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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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<sup>1</sup> Pierre Tattevin and Cécile Vigneau co-directed this work

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

## 1 **Abstract**

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

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

14 *Results.* Among the 8,294 incident patients included, 1,849 (22.3%) received at least one  
15 pneumococcal vaccine before (n=542, 6.5%), or after (n=1,307, 15.8%) dialysis start, as  
16 follows: 13-valent pneumococcal conjugated vaccine (PCV13) followed by 23-valent  
17 pneumococcal polysaccharide vaccine (PPSV23), n=938 (50.7%); only PPSV23, n=650  
18 (35.1%); or only PCV13, n=261 (14.1%). Vaccinated patients were younger (mean,  $66.5 \pm 14.8$   
19 years vs.  $69.0 \pm 14.9$  years,  $P \leq 0.001$ ), more likely to suffer from glomerulonephritis (17.0%  
20 vs. 11.0%,  $P \leq 0.001$ ), and less likely to start dialysis in emergency (27.2% vs. 31.1%,  
21  $P=0.001$ ). On multivariate analysis, patients who received PCV13 and PPSV23, or only PCV13  
22 were less likely to die (respectively, HR=0.37; 95%CI 0.28-0.51, and HR=0.35; 95%CI 0.19-  
23 0.65).

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

27

## 28 1. Introduction

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

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

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

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

72

## 73 **2. Methods**

### 74 *2.1 Study design*

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

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

## 86 *2.2 Database linkage procedure*

87 In order to identify patients who received at least one anti-pneumococcal vaccine from  
88 two years before, to one year after dialysis start, data from REIN registry were linked to data  
89 from the SNIIRAM database. Because both databases contain anonymized patients  
90 information, a deterministic linkage method has been developed, in order to merge information  
91 from SNIIRAM to REIN, based on: sex, date of dialysis start (month and year), centre of first  
92 dialysis, birth date (month and year), and city of residence. Thanks to this linkage procedure,  
93 83% of REIN patients (n=8,294) have been identified in the SNIIRAM database (see flowchart,  
94 Figure 1).

## 95 *2.3 Data collection*

96 From the REIN registry, we extracted socio-demographic data, primary kidney disease,  
97 comorbidities, characteristics and context of dialysis start, and any medical event reported after  
98 dialysis start. Primary outcome was all-cause mortality, mortality related to infection, and  
99 mortality non-related to infection. Age was categorized in five groups (18-39, 40-59, 60-69, 70-  
100 79,  $\geq 80$  years), serum albumin was categorized in two groups ( $<30$ ,  $\geq 30$  g/L), hemoglobin  
101 level in three groups ( $<10$ , 10-12,  $>12$  g/dL); body mass index (BMI) in four groups ( $<18.5$ ,  
102 18.5-23, 23-25,  $\geq 25$  kg/m<sup>2</sup>), smoking status in two groups (never smoke, current/former  
103 smoker), and context of dialysis start in two groups (emergency vs planned first dialysis). Data  
104 related to anti-pneumococcal vaccination were extracted from the SNIIRAM database,  
105 including type of vaccine (PPSV23 or PCV13, the two anti-pneumococcal vaccines available  
106 during the study period), date of vaccination, and medical specialty of the prescribing

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

109

#### 110 *2.4 Statistical analyses*

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

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

#### 128 *2.5 Ethics Statement*

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

### 133 3. Results

#### 134 3.1 Patients characteristics

135 Of the 11,083 patients who started chronic dialysis in 2015 in France, 9,184 (82.9%)  
136 could be linked in the two databases, and 8,294 (74.8% of total) were analysed (Figure 1). There  
137 were 5,368 males (64.7%), and 2,926 females (35.3%), with a mean age of  $68.5 \pm 15.2$  years  
138 by the time dialysis was initiated (Table 1). Main primary causes of ESRD were hypertension  
139 ( $n=2242$ , 27.0%), and diabetes ( $n=1911$ , 23.0%). Dialysis was started in emergency for 503  
140 patients (27.2%), and could be planned for 1,346 (72.8%). Most patients started HD ( $n=7578$ ,  
141 91.4%), while only 716 (8.6%) started PD (Table 1).

