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Pneumococcal vaccination coverage at the initiation of chronic dialysis, and its association with mortality during the first year

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Keywords: end-stage renal disease; dialysis; pneumococcal vaccination; vaccination coverage; mortality

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Abstract

*Objectives***.** Pneumococcal immunization is recommended in dialysis patients. We aimed to estimate pneumococcal vaccination coverage among patients who initiate dialysis in France, and its association with mortality.

*Methods***.** Data were extracted from two prospective national databases, merged using a deterministic linkage method: renal epidemiology and information network (REIN) registry, which includes all patients on dialysis and kidney transplants recipients in France, and the national health insurance information system (SNIIRAM) which collects individual data on health expenditure reimbursement, including vaccines. We enrolled all patients who initiated chronic dialysis in 2015. Data on health status at dialysis initiation, dialysis modalities, and pneumococcal vaccine prescribed from 2 years before to 1 year after dialysis start were collected. Univariate and multivariate Cox proportional hazard models were used to assess one-year all-cause mortality.

*Results***.** Among the 8,294 incident patients included, 1,849 (22.3%) received at least one pneumococcal vaccine before (n=542, 6.5%), or after (n=1,307, 15.8%) dialysis start, as follows: 13-valent pneumococcal conjugated vaccine (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23), n=938 (50.7%); only PPSV23, n=650 (35.1%); or only PCV13, n=261 (14.1%). Vaccinated patients were younger (mean, 66.5 $\pm$ 14.8 years vs. 69.0 $\pm$ 14.9 years, $P \leqslant 0.001$), more likely to suffer from glomerulonephritis (17.0% vs. 11.0%, $P \leqslant 0.001$), and less likely to start dialysis in emergency (27.2% vs. 31.1%, $P=0.001$). On multivariate analysis, patients who received PCV13 and PPSV23, or only PCV13 were less likely to die (respectively, HR=0.37; 95%CI 0.28-0.51, and HR=0.35; 95%CI 0.19-0.65).

*Conclusions***.** Pneumococcal immunization with PCV13 followed by PPSV23, or with PCV13 alone, but not with PPSV23 alone, is independently associated with decreased one year-mortality in patients who start dialysis.

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1. Introduction

Mortality among patients with chronic kidney diseases (CKD) who require dialysis remains high despite recent improvement. Infection is the second leading cause of death in patient with end-stage renal diseases (ESRD), after cardiovascular events (1). Prevention is key to reduce infection-related morbidity and mortality. *Streptococcus pneumoniae* is a major cause of community-acquired pneumonia (CAP), in adults and children, and invasive pneumococcal diseases (IPD) disproportionately affect patients with ESRD (2–4). Of note, ESRD is also associated with worse outcomes in patients who develop CAP or IPD (5–7). Anti-pneumococcal vaccines are recommended in patients with CKD (8)(9)(10), although clinical data on the impact of pneumococcal immunization in haemodialysis patients remain scarce. Patients with ESRD have impaired immune response to different vaccines (11), including anti-pneumococcal vaccines (12,13). During the study period, and up to March 2023, two different types of pneumococcal vaccines have been available in France: a 23-valent pneumococcal polysaccharide vaccine (PPSV23), and a 13-valent pneumococcal conjugate vaccine (PCV13). Because of its thymus-independence, PPSV23 is associated with poor immunogenicity in children under 2 years of age, and in immunocompromised patients. In addition, it does not induce an anamnestic antibody response, and has been associated with decreased responsiveness in case of multiple exposures. On the other hands, as a thymo-dependent vaccine, PCV13 increases serotype-specific memory B-cell responses, and induces robust T-cell–dependent memory responses (8).

Studies on the impact of anti-pneumococcal vaccination in patients with CKD, including ESRD have demonstrated lower seroconversion rates, lower peak antibody titers, and more rapid decline of immune correlates of protection as compared to other populations (13,14), but they had limitations, including small sample size, retrospective design, or single-centre design. Few studies assessed the impact of anti-pneumococcal vaccination on mortality and morbidity in patients with ESRD, including patients on chronic dialysis (15)(16). To the best of our knowledge, no study evaluated the clinical impact of various anti-pneumococcal vaccines

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types, and schedules, in this population. The World Health Organization, doesn't recommend anti-pneumococcal vaccination for healthy or immunocompromised adults in the absence of robust evidence that it reduces morbidity and mortality in these populations, and because of the herd effect of anti-pneumococcal vaccination in children (17). Contrarily to the 2022 advisory committee on immunization practices (ACIP) guidelines (8), PPSV23 has long been recommended in CKD patients, considered as 'immunocompetent patients with risk factors for IPD'. French recommendations changed in 2017, when anti-pneumococcal vaccine schedules were homogenized for all persons over 2 years with risk factor(s) for IPD: first, PCV13, then PPSV23 two months later. Selection of those anti-pneumococcal vaccination schedules in USA and in France were based on studies evaluating cost-effectiveness, quality-adjusted life years gained, and averted IPD cases. No randomized controlled clinical trial documented the benefit of anti-pneumococcal vaccines in patients with CKD or ESRD, or compared different vaccination schedules in these populations.

