Influenza and pneumococcus vaccination rates in pediatric dialysis patients in Europe: recommendations vs reality

A European Pediatric Dialysis Working Group and European Society for Pediatric Nephrology Dialysis Working Group study

Abstract

Background/aim: Children on dialysis are under increased risk of influenza and invasive pneumococcal disease. Although, vaccination against these microorganisms are recommended in dialysis patients and despite the fact that these vaccines can reduce disease burden and rates of hospitalization due to infection, vaccination rates are below expected and desired. We aimed to evaluate influenza and pneumococcal vaccination and infection rates in European pediatric dialysis centers.

Materials and Methods: In 16 centers from 11 countries, 357 pediatric dialysis patients were evaluated retrospectively during one year of observation period between 01.01.2014 and 01.01.2015.

Results: In all centers, vaccination policy included immunization of dialysis patients with inactive influenza vaccine and pneumococcal conjugate vaccine (PCV). 50% of centers recommended pneumococcal polysaccharide vaccine following routine PCV series. Significantly higher pneumococcal vaccination rate (43.9 %) was seen in PD patients compared to those on HD (32.9 %) (p=0.035), while the rates for influenza were similar (42.4 % and 46.1 respectively, p=0.496). Among all dialysis patients, 2,2 % (n=8) developed pneumonia and 6.4 % (n=23) infected by Influenza. Pneumococcic pneumonia rate was 5 % for 140 patients who received anti-pneumococcal vaccine, while only one pneumonia episode was recorded out of

217 unvaccinated patients (p=0.007). The influenza virus infection rates were similar for patients vaccinated and non-vaccinated (7 % and 6 %, respectively).

Conclusions: Although influenza and pneumococcal vaccines are highly recommended in pediatric dialysis patients, vaccination rates were lower than expected. Pneumococcal vaccination rates were higher in PD compared to the patients on HD. The rate of children with influenza infection was higher than pneumonia. The efficacy of influenza and pneumococcal vaccines was highlighted by the low infection rates. Higher pneumonia rates in patients vaccinated against pneumococcus compared to unvaccinated ones might be due to coexisting risk factors.

Key words: Dialysis, immunization, influenza vaccine, pneumococcal vaccine, vaccination

1. Introduction

Although in recent years, widespread vaccination in the general pediatric population has significantly reduced the circulation of vaccine-preventable infections, which indirectly reduces the risk for infections in children with chronic kidney disease (CKD) [1], patients on dialysis and candidates of renal transplantation (RT) still require immunizations not routinely provided to healthy children at all age groups [2] including influenza and pneumococcal polysaccharide vaccines (PPSV) due to disease-related complications [1-4].

Children with CKD and RT are at a high risk of developing invasive pneumococcal disease (IPD) [5]. Since 23-valent pneumococcal vaccine decreases the incidence of IPD [6], PPSV should be advocated in all patients with CKD (adult and pediatric), as early in their disease course as possible [6,7].

The influenza virus is highly contagious and its epidemics lead to increased morbidity and mortality with high complication rates principally among people at risk including patients

with CKD receiving immunosuppressive treatment and patients on dialysis [8,9]. Despite potentially impaired antibody responses, adult studies showed that vaccinated patients on dialysis had a significant lower rate of all-cause hospitalization risk and mortality rate related to influenza when compared to the unvaccinated ones [9,10]. Many national immunization advisory groups recommend annual influenza vaccination for patients with end stage renal disease (ESRD) including those on dialysis [6,11-13].

Despite the benefits and vaccination recommendations, studies in chronic kidney patients, including dialysis and kidney transplant candidates, show that actual vaccination rates seem to be lower than expected and desired [4,14-17]. Since the data about the immunization status against influenza and pneumococcus in children maintained by dialysis is rare, we aimed to evaluate influenza and pneumococcal vaccination and respective infection rates in European pediatric dialysis patients.

2. Patients and Methods

This was a multi-national, multi-center, retrospective study including patients from 16 tertiary pediatric nephrology centers from 11 European countries (Belgium, Czech Republic, France, Germany, Greece-2 centers, Italy-3 centers, Lithuania, Poland, Spain, Turkey-3 centers, and United Kingdom). Influenza (inactive influenza vaccine) and pneumococcal vaccination (pneumococcal conjugate vaccine [PCV] and PPSV) rates in 357 prevalent dialysis patients (205 peritoneal dialysis (PD), 152 hemodialysis (HD)) who were younger than 18 year and under regular follow-up were recorded during the one year period between 01.01.2014 and 01.01.2015. When evaluating the influenza vaccine coverage, vaccinations for 2014-2015 influenza season were included. Influenza and pneumonia episodes in dialysis patients during the one year study period were also noted. Data were obtained from each center through a

questionnaire completed by pediatric nephrologists. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 23 software. The study design was approved by the ethics committee of the coordinating center (Gazi University Non-interventional Clinical Research Ethics Committee, approval number and date: 139/14.12.2015) and we conducted this study in accordance with Good Clinical Practice Guidelines.