#### 142 3.2 Anti-pneumococcal vaccination

143 Overall, 1,849 patients (22.3%) received at least one anti-pneumococcal vaccine during  
144 the 2 years before the dialysis initiation, and the year after. Compared with patients who  
145 received no anti-pneumococcal vaccination, vaccinated patients were younger (mean,  $66.5 \pm$   
146  $14.8$  years vs.  $69.0 \pm 14.9$  years,  $P \leq 0.001$ ), more likely to be smoker or former smoker (41.4%  
147 vs. 35.4%,  $P \leq 0.001$ ), with chronic respiratory disease (19.8% vs. 15.1%,  $P \leq 0.001$ ), to have  
148 glomerulonephritis as primary cause of ESRD (17.0% vs. 11.0,  $P \leq 0.001$ ), and less likely to  
149 start dialysis in emergency (27.2% vs. 31.1%,  $P=0.001$ ).

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

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



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

### 162 *3.3 Univariate and multivariate analysis of variables associated with mortality*

163 Of 8,294 patients analysed, 1,157 (13.9%) died. Causes of mortality in patients who  
164 received the anti-pneumococcal vaccine, and those who did not, are reported in Table 3.  
165 Unadjusted models showed that pneumococcal vaccination was associated with a decreased  
166 hazard for death (HR 0.51, 95% CI 0.43-0.60,  $P \leq 0.0001$ , Figure 2). Association with survival  
167 remained significant in subgroups of patients who received PCV13 + PPSV23 and PCV13  
168 alone, but not in those who received PPSV23 alone. After adjustment for patient characteristics  
169 and comorbidities, receipt of anti-pneumococcal vaccine was still associated with survival, with  
170 a HR for death of 0.62 (95%CI, 0.52-0.73,  $P \leq 0.0001$ ). Association with survival remained  
171 independently significant in subgroups of patients who received PCV13 + PPSV23 (HR 0.37,  
172 95%CI 0.28-0.51,  $P \leq 0.0001$ ), and in those who received PCV13 alone (HR 0.35, 95%CI 0.19-  
173 0.65,  $P \leq 0.0001$ ), but not in those who received PPSV23 alone (HR 0.96, 95%CI 0.78-1.19,  
174  $P=0.740$ ) (Table 4, Figure 3). Those results remained similar after adjustment on geographical  
175 area, and inscription on transplantation list.

176

### 177 **3. Discussion**

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

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

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

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

212 based case-control study from 1984 to 1990 estimated the protection afforded by PPSV23 in  
213 adults at 56% overall: 61% in immunocompetent and 21% in immunocompromised (24).  
214 Among patients with CKD, PPSV23 protection against IPD was estimated at 27%, with a broad  
215 95%CI (-52% to 78%), and no or limited impact on survival (16,22,27,28). Andrews et al.  
216 estimated PPSV23 protective effect against IPD at 60-65% among elderly patients between the  
217 ages of 65 and 84 years, with no significant protection, in the absence of conjugated vaccines  
218 in patients older than 85 years and in immunocompromised patients. In addition, protection was  
219 estimated to be lost in medium- and high-risk patients 5 years after PPSV23 vaccination (29).