Finally, current data suggest that anti-pneumococcal vaccination coverage is low in patients with CKD and ESRD, in different countries (15,18,19). We aimed to determine anti-pneumococcal vaccination coverage in patients who initiate chronic dialysis in France, the current vaccination schedules, and their association with one-year mortality.

2. Methods

2.1 Study design

This study was performed in France, a country with health care system ensuring equal access to primary care, free of charge, irrespective of social status and insurance coverage. We cross-linked two prospective national databases: i) the renal epidemiology and information network (REIN) registry, established in 2002, that covers all regions in the country since 2011, and includes all patients on dialysis, either haemodialysis (HD), or peritoneal dialysis (PD), as well as kidney transplant recipients (20); ii) the French national health insurance information system (*système national d'information inter-régimes de l'assurance maladie*, SNIIRAM), a

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claim database covering 97% of French inhabitants, which collects individual data on all health expenditure reimbursements for people leaving in France. We enrolled all incident adult patients (i.e., at least 18 year-old), who started dialysis therapy - HD or PD - in 2015 in France. We extracted data from January 2013 to December 2016.

2.2 Database linkage procedure

In order to identify patients who received at least one anti-pneumococcal vaccine from two years before, to one year after dialysis start, data from REIN registry were linked to data from the SNIIRAM database. Because both databases contain anonymized patients information, a deterministic linkage method has been developed, in order to merge information from SNIIRAM to REIN, based on: sex, date of dialysis start (month and year), centre of first dialysis, birth date (month and year), and city of residence. Thanks to this linkage procedure, 83% of REIN patients (n=8,294) have been identified in the SNIIRAM database (see flowchart, Figure 1).

2.3 Data collection

From the REIN registry, we extracted socio-demographic data, primary kidney disease, comorbidities, characteristics and context of dialysis start, and any medical event reported after dialysis start. Primary outcome was all-cause mortality, mortality related to infection, and mortality non-related to infection. Age was categorized in five groups (18-39, 40-59, 60-69, 70-79, ⩾80 years), serum albumin was categorized in two groups (<30, ⩾30 g/L), hemoglobin level in three groups (<10, 10-12, >12 g/dL); body mass index (BMI) in four groups (<18.5, 18.5-23, 23-25, ⩾25 kg/m^2), smoking status in two groups (never smoke, current/former smoker), and context of dialysis start in two groups (emergency vs planned first dialysis). Data related to anti-pneumococcal vaccination were extracted from the SNIIRAM database, including type of vaccine (PPSV23 or PCV13, the two anti-pneumococcal vaccines available during the study period), date of vaccination, and medical specialty of the prescribing

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practitioner (general practitioner, nephrologist, others). Vaccinated patients were categorized in three groups: PCV13 only, PPSV23 only, and PCV13 + PPSV23.

2.4 Statistical analyses

Patients baseline characteristics were expressed as frequencies and percentages for categorical variables, and as mean (standard deviation) for continuous variables. Demographic and clinical features were described by subgroups and compared using chi-square or exact Fischer tests, according to anti-pneumococcal vaccine status: i) vaccinated vs non-vaccinated; ii) non-vaccinated vs vaccinated with PPSV23 only vs vaccinated with PCV13 vs vaccinated by PCV13 + PPSV23

Before the implementation of the survival models for each outcome, missing data were handled by using multiple imputation by chained equations (MICE) with ten imputations and five cycles. The association between patient-related data and one-year all-cause mortality was assessed by using univariate and multivariate Cox proportional hazard models. Because few patients died due to infectious causes, survival couldn't be studied specifically for this mortality category. Time to outcome was measured from dialysis start to death, or the endpoint (at least one year after dialysis start). Kaplan-Meier survival curves have been established and compared using the log-rank test. Variables with a *P*-value <0.20 in univariable models were included in the multivariable models. A *P*-value <0.05 was considered statistically significant. Results were reported as hazard ratios (HR) with 95% confidence intervals (95% CI). All statistical analyses were performed with the STATA 13.1 software.

2.5 Ethics Statement

This study was approved by the CERES (*Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé*) and the national committee for liberty and data processing, the CNIL (*Commission Nationale de l'Informatique et des Libertés*). Written informed consent was waived because patients enrolled in the REIN database were

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3. Results

3.1 Patients characteristics

Of the 11,083 patients who started chronic dialysis in 2015 in France, 9,184 (82.9%) could be linked in the two databases, and 8,294 (74.8% of total) were analysed (Figure 1). There were 5,368 males (64.7%), and 2,926 females (35.3%), with a mean age of 68.5 ± 15.2 years by the time dialysis was initiated (Table 1). Main primary causes of ESRD were hypertension (n=2242, 27.0%), and diabetes (n=1911, 23.0%). Dialysis was started in emergency for 503 patients (27.2%), and could be planned for 1,346 (72.8%). Most patients started HD (n=7578, 91.4%), while only 716 (8.6%) started PD (Table 1).

3.2 Anti-pneumococcal vaccination

Overall, 1,849 patients (22.3%) received at least one anti-pneumococcal vaccine during the 2 years before the dialysis initiation, and the year after. Compared with patients who received no anti-pneumococcal vaccination, vaccinated patients were younger (mean, 66.5 ± 14.8 years vs. 69.0 ± 14.9 years, $P \leqslant 0.001$), more likely to be smoker or former smoker (41.4% vs. 35.4%, $P \leqslant 0.001$), with chronic respiratory disease (19.8% vs. 15.1%, $P \leqslant 0.001$), to have glomerulonephritis as primary cause of ESRD (17.0% vs. 11.0, $P \leqslant 0.001$), and less likely to start dialysis in emergency (27.2% vs. 31.1%, $P=0.001$).