3. Results

Policies about influenza and pneumococcus vaccinations in the centers participating in the study are summarized in Table 1. In all centers, vaccination policy includes vaccination of dialysis patients against influenza; with double-dose being administered in Spain and UK. Vaccination with PCV which was included in national universal immunization programme of all participating countries also recommended for children with CKD. Following routine PCV series in infancy, dialysis patients are recommended to be vaccinated by PPSV in eight centers from seven countries.

Details on vaccination status are given in Table 2. 39.2 % (n=140; 90 on PD and 50 on HD) of 357 prevalent dialysis patients were vaccinated against pneumococcus with PCV, while 44 % (157: 87 on PD and 70 on HD) against influenza, and the vaccination rates were similar (p= 0.197). 17.6% of patients (n=63) were also vaccinated with PPSV. When compared by dialysis modality, higher pneumococcal vaccination rate (43.9 %) was seen in 205 PD patients compared to 152 on HD (32.9 %), and this rate was found to be statistically significant (p=0.035). 20.4 % of 152 HD patients were vaccinated with PPSV after completion of routine PCV series, while this rate was 15.6% among 205 PD patients (p=0.241). Patients receiving

PPSV after completion of PCV series were older than 2 years. 42.4 % of the PD patients and 46,1 % of the HD patients were vaccinated against influenza (p=0.496).

During the study period, it was reported that among all dialysis patients, 8 patients (2.2%) developed pneumonia and 23 (6.4%) infected by influenza. Among 140 patients vaccinated against pneumococcus, seven (5 %) experienced pneumonia, while only one pneumonia episode was recorded out of 217 unvaccinated patients; there was a statistically significant difference (p=0.007). Three patients had pulmonary comorbidity and one had immune deficiency. PPSV had been applied to only one of the 7 vaccinated patients. All pneumonia episodes required hospitalization and resulted in partial or complete recovery.

In 157 patients vaccinated against influenza, 11 influenza episodes (7 %) were recorded, while 12 episodes occurred in the 200 unvaccinated ones (6 %), the difference was not statistically significant (p=0.867). Six of the vaccinated patients hospitalized for influenza and recovered without any complications. Two patients had both influenza and pneumonia during the observation period; one of them was 10 year-old female with no comorbid condition and had been on HD for 66 months, and the other was a 2-year old patient on PD for 15 months who had pulmonary dysplasia. The detailed data of vaccinated patients experienced pneumonia and influenza are given in Table 3.

4. Discussion

In this multinational study, we evaluated influenza and pneumococcal vaccination recommendations and vaccination coverage among 16 European pediatric nephrology centers. According to this study, in all participating centers, pediatric dialysis patients were recommended to be vaccinated with inactive influenza vaccine and PCV. Following routine

PCV series in infancy in all centers, dialysis patients were recommended to be vaccinated with polysaccharide vaccine in half of the centers.

Although CKD patients have for long been included in the high-risk population groups who should receive anti-pneumococcal vaccine and should annually vaccinated against influenza, and these recommendations were fully accepted for pediatric nephrology centers, it was observed that, among 357 prevalent dialysis patients, 39 % were vaccinated with PCV and 44 % received influenza vaccine. 17.6% of patients were also vaccinated with PPSV. Despite the well known risks and vaccine recommendations, other studies in CKD patients have also demonstrated that vaccination rates are below expected and desired [4,14-17]. A study analyzing the rate of immunization in 62 children undergoing dialysis and RT between 1987 and 2000, showed that 16 patients (25.8%) either on PD or with nephrotic syndrome were vaccinated with the non-conjugate 23-valent vaccine against *S. pneumoniae* [4]. According to the United States Renal Data System (USRDS) data, between 2005 and 2008, 32% of patients between 0-19 age group with ESRD had influenza vaccine and 13% had pneumococcal vaccine [14]. Between 2008 and 2011, these rates were reported as 40% and 16% respectively [15]. Pneumococcal and influenza vaccination rates revealed in our study were higher compared to USRDS 2008-2011 pediatric dialysis vaccination data. In a single center study from Brazil evaluating the vaccination status in pediatric renal transplant recipients, 10.8% of patients had received anti-pneumococcal vaccine prior to RT [16]. A recent multicenter retrospective study evaluating vaccination coverage in 254 European (from Germany, Italy, Turkey and the United Kingdom) children with end-stage kidney disease and those on dialysis prior to RT, showed that these rates still remain low: 42% of patients received a complete vaccination schedule against pneumococcal infections and 43.3% of transplant candidates received at least one dose