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

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

244 Our study has limitations: Firstly, due to its observational design, potential biases may be  
245 involved, and no causal link can be inferred from the association between anti-pneumococcal  
246 vaccine, and survival, although it remained significant on multivariate analysis after  
247 adjustment. For example, patients who were vaccinated may have been followed by doctors  
248 more aware of guidelines, which may also imply better management of other comorbidities  
249 (hypertension, diabetes, etc.). We could not control these potential biases. Secondly, our  
250 findings apply to the situation in France, during years 2013-2016, but it may not be  
251 generalizable, as differences in population of patients who initiate dialysis, in practices, and in  
252 health care systems, may modify the association between anti-pneumococcal vaccination, and  
253 survival. In particular, due to the herd effect, the impact of anti-pneumococcal vaccine in  
254 patients who start dialysis may be more limited in countries with higher anti-pneumococcal  
255 vaccine coverage overall. Thirdly, we had no information about pneumococcal vaccine outside  
256 of the study period (i.e. 2013-2016). Hence patients who were vaccinated before 2013 have  
257 been misclassified as unvaccinated, although they may have been at least partly protected. In  
258 addition, our follow-up was limited at one year after dialysis start, so that we could not estimate  
259 association with long-term outcome. Finally, our study was performed before the advent of the  
260 20-valent pneumococcal conjugated vaccine (PCV20), which may change the impact of anti-  
261 pneumococcal vaccine, as well as recommended schedules, as the benefit of secondary PPSV23  
262 vaccine will necessarily be reduced in terms of expanded serotypes coverage. Indeed, PCV20  
263 provides additional protection against serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F as  
264 compared to PCV13. The proportion of strains responsible for IPD in 2021 in France included  
265 in conjugated vaccines was 23.6% for PCV13, 27.4% for PCV15, and 56.9% for PCV20 (35).

266 PPSV23 would only marginally expand this coverage. Our study also has strengths, including  
267 large sample size, prospective and standardized collection of data, and fair representability, as  
268 75% of all patients who initiated dialysis in France in 2015 were enrolled.

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

275

276

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280

#### 281 **Declaration of Competing Interest**

282 The authors declare that they have no known competing financial interests or personal  
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284