Regarding anti-pneumococcal vaccination schedules, patients who received PPSV23 alone were older, more likely to suffer from chronic respiratory disease, with cardiovascular risk factors, malnutrition and diabetes, as compared to patients who received PCV13, alone or in combination with PPSV23 (Table 2). Anti-pneumococcal vaccination has been mainly prescribed by a general practitioner (n=1161, 62.8%), or by a nephrologist (n=400, 21.6%). Nephrologists were more likely to prescribe PCV13, with or without PPSV23, while general practitioners were more likely to prescribe PPSV23 alone.

Among vaccinated patients, 1,307 (70.7%) were vaccinated after dialysis start. Anti-pneumococcal vaccination was more likely to be initiated after dialysis start in patients who initiated dialysis in emergency (74%), and to include PCV13 with or without PPSV23

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(respectively, 82.1% and 88.1%). Nephrologists represented only 5.9% of anti-pneumococcal vaccine prescribers before dialysis start, but this proportion raised to 28.4% after dialysis start.

3.3 Univariate and multivariate analysis of variables associated with mortality

Of 8,294 patients analysed, 1,157 (13.9%) died. Causes of mortality in patients who received the anti-pneumococcal vaccine, and those who did not, are reported in Table 3. Unadjusted models showed that pneumococcal vaccination was associated with a decreased hazard for death (HR 0.51, 95% CI 0.43-0.60, $P \leqslant 0.0001$, Figure 2). Association with survival remained significant in subgroups of patients who received PCV13 + PPSV23 and PCV13 alone, but not in those who received PPSV23 alone. After adjustment for patient characteristics and comorbidities, receipt of anti-pneumococcal vaccine was still associated with survival, with a HR for death of 0.62 (95%CI, 0.52-0.73, $P \leqslant 0.0001$). Association with survival remained independently significant in subgroups of patients who received PCV13 + PPSV23 (HR 0.37, 95%CI 0.28-0.51, $P \leqslant 0.0001$), and in those who received PCV13 alone (HR 0.35, 95%CI 0.19-0.65, $P \leqslant 0.0001$), but not in those who received PPSV23 alone (HR 0.96, 95%CI 0.78-1.19, $P=0.740$) (Table 4, Figure 3). Those results remained similar after adjustment on geographical area, and inscription on transplantation list.

3. Discussion

The major findings of this nationwide prospective cohort study are the followings: i) prescription of at least one anti-pneumococcal conjugate vaccine was independently associated with survival in patients who started dialysis, after adjustment for major factors associated with mortality; ii) anti-pneumococcal vaccine coverage was very low in France, in 2015, in this population, estimated at 1,849/8,294 (22.3%), taking into account all anti-pneumococcal vaccines received from two years prior, until one year after, dialysis start. Of note, prescription of only PPSV23, in the absence of PCV13, was not associated with survival, in line with the

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lower immunogenicity of polysaccharide vaccines in the absence of priming with conjugated vaccine (21,22)(23)(24).

Infection is the second cause of death for patients with ESRD, especially in those who require dialysis (1). Pneumococcal is among the most virulent, and the most common pathogens reported in different case series. Hence, prevention of IPD is of paramount importance in patients who start chronic dialysis. Our findings that anti-pneumococcal immunization that includes conjugated anti-pneumococcal vaccine PCV13 is independently associated with survival in this population strongly advocate for urgent actions to promote vaccine coverage in countries where this is dramatically low, as in France. The rate of anti-pneumococcal vaccine coverage in patients who started dialysis in France in 2015, although desperately low in this study (i.e. less than one in four patients), is in line with estimates in other groups with official recommendations for anti-pneumococcal vaccination in France (25)(26). Previous studies on anti-pneumococcal vaccine coverage in patients who start dialysis have documented broad heterogeneity from one country to another: estimated at 45.5% in the United States (15), but similar to our findings in England, at 22% (19). This heterogeneity probably reflects a broad area of parameters, including vaccine hesitancy, robustness of immunization programme in the general population and in at-risk categories, as well as health care systems. In line with previous studies on the same population in other countries (15,25,26), patients who combine different indications for anti-pneumococcal vaccination, including smokers, patients with chronic respiratory diseases and elderly patients, had better vaccine coverages in our study, although the rates remain well below the objectives.

Previous studies have found an association between anti-pneumococcal vaccine coverage in patients on chronic dialysis, and survival, with adjusted HR from 0.76 to 0.89 (15), but the impact of pneumococcal vaccine type (i.e. polysaccharide vs conjugated, or a combination of both), could not be ascertained. The prevention of IPD by PPSV23 has been documented in different populations (21,23,24). PPSV23 immunogenicity is impaired in immunocompromised patients, and its clinical effectiveness remains uncertain in many settings. A landmark hospital-

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based case-control study from 1984 to 1990 estimated the protection afforded by PPSV23 in adults at 56% overall: 61% in immunocompetent and 21% in immunocompromised (24). Among patients with CKD, PPSV23 protection against IPD was estimated at 27%, with a broad 95%CI (-52% to 78%), and no or limited impact on survival (16,22,27,28). Andrews et al. estimated PPSV23 protective effect against IPD at 60-65% among elderly patients between the ages of 65 and 84 years, with no significant protection, in the absence of conjugated vaccines in patients older than 85 years and in immunocompromised patients. In addition, protection was estimated to be lost in medium- and high-risk patients 5 years after PPSV23 vaccination (29).