of influenza vaccine [17]. Vaccinations of children with CKD might be overlooked as “minor” problems compared with growth, nutrition, dialysis, and social difficulties [4]. Although, anti-pneumococcal vaccine rates showed improvement from year to year while influenza vaccine rates remained relatively constant, the higher rates of influenza vaccination compared to pneumococcus in those studies, including the current one, might be due to the impact of annual reminders by health-care providers or media for seasonal use.

According to the 2013 United States Renal Data System (USRDS) report, pediatric HD patients are more likely to be vaccinated against Influenza than children on PD or those with a functioning kidney transplant [15]. In this study, vaccination rates with PPSV and inactive influenza vaccine were similar for the PD and HD patients, however PD patients were more likely to be vaccinated with anti-pneumococcal vaccine with a rate of 43.9 % compared to those on HD (32.9%). This may be related to younger age of the PD patients in whom vaccination is pursued more seriously.

In this study, the rate of children on dialysis with influenza infection was found to be higher (6.4 %) than pneumonia (2.2 %). CKD patients remain particularly vulnerable to invasive pneumococcal infection due to reduced immune protection, in particular, children with nephrotic syndrome and elderly on dialysis are at highest risk [18]. In a study, with a 25.8 % rate of PPSV vaccination in 62 patients, only one episode of peritonitis reported which was caused by *S.pneumoniae* [4]. In the present study, 5 % of patients vaccinated against pneumococcus experienced pneumonia while only one pneumonia episode was recorded in unvaccinated children. Half of the patients who experienced pneumococcic pneumonia had comorbid conditions increasing the risk of pneumonia. It was reported that, PPSV had been applied to only one of the 7 vaccinated patients and four patients who had comorbidity did not

receive PPSV. All pneumonia episodes required hospitalization, but there was no death associated with pneumonia. More pneumonia episodes, in vaccinated compared to nonvaccinated patients may be due to comorbid conditions and low rate of PPSV vaccination, or may be more attention had been paid on vaccination in high risk patients with comorbidities. Nonetheless, the low rate of pneumococcal pneumonia in all dialysis patients is a promising finding that may indicate the effectiveness of the vaccine.

Patients with ESRD have lower response to influenza vacinnees, but still, the vaccines had significantly lower infection-related hospitalization rates and mortality than those who were not vaccinated [18]. Throughout the study period, influenza infection rates were similar between vaccinated and unvaccinated patients (7 % vs 6 %). All of the vaccinated patients recovered with complete recovery and only half of them hospitalized for influenza. These results supports the view that the influenza vaccine reduces infection related complications and hospitalization [9,10]. In a previous study reporting a high influenza immunization rate (70.9 % of 62 children) and low prevalence of influenza in children undergoing dialysis and RT, none of the patients, including those who were not vaccinated, developed a “flu-like” syndrome requiring hospital admission [4]. The vaccine efficacy may be measured by the absence or low prevalance of disease, but of course, it should be confirmed in large cohort studies. Our study included a higher number of dialysis patients. Although the number of patients vaccinated with influenza was more than those vaccinated with anti-pneumococcal vaccine, the higher rate of influenza infection and similar rates between the vaccinated and non-vaccinated group can be explained by the fact that influenza is more contagious and the vaccination rate is low in the whole population.

It is important to prevent influenza and pneumococcal infections in these patients who may experience very serious consequences as a result of their already existing serious chronic diseases and other comorbid conditions. As underlined in a study [4], to increase the vaccination coverge in dialysis patients, vaccinations in these population should not be overlooked, have to be assessed as a part of the primary work-up, and the renal team should take over the responsibility for the reviewing, monitoring and administration of the vaccines. The household contacts of these patients should also be vaccinated against Influenza and *S. pneumoniae* [4]. Especially, annual vaccination of household contacts with influenza vaccine may reduce the exposure of dialysis patients to the virus.