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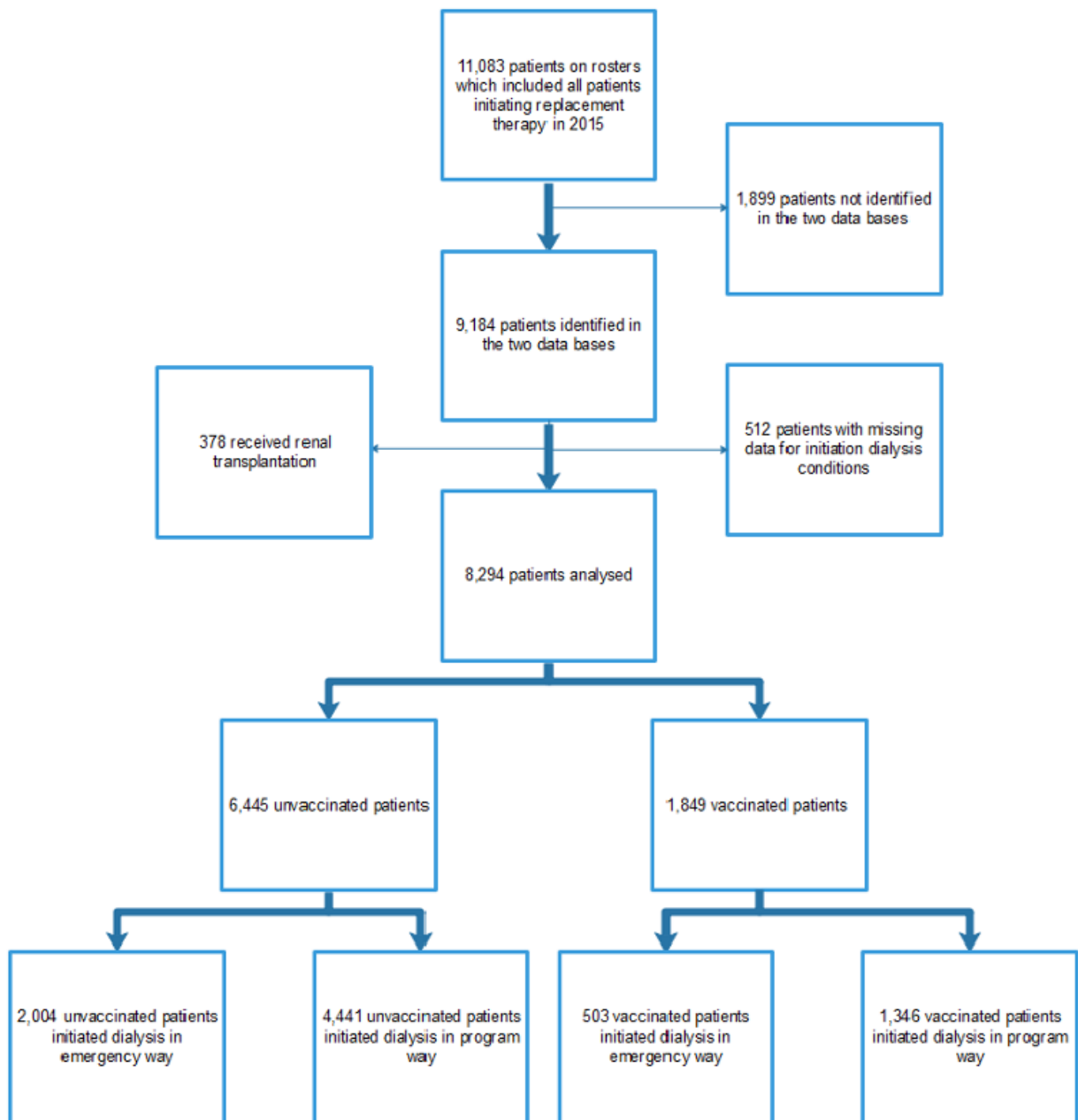
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