To the best of our knowledge, our study is the first clinical study to compare different anti-pneumococcal vaccine schedules in patients with ESRD. We found that schedules including one conjugate vaccine (i.e. PCV13, the only conjugated anti-pneumococcal vaccine available in France during the study period and up to 2023), were independently associated with one year-survival after adjustment on major cofactors, while PPSV23 was not. Although primarily developed for infants and toddlers, the immunogenicity of PCV13 has been well documented in adults (30): In two randomized controlled trials (30,31), serotype-specific opsono-phagocytic activity responses were more robust after PCV13 than after PPSV23 for 8 of the 12 serotypes targeted by both vaccines, among non-immunocompromised adults with chronic diseases at risk of IPD. PCV13 efficacy has also been documented in people living with HIV (32), and in healthy patients >65 year-old (33). Although not supported by any randomized clinical trial, the theoretical advantages of anti-pneumococcal conjugated vaccines include more robust initial immune response, especially in patients with impaired immunity related to age, or any other conditions, longer persistence of protection, and limited or no loss of efficacy with repeated administration over time. In addition, the nature of the first anti-pneumococcal vaccine may be particularly important, due to the priming effect: vaccine schedules initiated by PPSV23 would elicit sub-optimal immune responses, as compared to vaccine schedules using conjugated vaccines as the primer anti-pneumococcal vaccine. For all these reasons, French guidelines recommend one dose of PCV13 followed by one dose of PPSV23 at least 8 weeks later, then

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another dose of PPSV23 at least 5 years after previous PPSV23, in patients with CKD not previously vaccinated (34). Our findings are in line with these recommendations, although we were not adequately powered to estimate i) the consequences of using PPSV23 as the first anti-pneumococcal vaccine; ii) the impact of time elapsed between PCV13, and PPSV23 administration.

Our study has limitations: Firstly, due to its observational design, potential biases may be involved, and no causal link can be inferred from the association between anti-pneumococcal vaccine, and survival, although it remained significant on multivariate analysis after adjustment. For example, patients who were vaccinated may have been followed by doctors more aware of guidelines, which may also imply better management of other comorbidities (hypertension, diabetes, etc.). We could not control these potential biases. Secondly, our findings apply to the situation in France, during years 2013-2016, but it may not be generalizable, as differences in population of patients who initiate dialysis, in practices, and in health care systems, may modify the association between anti-pneumococcal vaccination, and survival. In particular, due to the herd effect, the impact of anti-pneumococcal vaccine in patients who start dialysis may be more limited in countries with higher anti-pneumococcal vaccine coverage overall. Thirdly, we had no information about pneumococcal vaccine outside of the study period (i.e. 2013-2016). Hence patients who were vaccinated before 2013 have been misclassified as unvaccinated, although they may have been at least partly protected. In addition, our follow-up was limited at one year after dialysis start, so that we could not estimate association with long-term outcome. Finally, our study was performed before the advent of the 20-valent pneumococcal conjugated vaccine (PCV20), which may change the impact of anti-pneumococcal vaccine, as well as recommended schedules, as the benefit of secondary PPSV23 vaccine will necessarily be reduced in terms of expanded serotypes coverage. Indeed, PCV20 provides additional protection against serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F as compared to PCV13. The proportion of strains responsible for IPD in 2021 in France included in conjugated vaccines was 23.6% for PCV13, 27.4% for PCV15, and 56.9% for PCV20 (35).

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PPSV23 would only marginally expand this coverage. Our study also has strengths, including large sample size, prospective and standardized collection of data, and fair representability, as 75% of all patients who initiated dialysis in France in 2015 were enrolled.

In conclusion, we found that prescription of at least one anti-pneumococcal conjugate vaccine was independently associated with one-year survival in patients who start dialysis. Given the low anti-pneumococcal vaccine coverage in many countries, these findings advocate for actions to promote anti-pneumococcal vaccine in patients with ESRD, ideally before dialysis start, with conjugated anti-pneumococcal vaccine followed by PPSV23 at least 8 weeks later, pending the advent of PCV20.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper

