitis A	CZ, GR, TR, PL ⁴	BE, ES, IT, FI	DE, FR, LT, UK
Hepatitis B**	BE, CZ, DE, ES, FR, GR, IT, LT, PL, TR	FI, UK	–
PCV	All countries	All countries	–
PPSV	–	CZ, DE, FR, GR	BE, ES, FI, IT, LT, PL, TR, UK
Influenzae virus***	PL ⁵	BE, CZ, DE, ES, FI, FR, GR, IT, LT, TR, UK	–
Rotavirus	BE, CZ ⁶ , FI, DE, GR, PL ⁴ , UK	–	ES, FR, IT, LT, TR
MMR	All countries	All countries	–
Varicella zoster	CZ ⁶ , DE, GR, ES, IT, TR	BE, FR, PL, UK, FI	LT
HPV	BE ⁷ , CZ ⁴ , DE ⁷ , ES ⁷ , FI, FR ⁷ , GR ⁷ , IT ⁷ , LT, PL ⁴ , UK ⁷	–	TR
Meningococcal vaccines	BE, CZ ⁴ , DE, ES, FR, GR, IT, PL ⁵ , UK	FI	LT, TR

Belgium (BE), Czech Republic (CZ), Finland (FI), France (FR), Germany (DE), Greece (GR), Italy (IT), Lithuania (LT), Poland (PL), Spain (ES), Turkey (TR) and United Kingdom (UK).

BCG, Bacille Calmette-Guérin vaccine; DTaP, diphtheria and tetanus toxoid with acellular pertussis vaccine; DTwP, diphtheria and tetanus toxoid with whole cell pertussis vaccine; IPV, inactive polio vaccine; HAV, hepatitis A virus; HBV, hepatitis B virus; Hib, haemophilus influenzae type b; HPV, human papillomavirus; MMR, Measles Mumps Rubella; OPV, oral polio vaccine; PCV, pneumococcal conjugated vaccine; PPSV, pneumococcal polysaccharide vaccine.

¹ Recommended to all CKD children below 6 years of age and to children above 6 years if quantiferon negative. ² Recommended for health workers at high risk. ³ DTwP only in Poland (in Poland DTwP is in national programme; DTaP is recommended for risk groups).

⁴ Recommended but not funded by the National Health system. ⁵ Recommended, but not mandatory and not funded by the National Health system. ⁶ Recommended only. Not included in the national immunization schedule. ⁷ Recommended for girls. * Not recommended in immunocompromised children, ** Double dose in CKD/dialysis patients except Poland, *** Double dose in CKD/dialysis patients in Finland, Spain and UK.

nurses. The record of vaccinations of dialysis patients was assigned to pediatric nephrologists in 13 centers, to both pediatric nephrologist and dialysis nurses in 3 centers. Since dialysis nurses have a closer contact with patients compared to doctors, they may more successfully collect update vaccination records.

In this study, based on a European survey including 18 centers from 12 countries, we observed that most of the

currently recommended vaccines are provided free of cost by the national health system to CKD and dialysis patients with only a few exceptions and some differences among countries (Table 1). Vaccination policies across Europe are routinely reviewed and coming close to an ideal immunization schedule. However, in practice, in addition to the aforementioned reasons, incomplete vaccination records due to heavy work load, the complex na-

Table 2. Center policy for particular tests and vaccines in CKD and dialysis patients

	Applied (n)	Not applied (n)
PPD skin test or Quantiferon before RTx	DE, ES, FR, GR (I), IT (I, III), PL, TR (I–IV), UK (12)	BE, CZ, FI, GR II, IT II, LT (6)
Annual inactive influenza virus vaccine	BE, CZ, DE, ES, FI, GR (I, II), IT (I–III), PL, TR (I–IV), UK (16)	FR, LT (2)
PPSV after completion of PCV	CZ, DE, ES, FR, GR (I, II), TR (I, III), UK (9)	BE, FI, IT (I–III), LT, PL, TR (II, IV) (9)

Belgium (BE), Czech Republic (CZ), Finland (FI), France (FR), Germany (DE), Greece (GR), Italy (IT), Lithuania (LT), Poland (PL), Spain (ES), Turkey (TR) and United Kingdom (UK). CKD, chronic kidney disease; PCV, pneumococcal conjugated vaccine; PPSV, pneumococcal polysaccharide vaccine; PPD, purified protein derivative skin test.