5. Conclusion: Despite the fully recommendation of inactive influenza and routine PCV series for pediatric dialysis patients, and in half of the centers PPSV was recommended, vaccination rates with all three vaccines were suboptimal; nevertheless, vaccination rates against Influenza and *S.pneumoniae* were higher compared to those of the United States. Pneumococcal vaccination rates were higher in PD patients compared to the ones on HD. The respective infection rates were generally low, while the rate of children on dialysis with influenza infection was higher than pneumonia. Higher pneumonia rates in patients vaccinated against pneumococcus compared to unvaccinated ones may be due to coexisting risk factors. The efficacy of influenza and pneumococcal vaccines was highlighted by the low infection rates, and the importance of influenza vaccine had been shown by the results that half of the infected dialysis patients did not necessitated hospitalization and all showed complete recovery. Strategies should be developed to increase vaccination coverage in this patient group.

Author contributions: All authors contributed to the conception and design of the manuscript and approved the final version.

Disclaimer/Conflict of interest: All authors declare no competing financial disclosure. All authors declare no competing conflict of interest.

Funding: No funding was received for this study.

Compliance with Ethical Statements

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Esposito S, Mastrolia MV, Prada E, Pietrasanta C, Principi N. Vaccine administration in children with chronic kidney disease. Vaccine 2014 Nov 20;32(49):6601-6606. doi: 10.1016/j.vaccine.2014.09.038
2. Neu AM. Immunizations in children with chronic kidney disease. Pediatric Nephrology 2012;27(8):1257-1263. doi:10.1007/s00467-011-2042-3
3. Neuhaus TJ. Immunization in children with chronic renal failure: a practical approach. Pediatric Nephrology 2004 Dec;19(12):1334-1339. doi: 10.1007/s00467-004-1597-7
4. Laube GF, Berger C, Goetschel P, Leumann E, Neuhaus TJ. Immunization in children with chronic renal failure. Pediatric Nephrology 2002;17(8):638-642. doi:10.1007/s00467-002-0869-3
5. Hjuler T, Wohlfahrt J, Staum Kaltoft M, Koch A, Biggar RJ et al. Risks of invasive pneumococcal disease in children with underlying chronic diseases. Pediatrics 2008; 122(1): e 26-32. doi: 10.1542/peds.2007-1510

6. Vandecasteele SJ, Ombelet S, Blumental S, Peetermans WE. The ABC of pneumococcal infections and vaccination in patients with chronic kidney disease. Clinical Kidney Journal 2015; 8(3): 318–324. doi: 10.1093/ckj/sfv030
7. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R et al. Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clinical Infectious Diseases 2014 Feb;58(3):309-18. doi: 10.1093/cid/cit816. Erratum in: Clinical Infectious Diseases 2014 Jul 1;59(1):144.
8. Mastalerz-Migas A, Gwiazda E, Brydak LB. Effectiveness of influenza vaccine in patients on hemodialysis--a review. Medical Science Monitor 2013;19: 1013-1018. Published 2013 Nov 18. doi:10.12659/MSM.889671
9. Kunisaki KM, Janoff EN: Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infectious Diseases 2009; 9(8): 493–504. doi: 10.1016/S1473-3099(09)70175-6
10. Gilbertson DT, Unruh M, McBean AM, Kausz AT, Snyder JJ et al. Influenza vaccine delivery and effectiveness in end stage renal disease. Kidney International 2003; 63(2): 738–743. doi: 10.1046/j.1523-1755.2003.00787.x
11. Grzegorzewska AE. Prophylactic vaccinations in chronic kidney disease: Current status. Human Vaccines &Immunotherapeutics 2015; 11(11):2599-2605. doi: 10.1080/21645515.2015.1034915
12. Centers for Disease Control and Prevention (CDC): Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices–United States, 2013–2014. MMWR Recommendations and Reports 2013; 62 (RR07):1–43

13. National Advisory Committee on Immunization (NACI): Statement on Seasonal Influenza Vaccine for 2013–2014. Canada Communicable Disease Report. October 2013, Volume 39, ACS-4; doi: 10.14745/ccdr. v39i00a04
14. U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010
15. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013
16. Chaves TSS, Pereira LM, De Santos SS, David-Neto E, Lopes MH. Evaluation of the vaccination status in pediatric renal transplant recipients. Pediatric Transplantation. 2008 Jun;12(4):432-435. doi: 10.1111/j.1399-3046.2007.00820.x
17. Höcker B, Aguilar M, Schnitzler P, Pape L, Dello Strologo L et al. Incomplete vaccination coverage in European children with end-stage kidney disease prior to renal transplantation. Pediatric Nephrology 2018 Feb; 33(2):341-350. doi: 10.1007/s00467-017-3776-3
18. Bitsori M, Galanakis E. Vaccine-preventable infection morbidity of patients with chronic kidney disease and cocoon vaccination strategies. Expert Review of Vaccines. 2015;14(10):1385-1395. doi: 10.1586/14760584.2015.1075397