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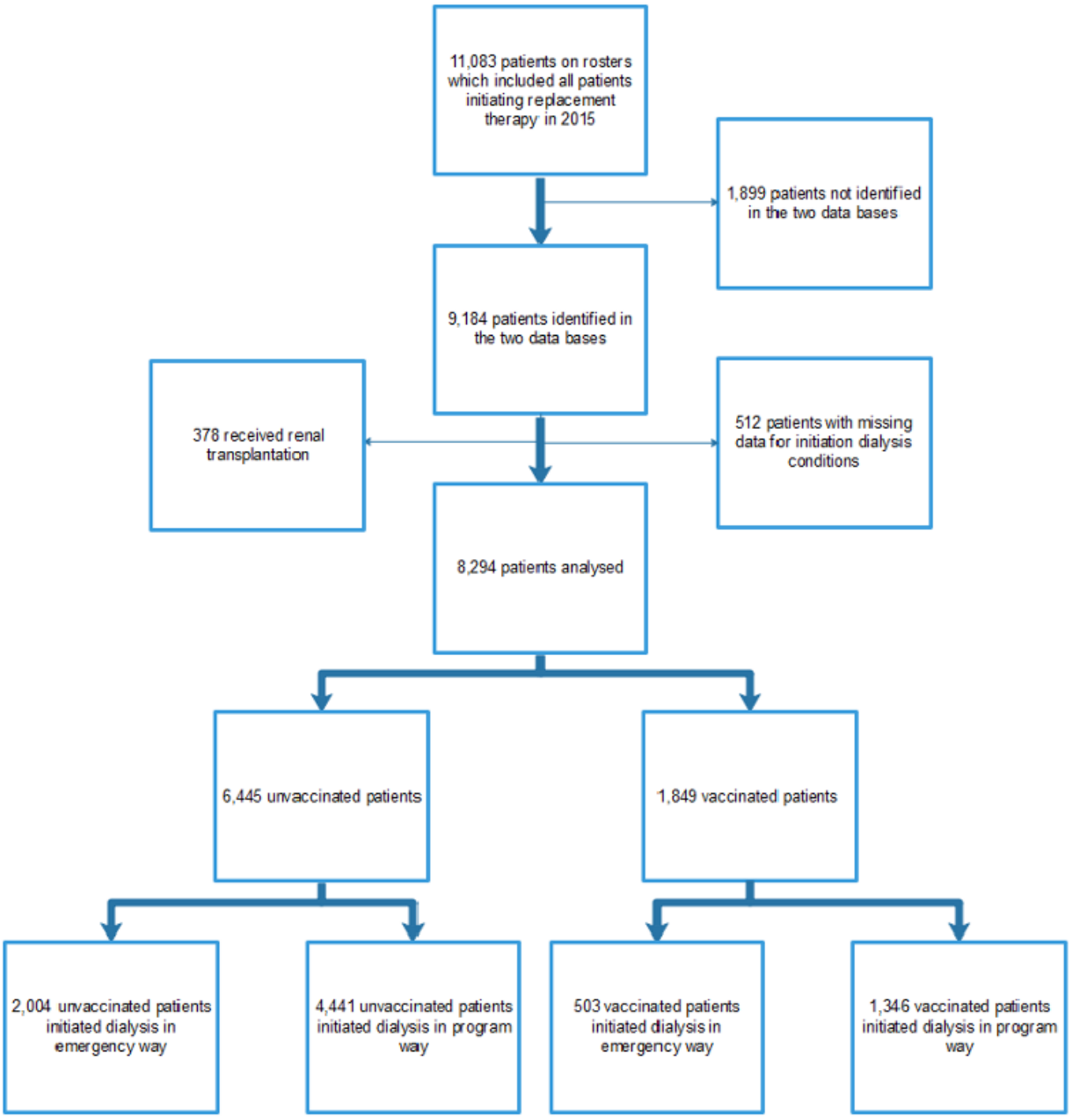
392 **Figure 1.** Study flow chart



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393 **Figure 2.** Kaplan-Meier survival curve one year after dialysis startaccording to anti-