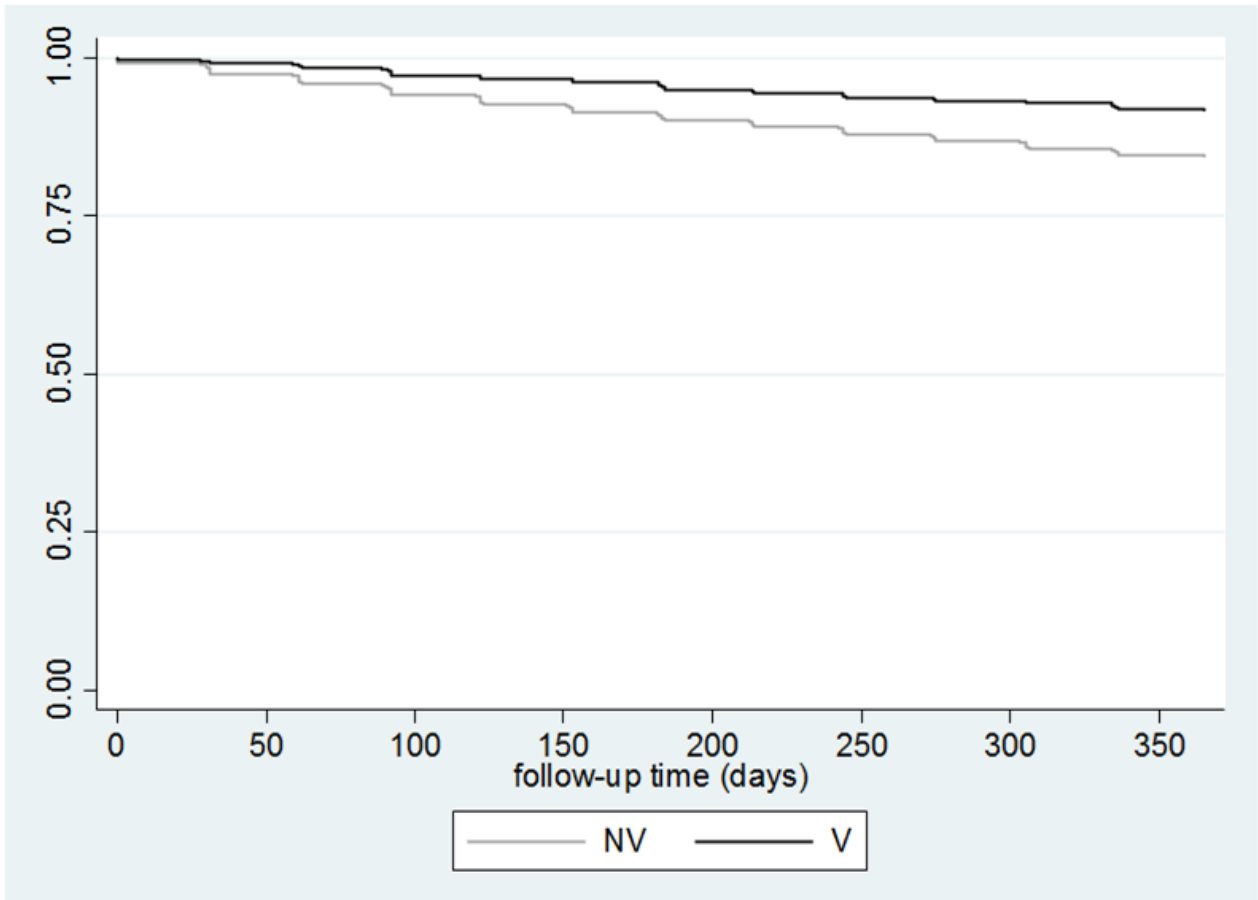
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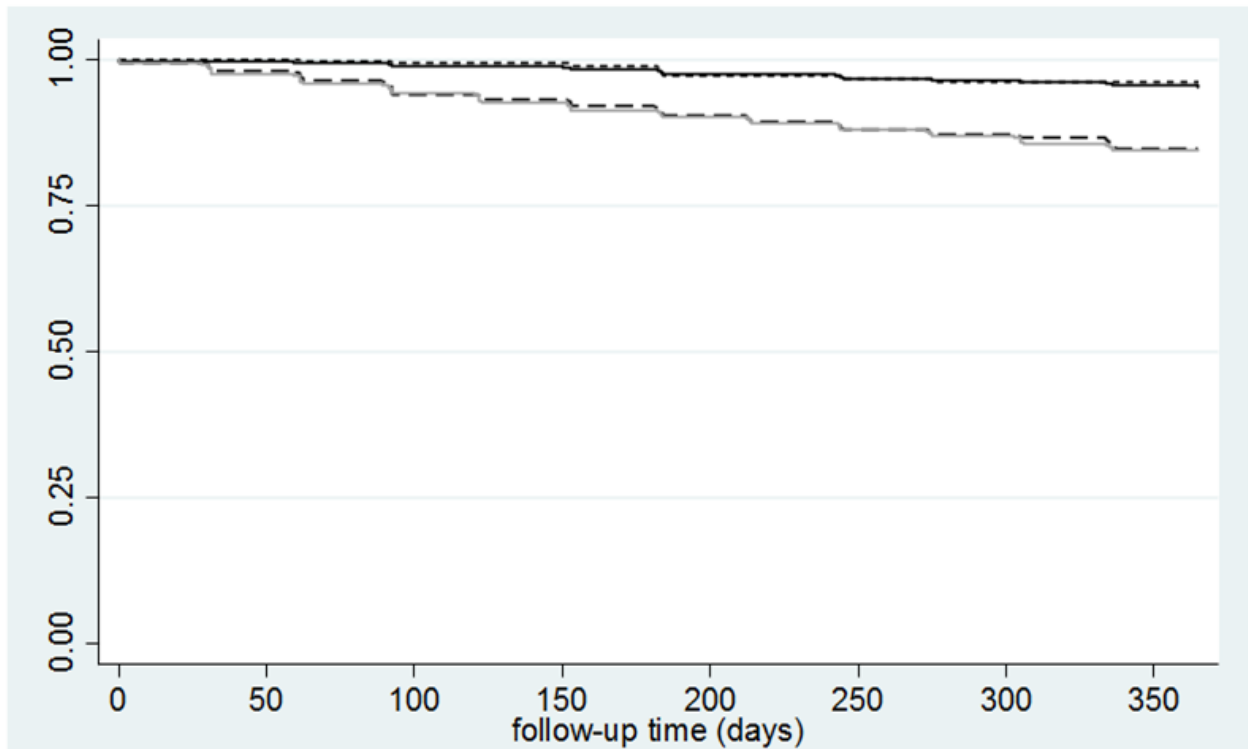