Table 1. Center policy for influenza and pneumococcal vaccines in CKD and dialysis patients

Vaccine	recommended	not recommended
Inactive annual influenza	all centers	-
PCV	all centers	-
PPSV after completion of PCV	CZ, DE, ES, FR, GR (I, II), TR (I), UK	BE, IT (I–III), LT, PL, TR (II, III)

BE: Belgium, CZ:Czech Republic, DE:Germany, ES: Spain, FR: France, GR:Greece, IT:Italy, LT:Lithuania, PCV:pneumococcal conjugated vaccine, PL:Poland, PPSV:pneumococcal polysaccharide vaccine, TR:Turkey , UK:United Kingdom

285 **Table 2. Prevalent dialysis patients and their vaccinations against pneumococcus and**

286 **influenza**

Country	Prevalent dialysis patients HD/PD (n)	Patients vaccinated with PCV (n) HD/PD	Patients vaccinated with PPSV after completion of PCV (n) HD/PD	Patients vaccinated against influenza (n) HD/PD
BE	9/0	1/0	1/0	1/0
CZ	5/12	1/6	0/0	1/2
FR	6/5	6/5	6/5	2/2
DE	10/27	8/16	1/4	9/18
GR	11/18	6/7	6/7	11/14
IT	31/34	5/20	0/1	19/16
LT	1/5	1/1	0/0	0/0
PO	6/4	2/3	0/0	2/2
ES	8/3	7/2	7/2	8/3
TR	37/76	9/20	6/4	8/9
UK	28/21	4/10	4/9	9/21
Total	**152/205**	**50 /90**	**31/32**	**70/87**

287 BE: Belgium, CZ:Czech Republic, DE:Germany, ES: Spain, FR: France, GR:Greece,

288 HD:hemodialysis, IT:Italy, LT:Lithuania, PCV:pneumococcal conjugated vaccine, PD:

peritoneal dialysis, PL:Poland, PPSV:pneumococcal polysaccharide vaccine, TR:Turkey , UK:United Kingdom

312 **Table 3. Vaccinated patients developed pneumonia and influenza infection**

Patient	**Age (months)**	**Sex**	**Dialysis modality**	**Time on dialysis (months)**	**Primary renal disease**	**Comorbidity**	**Vaccine**	**Hospitalization**
Pneumonia								
1	19	male	PD	15	CAKUT	Pulmonary hypoplasia	PCV13	+
2	21	female	PD	14	CAKUT	-	PCV13	+
3	23	male	PD	21	CAKUT	-	PCV13	+
4	25	male	HD	19	CAKUT	Chronic lung disease	PCV13	+
5	41	male	HD	36	ARPKD	Pulmonary hypoplasia	PCV13	+
6	121	female	HD	66	RVT	-	PCV7 + PPSV	+
7	148	male	PD	80	FSGS	Schimke immuno-osseous dysplasia	PCV7	+
Influenza								
1	19	male	PD	15	CAKUT	Pulmonary hypoplasia	1 dose	+

2	24	male	HD	7	Congenital nephrotic syndrome	-	1 dose	+
3	30	male	PD	9	Neonatal cortical necrosis	Severe neurologic impairment	1 dose	+
4	35	male	PD	28	CAKUT	-	1 dose	-
5	47	male	HD	17	Unknown	-	1 dose	+
6	93	female	PD	9	Chronic tubulointerstitial nephritis	-	1 dose	-
7	121	female	HD	66	RVT	-	1 dose	-
8	150	male	PD	25	Cystinosis	-	1 dose	-
9	158	male	HD	63	CAKUT	Autism	1 dose	-
10	172	male	HD	25	CAKUT	-	1 dose	+
11	207	male	HD	44	HIV associated nephropathy	-	1 dose	+

313 ARPKD: Autosomal recessive polycystic kidney disease, CAKUT: Congenital
314 anomalies of the kidney and urinary tract, FSGS: Focal segmental glomerulosclerosis,
315 HD: hemodialysis, PD: peritoneal dialysis, RVT: renal vein thrombosis