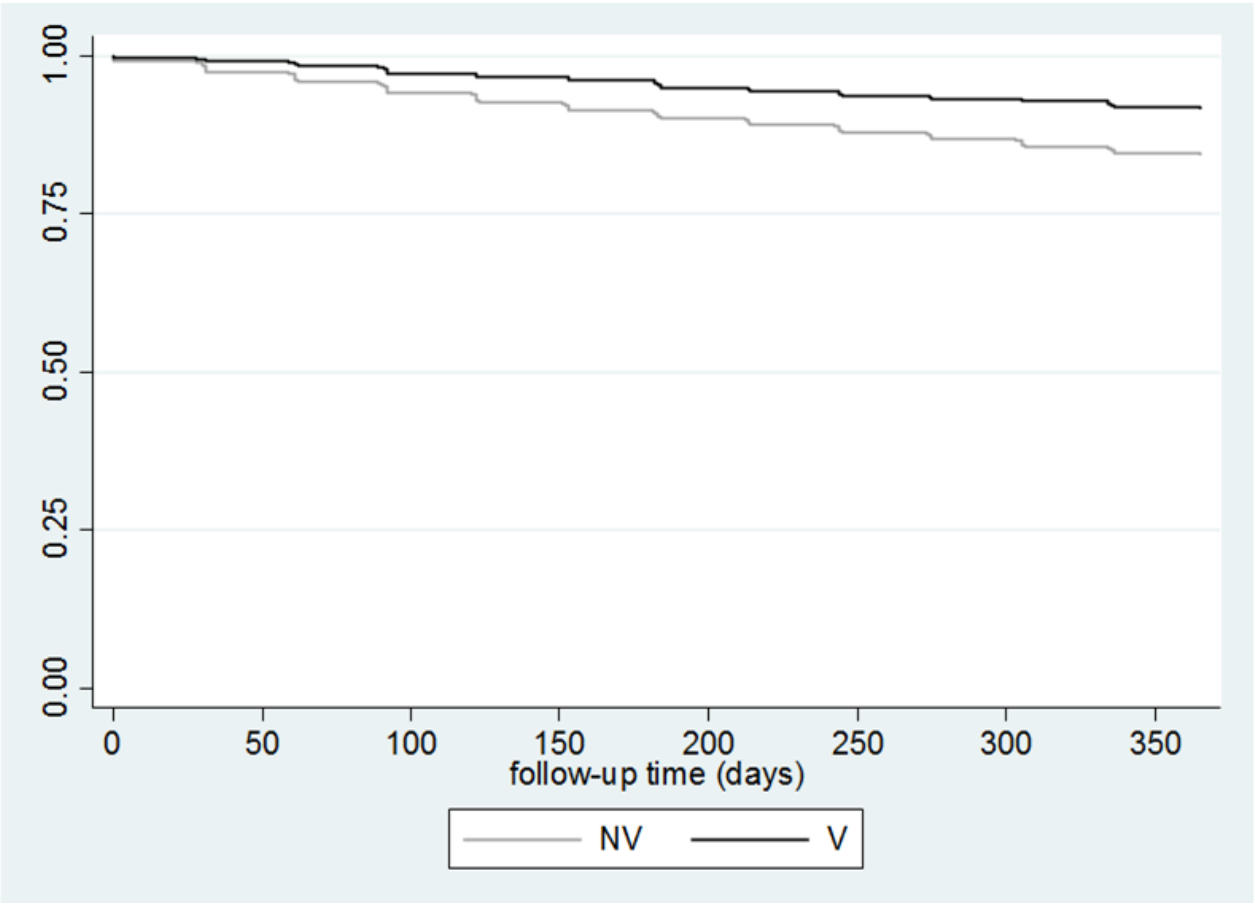

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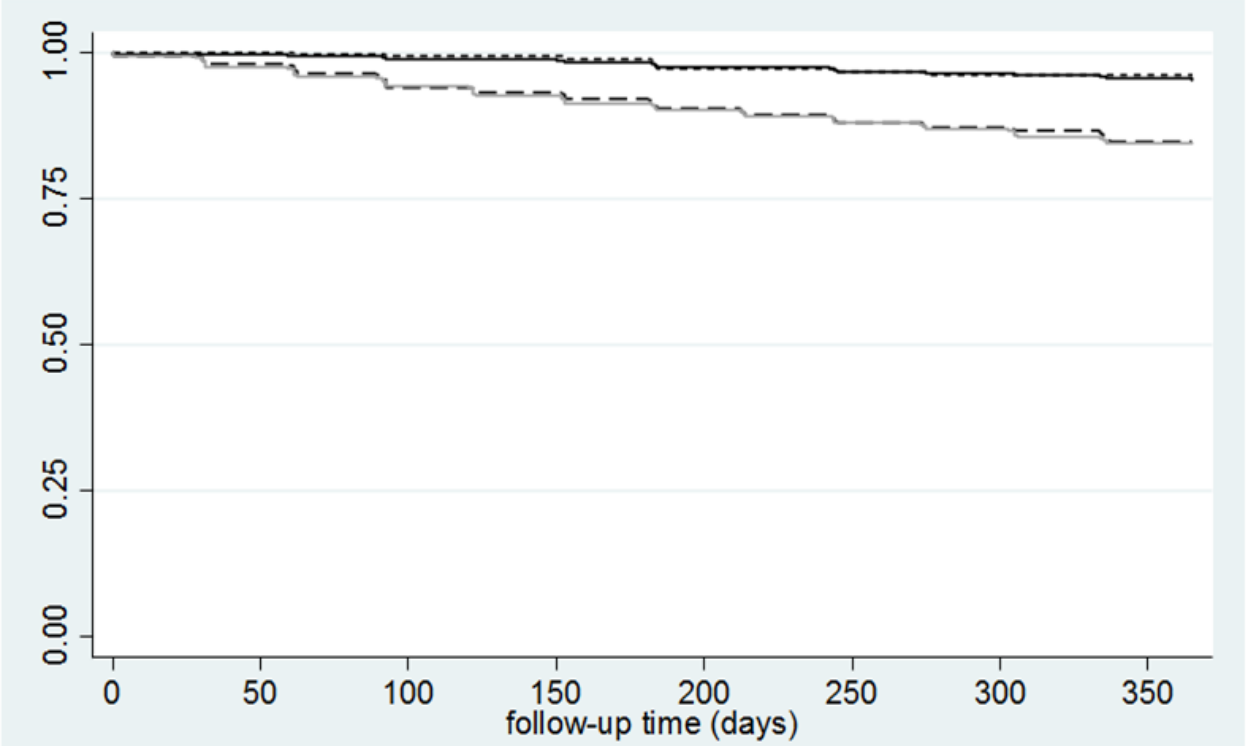
Figure 3. Kaplan-Meier survival curve one year after dialysis start according to anti-pneumococcal vaccination schedule (upper lines: patients who received the 13-valent conjugated vaccine, with or without 23-valent polysaccharide vaccine; lower lines, patients not-vaccinated, or who received only the 23-valent polysaccharide vaccine)