Table 3. Centers' policy for antibody screening

Policy	Antibody (IgG) titer measurement after completion of vaccination or at regular intervals (n/%)		Antibody (IgG) titer measurement before RTx, despite proper vaccination or disease history (n/%)	
	yes	no	yes	no
HBV	BE, CZ, DE, ES, FR, GR (I, II), IT III, PL, TR (I–IV), UK (14/77.7)	FI, IT (I, II), LT (4/22.2)	BE, CZ, FR, GR (I, II), IT (I–III), LT, PL, TR (I–IV) (14/77.7)	DE, ES, FI, UK (4/22.2)
HAV	BE, CZ, DE, ES, FR, TR (I, III, IV) (8/44.4)	FI, GR (I, II), IT (I–III), LT, PL, TR II, UK (9/50)	BE, CZ, FR, GRI, IT (I–III), TR (I–IV) (11/61.1)	DE, ES, FI, GR II, LT, PL, UK (7/38.8)
MMR	BE, CZ, DE, ES, FR, GRI, TR (I, III), UK (9/50)	FI, GR II, IT (I–III), LT, PL, TR (II, IV) (9/50)	BE, CZ, FR, GRI, IT (I, II), TR (I–III) (9/50)	DE, ES, FI, GR II, IT III, LT, PL, TR IV, UK (9/50)
VZV	BE, CZ, DE, ES, FR, GRI, IT III, TR (I, III), UK (10/50)	FI, GR II, IT (I, II), LT, PL, TR (II, IV) (8/44.4)	BE, CZ, FR, GR I, IT (I–III), LT, TR (I–IV) (12/66.6)	DE, ES, FI, GR II, PL, UK (6/33.3)

Belgium (BE), Czechia (CZ), Finland (FI), France (FR), Germany (DE), Greece (GR), Italy (IT), Lithuania (LT), Poland (PL), Spain (ES), Turkey (TR) and United Kingdom (UK). HAV, hepatitis A virus; HBV, hepatitis B virus; MMR, Measles Mumps Rubella;

ture of the disease course in CKD requiring detailed clinical and laboratory examinations during clinical visits, comorbid conditions, frequent non-communicable infectious diseases, early neonatal onset of CKD, and negative basic attitude of parents in some countries may hinder or delay scheduled routine immunization. Parental refusal of vaccines is a growing concern for the increased incidence of vaccine-preventable diseases [11]. Reasons why parents delay, refuse, or hesitate to vaccinate their children are religious beliefs, philosophical reasons such as believing that natural immunity is better than that acquired through vaccination, safety concerns, and desire for more information from healthcare professionals [11]. According to our data, refusal of vaccination was report-

ed from 4 centers because of parental beliefs about possible adverse reactions due to the vaccines or for ideological reasons. These families should be informed about how essential vaccination is before RTx and if a family refuses to vaccinate their child they might even prevent their own child's chance of receiving an allograft simply because of their prejudice.

In this survey, immunization against diphtheria, tetanus, pertussis, *H. influenzae* type b, polio, MMR, and pneumococcus (conjugated vaccine) are included in the universal immunization schedule in all countries, while vaccination against HAV and HBV, VZV, tuberculosis, rotavirus, human papilloma virus, and meningococcus are not. Hepatitis B has become very rare in some West-

ern countries due to vaccination programs. However, it is still highly prevalent in other areas, affecting up to one-third of dialyzed children [4]. Hepatitis B vaccination is applied to dialysis patients in all surveyed centers, and is administered as augmented (double) shots in 11 countries. Hepatitis B antibodies are regularly checked in the vast majority (17) of the centers and augmented boosters are given when titers decline below protective levels. Although HAV vaccine is routinely administered only in Turkey, Poland, Czech Republic, and Greece as well as in 4 additional countries (Belgium, Finland, Spain, and Italy), it is indicated for risk groups.

BCG vaccine is routinely performed in 5 countries (Greece, Lithuania, Poland, Turkey, and the UK), while PPD or Quantiferon test is applied to CKD patients in 12 centers from 8 countries. The difference among national immunization programs may be partly due to the low prevalence of tuberculosis and hepatitis A in some European countries, so that health authorities do not recommend vaccines against them.

Influenza virus immunization is included in the national program for universal vaccination only in Finland. However, high risk influenza virus vaccination is included in all the countries studied and is paid by social security in all countries except Poland. Despite this, 2 centers from 2 countries in the study reported that they did not administer annual influenza vaccination to dialysis patients. On the other hand, pneumococcal polysaccharide vaccine has been officially included in the national program to be applied to children with chronic disease in not only 4 countries, but also 9 centers from 7 countries reported to administer polysaccharide vaccine to their CKD patients. In the US, a recent study showed that influenza and pneumococcal vaccination rates among children with CKD remained low despite the inclusion of these vaccines as quality and performance indicators for ESRD facilities by Medicaid: only one third of children on dialysis or with an RTx who were 14 years or younger received influenza vaccine between 2008 and 2011. Pneumococcal vaccination rates were even lower during the same time period; about 20% of adolescents and just 10% of children received pneumococcal vaccinations [5, 12]. Since prophylactic vaccinations against influenza viruses and pneumococci can reduce disease burden and rates of hospitalization due to infection, seasonal influenza vaccination is recommended for patients with CKD, despite inferior efficacy among these patients [13, 14].