393 **Figure 2.** Kaplan-Meier survival curve one year after dialysis start according to anti-



394 **Figure 3.** Kaplan-Meier survival curve one year after dialysis start according to anti-  
395 pneumococcal vaccination schedule (upper lines: patients who received the 13-valent  
396 conjugated vaccine, with or without 23-valent polysaccharide vaccine; lower lines, patients not-  
397 vaccinated, or who received only the 23-valent polysaccharide vaccine)  
398



Characteristics	Pneumococcal vaccination			P-value
	All, <i>n</i> (%)	Vaccinated, <i>n</i> (%)	Not vaccinated, <i>n</i> (%)	
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)	≤0.001
• Diabetes	1911 (23.0)	338 (18.28)	1573 (24.41)	
• 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/m <sup>2</sup>	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 (%)

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

Characteristics	Pneumococcal Vaccination Schedules			P-value
	PPSV23, <i>n</i> (%)	PCV13 + PPSV23, <i>n</i> (%)	PCV13, <i>n</i> (%)	
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/m <sup>2</sup>	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 (%)

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

Causes of mortality	Deaths among vaccinated patients, <i>n</i> (%)	Deaths among non-vaccinated patients, <i>n</i> (%)	<i>P</i> -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

Variables	Univariate Cox model		Multivariate Cox model	
	Hazard Ratio (95%CI)	<i>P</i> -value	Hazard Ratio (95%CI)	<i>P</i> -value
- Age >65 years	3.44 (2.91 – 4.06)	≤ 0.0001	2.28 (1.91 – 2.71)	≤ <b>0.0001</b>
- 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)	<b>0.011</b>
• Unknown	2.10 (1.63 – 2.72)	≤0.0001	1.34 (1.03 – 1.74)	<b>0.028</b>
- Dialysis start in emergency	1.66 (1.47 – 1.86)	≤0.0001	1.19 (1.06 – 1.35)	<b>0.005</b>
- 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/m <sup>2</sup>	1.57 (1.18 – 2.09)	0.002	1.52 (1.12 – 2.06)	<b>0.008</b>
- 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)	<b>0.004</b>
- Vascular risk factors				
• 1	1.93 (1.64 – 2.27)	≤0.0001	1.42 (1.21 – 1.68)	≤ <b>0.0001</b>
• ≥2	2.99 (2.59 – 3.45)	≤0.0001	1.89 (1.61 – 2.21)	≤ <b>0.0001</b>
- 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)	≤ <b>0.0001</b>
- Cancer	2.73 (2.37 – 3.14)	≤0.0001	2.20 (1.91 – 2.54)	≤ <b>0.0001</b>
- Serum albumin <30 g/L	2.26 (1.99 – 2.56)	≤0.0001	1.69 (1.48 – 1.93)	≤ <b>0.0001</b>
- 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)	≤ <b>0.0001</b>
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)	≤ <b>0.0001</b>
- PCV 13 alone	0.23 (0.12 – 0.43)	≤0.0001	0.35 (0.19 – 0.65)	≤ <b>0.0001</b>

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.