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399 **Table 1.** Comparison of patients with, and without pneumococcal vaccine

Characteristics	Pneumococcal vaccination			
	All, *n (%)*	Vaccinated, *n (%)*	Not vaccinated, *n (%)*	*P*-value
All	8,294 (100)	1,849 (100)	6,645 (100)	
Age, years	68.5 (15.2)	66.5 (14.8)	69.0 (14.9)	≤0.001
Sex				
• Men	5368 (64.7)	1244 (67.28)	4124 (63.99)	0.009
• Women	2926 (35.3)	605 (32.72)	2321 (36.01)	
Dialysis characteristics				
- Primary cause of ESRD				
• Hypertension	2242 (27.0)	461 (24.93)	1781 (27.63)	
• Diabetes	1911 (23.0)	338 (18.28)	1573 (24.41)	≤0.001
• Glomerulonephritis	1024 (12.4)	314 (16.98)	710 (11.02)	
• Other	1887 (22.8)	451 (24.39)	1436 (22.28)	
• Unknown	1230 (14.8)	285 (15.41)	945 (14.66)	
- Context of dialysis start				
• planned	5787 (69.8)	1346 (72.8)	4441 (68.9)	0.001
• emergency	2507 (30.2)	503 (27.2)	2004 (31.1)	
- Dialysis modality				
• Hemodialysis	7578 (91.4)	1684 (91.1)	5894 (91.4)	0.613
• Peritoneal dialysis	716 (8.6)	165 (8.9)	551 (8.6)	
Comorbid conditions				
- BMI, kg/m²	26.75	26.86	26.71	0.399
- Tobacco				
• Non-smoker	3895 (47.0)	773 (41.8)	3122 (48.4)	≤0.001
• Active/former	3047 (36.7)	765 (41.4)	2282 (35.4)	
• Unknown	1352 (16.3)	311 (16.8)	1041(16.2)	
- Chronic respiratory disease	1342 (16.2)	366 (19.8)	976 (15.1)	≤0.001
- Cardiovascular risk factors				
• 1	2028 (24.5)	463 (25.0)	1565 (24.3)	≤0.001
• ≥ 2	2572 (31.0)	479 (25.9)	2093 (32.5)	
- Diabetes	3701 (44.6)	734 (39.7)	2967 (46.0)	≤0.001
- Cancer	854 (10.3)	161 (8.7)	693 (10.8)	0.038
- Immunosuppression				
• HIV	61 (0.7)	26 (1.4)	35 (0.5)	0.001
- Serum albumin, g/L	34.3 (6.1)	34.8 (6.1)	34.3 (6.1)	0.09
- Hemoglobin, g/dL	10.1 (1.6)	10.3 (1.6)	10.1 (1.6)	0.004

400 * BMI, body mass index; HIV, human immunodeficiency virus

401 Quantitative data are presented as mean (standard deviation), qualitative data as numbers (%)

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402 **Table 2.** Patients characteristics according to pneumococcal vaccination schedules

Characteristics	Pneumococcal Vaccination Schedules			
	PPSV23, *n (%)*	PCV13 + PPSV23, *n (%)*	PCV13, *n (%)*	*P*-value
All	650	938	261	
Age, years	73.4 (11.25)	62.7 (13.4)	62.1 (15.5)	0.0001
Sex				0.135
• Men	421 (64.8)	651 (69.4)	172 (65.9)	
• Women	229 (35.2)	287 (30.6)	89 (34.1)	
Dialysis characteristics				
Primary cause of ESRD				≤ 0.001
• Hypertension	206 (31.7)	194 (20.7)	61 (23.4)	
• Diabetes	127 (19.5)	169 (18.0)	42 (16.1)	
• Glomerulonephritis	87 (13.4)	185 (19.7)	42 (16.7)	
• Other	130 (20.0)	245 (26.1)	76 (29.1)	
• Unknown	100 (15.4)	145 (15.5)	40 (15.3)	
Context of dialysis start				0,395
• planned	471 (72.5)	676 (72.1)	199 (76.2)	
• emergency	179 (27.5)	262 (27.9)	62 (23.8)	
Dialysis modality				0.497
• Hemodialysis	598 (92.0)	852 (90.8)	234 (89.7)	
• Peritoneal dialysis	52 (8.0)	86 (9.2)	27 (10.3)	
Comorbid conditions				
- BMI, kg/m²	27.6 (6.2)	26.4 (5.7)	26.6 (7.1)	0.183
- Tobacco				0.045
• Non-smoker	282 (43.4)	381 (40.6)	110 (42.2)	
• Active / Former	252 (38.8)	412 (43.9)	101 (38.7)	
• Unknown	116 (17.9)	145 (15.5)	50 (19.2)	
- Chronic respiratory failure	183 (28.2)	154 (16.4)	29 (11.1)	≤ 0.001
- Vascular risk factors				≤ 0.001
• 1	187 (28.8)	214 (22.8)	62 (23.8)	
• ≥ 2	218 (33.5)	203 (21.6)	58 (22.2)	
- Diabetes	295 (45.4)	351 (37.4)	88 (33.7)	≤ 0.001
- Cancer	66 (10.2)	74 (7.9)	21 (8.1)	0.479
- HIV	2 (0.3)	18 (1.9)	6 (2.3)	0.010
Vaccine prescriber				≤ 0.001
- General practitioner	487 (74.9)	541 (57.7)	133 (51.0)	
- Nephrologist	87 (13.4)	229 (24.4)	84 (32.2)	
- Others / unknown	76 (11.7)	168 (17.9)	44 (16.9)	
Vaccination Time				≤ 0.001
• Before dialysis	343 (52.8)	168 (17.9)	31 (11.9)	
• After dialysis start	307 (47.2)	770 (82.1)	230 (88.1)	