VZV vaccine is recommended for all children in 6 countries (Czech Republic, Germany, Greece, Spain,

Italy, and Turkey), and only for risk groups in 5 countries (Belgium, France, Finland, Poland, and the United Kingdom). Again, in practice, booster or a second dose of some vaccines (measles, pneumococcus, varicella, influenza, and hepatitis) are not routinely given in certain centers.

In CKD and dialysis patients, there is no evidence that vaccination including live virus vaccines leads to reactivation of an underlying immune-related renal disease or aggravates CKD [4]. Inactivated or component vaccines have not shown to have any deleterious effect on renal function after RTx, and in particular, there was no evidence of an increased rate of graft rejection [4]. Most guidelines do not recommend live virus vaccines after RTx. However, 2 studies on live virus vaccination (varicella and measles) after RTx did not show any complications attributable to the vaccine except 1 out of 17 children with mild vaccination varicella [15, 16]. Despite these encouraging reports, live vaccines should better be administered before RTx. According to our survey, patients are currently vaccinated against these viruses before RTx. But a decade ago, a fatal measles infection in a pediatric RTx patient was reported from Turkey. He was born before 1980 when routine measles vaccination had just started in Turkey and transplanted abroad without antibody screening before the procedure [6]. Measles vaccine is now included in all national programs with 1 or 2 doses. On the contrary, varicella vaccine is not included in all national programs. Considering this, documentation of wild type infection history, immunization records, or protective antibody screening seem to be the best strategy to be adopted in pediatric renal centers. This may be an important issue not only for newly referred patients, but also for patients coming from foreign countries and for immigrant patients.

The duration of protection offered by standard vaccine administration is shorter for children with CKD on conservative treatment and those on dialysis than for healthy children [5]. Children who received RTx can have moderately or even severely impaired immune responses and can remain unprotected after vaccine administration. Antibody levels also decrease faster in children after RTx [5]. This has been demonstrated in a study of 35 children in whom antibody titers against MMR, varicella, hepatitis B, diphtheria, and tetanus were determined 1 month prior to transplantation. Only 26% of patients on dialysis listed for transplantation showed protective antibody titers against all tested pathogens. Particularly, low protection was found for hepatitis B

[17]. On the contrary, in Turkey, antibody titers were analyzed among children who had been admitted for RTx. These children had received age-appropriate vaccinations but only 84% had antibody titers positive for hepatitis B, 77% for hepatitis A, and 65–73% for mumps, measles, rubella, and varicella [18]. In a German study, antibody titers against diphtheria, tetanus, and HBV, but not varicella, significantly decreased between 1 and 2 years after immunization in children who received RTx [19]. Thus, regular surveillance of specific protective antibody titers against vaccine-preventable diseases (against at least measles, varicella, and HBV) is necessary in dialysis children and before and after RTx. In our study, we evaluated the policy of centers for screening antibody titers. HBV antibody titers were checked in 17 of 18 centers, HAV in 13 of 18, VZV in 15 of 18, and MMR in 12 of 18 before renal transplantation. Antibody screening in dialysis patients also varies somewhat among European countries. Dialysis patients are revaccinated for HBV with double dose vaccine in most centers in spite of a lack of data on the efficacy of this strategy in children [20]. Double dose influenza vaccine is administered in Finland, Spain, and the UK but as a single dose in the remaining countries.

In conclusion, vaccination in children with CKD and those on dialysis is an under-recognized area, with variations in practice across the EU, and deserves more attention in pediatric nephrology clinics. Dialysis children and transplant candidates should receive age-appropriate vaccinations before RTx and should be explicitly evaluated about vaccination status and protective antibody levels also after RTx and administered vaccine booster doses when titers decline. Vaccination records must be a routine part of written and electronic patient records for CKD patients. Also, we recommend completing the immunization before the transfer to an adult nephrology clinic. Vaccination policies in children with CKD should be routinely reviewed and an ideal immunization schedule should be generated.

Ethics Statement

This study did not require informed consent. Local Ethical Committee approval was obtained.

Disclosure Statement

The authors declare no conflicts of interest.

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