403 * BMI, Body Mass Index; HIV, Human Immunodeficiency Virus; PPSV23, 23-valent pneumococcal
404 polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; ESRD, end-stage renal
405 disease. Quantitative data are presented as mean (standard deviation), qualitative data as numbers (%)

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406 **Table 3.** Causes of mortality according to pneumococcal vaccination status

Causes of mortality	Deaths among vaccinated patients, *n (%)*	Deaths among non-vaccinated patients, *n (%)*	*P*-value
All	153	1004	0.292
- Infections	20 (13.1)	166 (16.5)	0.364
- Cardiovascular diseases	49 (32.0)	258 (25.7)	- -
- Kidney diseases	2 (1.3)	9 (0.9)	- -
- Respiratory diseases	7 (4.6)	30 (3.0)	- -
- Liver diseases	0	8 (0.8)	- -
- Cancer	22 (14.4)	114 (11.4)	- -
- Diabetes	0	1 (0.1)	- -
- Others	27 (17.7)	218 (21.7)	- -
- Unknown	26 (17.0)	200 (19.9)	- -

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411 **Table 4.** Univariate and multivariate analysis of risk factors for death

	Univariate Cox model		Multivariate Cox model	
Variables	Hazard Ratio (95%CI)	*P*-value	Hazard Ratio (95%CI)	*P*-value
- Age >65 years	3.44 (2.91 – 4.06)	≤ 0.0001	2.28 (1.91 – 2.71)	**≤0.0001**
- Female	1.03 (0.92 – 1.17)	0.543	1.06 (0.94 – 1.21)	0.343
- Cause of ESRD				
• Hypertension	2.14 (1.68 – 2.71)	≤0.0001	1.25 (0.98 – 1.60)	0.076
• Diabetes	1.58 (1.23 – 2.03)	≤0.0001	1.07 (0.83 – 1.39)	0.595
• Other	1.78 (1.39 – 2.27)	≤0.0001	1.39 (1.08 – 1.79)	**0.011**
• Unknown	2.10 (1.63 – 2.72)	≤0.0001	1.34 (1.03 – 1.74)	**0.028**
- Dialysis start in emergency	1.66 (1.47 – 1.86)	≤0.0001	1.19 (1.06 – 1.35)	**0.005**
- Peritoneal dialysis	1.01 (0.82 – 1.23)	0.950	- -	- -
- Initial catheter in hemodialysis	2.20 (1.94 – 2.49)	≤0.0001	- -	- -
- BMI <18.5 kg/m²	1.57 (1.18 – 2.09)	0.002	1.52 (1.12 – 2.06)	**0.008**
- Smoker	1.00 (0.86 – 1.17)	0.953	- -	- -
- Chronic respiratory failure	1.81 (1.57 – 2.09)	≤0.0001	1.26 (1.07 – 1.47)	**0.004**
- Vascular risk factors				
• 1	1.93 (1.64 – 2.27)	≤0.0001	1.42 (1.21 – 1.68)	**≤0.0001**
• ≥2	2.99 (2.59 – 3.45)	≤0.0001	1.89 (1.61 – 2.21)	**≤0.0001**
- Diabetes	1.12 (1.00 – 1.26)	0.047	- -	- -
- Liver disease	2.48 (1.92 – 3.20)	≤0.0001	2.71 (2.06 – 3.56)	**≤0.0001**
- Cancer	2.73 (2.37 – 3.14)	≤0.0001	2.20 (1.91 – 2.54)	**≤0.0001**
- Serum albumin <30 g/L	2.26 (1.99 – 2.56)	≤0.0001	1.69 (1.48 – 1.93)	**≤0.0001**
- Hemoglobin <10 g/dL	1.35 (1.18 – 1.54)	≤0.0001	- -	- -
Anti-pneumococcal vaccine	0.51 (0.43– 0.60)	≤0.0001	0.62 (0.52 – 0.73)	**≤0.0001**
Vaccination schedules				
- PPSV23 alone	0.97 (0.79 – 1.20)	0.799	0.96 (0.78 – 1.19)	0.740
- PCV13 + PPSV23	0.28 (0.21 – 0.38)	≤0.0001	0.37 (0.28 – 0.51)	**≤0.0001**
- PCV 13 alone	0.23 (0.12 – 0.43)	≤0.0001	0.35 (0.19 – 0.65)	**≤0.0001**

412 *CI: Confidence Interval; ESRD, End-Stage Renal Disease; BMI, Body Mass Index; PPSV23, 23-valent

413 Pneumococcal PolySaccharide Vaccine; PCV13, 13-valent Pneumococcal Conjugate Vaccine.

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