

# Vaccination Against COVID-19 in a Network of Hemodialysis Units in Portugal: A Promising Experience



## Vacinação Contra a COVID-19 numa Rede de Clínicas de Hemodiálise em Portugal: Uma Experiência Promissora

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### ABSTRACT

**Introduction:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for coronavirus disease 2019 (COVID-19) seriously affected Portugal, particularly in the elderly population with a high number of comorbidities, including patients with chronic kidney disease in stage 5 (CKD-5D) undergoing a regular dialysis program. The aims of this study were to identify the impact of vaccination on the incidence of new daily cases and mortality in the CKD-5D population.

**Material and Methods:** Prospective, observational study, involving patients with CKD-5D from 38 NephroCare clinics, Portugal. Daily SARS-CoV-2 infections and mortality among these patients was compared with the incidence in the general population. Three periods were analysed: before vaccination, during the vaccination process, and a third period after complete vaccination with the Pfizer-BioNTech Comirnaty<sup>®</sup> vaccine. The primary outcome was infection by the SARS-CoV-2 virus and the secondary outcome was death associated with the infection.

**Results:** A total of 4617 patients (average of 69.37 years of age) were analysed. During the first period, there was a significantly higher COVID-19 incidence of 14.9% in patients with CKD-5D compared with the general population (7.9%;  $p < 0.001$ ). During the fifteen days after the complete vaccination, results reverted to a significant decrease in COVID-19 cases was observed ( $p < 0.001$ ). The mortality rate among CKD-5D was significantly higher than in the general population ( $p < 0.001$ ).

**Conclusion:** Vaccination significantly reduced SARS-CoV-2 infection in patients with CKD-5D.

**Keywords:** COVID-19; COVID-19 Vaccines; Hemodialysis; Portugal; SARS-CoV-2

### RESUMO

**Introdução:** Portugal foi atingido severamente pela síndrome respiratória aguda grave (SARS-CoV-2), responsável pela doença por coronavírus 2019 (COVID-19). A população idosa e com comorbilidades, na qual estão incluídas as pessoas com doença renal crónica em estágio 5 em programa regular de hemodiálise (CKD-5D), foi particularmente afetada. Definimos como objetivos deste estudo a identificação do impacto da vacinação no surgimento de novos casos diários e a sua influência na mortalidade na população CKD-5D.

**Material e Métodos:** Estudo observacional, prospetivo, envolvendo doentes com CKD-5D de 38 clínicas da NephroCare, Portugal. A infeção e a mortalidade diárias por SARS-CoV-2 destes doentes foi comparada com a taxa de incidência na população em geral. Foram analisados três períodos: antes da vacinação, durante, e um terceiro período após a vacinação completa pela vacina Comirnaty<sup>®</sup>, da Pfizer-BioNTech. Foi considerado desfecho primário a infeção pelo vírus SARS-CoV-2 e como desfecho secundário, a morte associada à infeção.

**Resultados:** Foram analisados 4617 doentes com uma média de 69,37 anos. Durante o primeiro período, verificou-se uma taxa de incidência de COVID 19 de 14,9%, significativamente maior nos doentes CKD-5D quando comparado com a taxa de incidência de 7,9% da população em geral ( $p < 0,001$ ). Durante os quinze dias após a vacinação completa observámos uma reversão, com diminuição significativa de casos de COVID-19 ( $p < 0,001$ ). A mortalidade atribuível a COVID-19 no grupo CKD-5D foi significativamente superior ao da população em geral ( $p < 0,001$ ).

**Conclusão:** A vacinação reduziu significativamente a infeção por SARS-CoV-2 nos doentes CKD-5D.

**Palavras-chave:** COVID-19; Hemodiálise; Portugal; SARS-CoV-2; Vacinas contra a COVID-19

### INTRODUCTION

Since late 2019, more than 231,409,495 infections and 4,741,732 deaths were related to the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus worldwide, responsible for the 2019 coronavirus disease (COVID-19), according to data made available on 25 Sep 2021 by Johns Hopkins University (United States of America).<sup>1</sup> Following the identification of the first case of this new coronavirus in Wuhan city, Hubei province, Mainland China, it quickly spread to several regions, including Portugal.

The concept of 'syndemics',<sup>2</sup> first described by Merrill Singer in the 1990's, gained even more relevance during

this pandemic, [declared on 11/03/2020 by the World Health Organization (WHO)] due to the influence of inequalities on the course of the disease and especially on the outcomes, particularly on social inequalities, economic aspects, age groups, previous health conditions and access to health-care.<sup>3</sup>

In Portugal, between 02/03/2020 - the date of identification of the first case of COVID-19 - and 16/03/2021, 814,513 people were affected, including 36,031 active cases and 16,694 deaths at that date, mainly older patients with different comorbidities. The third wave of the pandemic that

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affected Portugal after Christmas, was particularly severe, inducing high pressure on healthcare systems in general, leading to overcrowding of beds in wards and even in Intensive Care Units (ICUs). Despite the measures implemented and/or reinforced in advance by haemodialysis (HD) clinics (HDC) - namely organisational, controlling people and workflows, especially hygiene and infection control processes - patients with stage 5 chronic kidney disease (CKD-5D) on regular renal replacement programme by in-centre haemodialysis were severely affected throughout the SARS-CoV-2 pandemic and particularly during the third wave.

This is a highly vulnerable group of patients,<sup>4</sup> not amenable to strict containment due to the need to receive regular treatment at least three times a week. There is therefore the need to travel in mostly shared transport which represents an increased risk, despite the efforts made by health authorities and all operators involved to ensure optimal safety conditions. Additionally, despite the use of personal protective equipment and hygiene and distancing measures, patients are exposed to multiple contacts, specifically during the treatment process, necessarily within a metre from caregivers.

The immune response of patients with chronic kidney diseases to the available vaccines, and which specific dose might be effective for this patient group, is unknown. However, HD patients and HDC staff were included within the first priorities for vaccination by the Portuguese health authorities. A significant logistical and operational task was required, in close collaboration with the vaccination task force of the Ministry of Health and the HDCs worked as vaccina-

tion outposts. Comirnaty® (Pfizer-BioNTech) vaccine was used in this priority group.

The universe of haemodialysis clinics in Portugal corresponds to a group with high protection rate, either through vaccination or through previous infection of patients and professionals. This study was aimed at assessing the impact of vaccination on the emergence of new daily cases and its influence on mortality in CKD-5D patients.

## MATERIAL AND METHODS

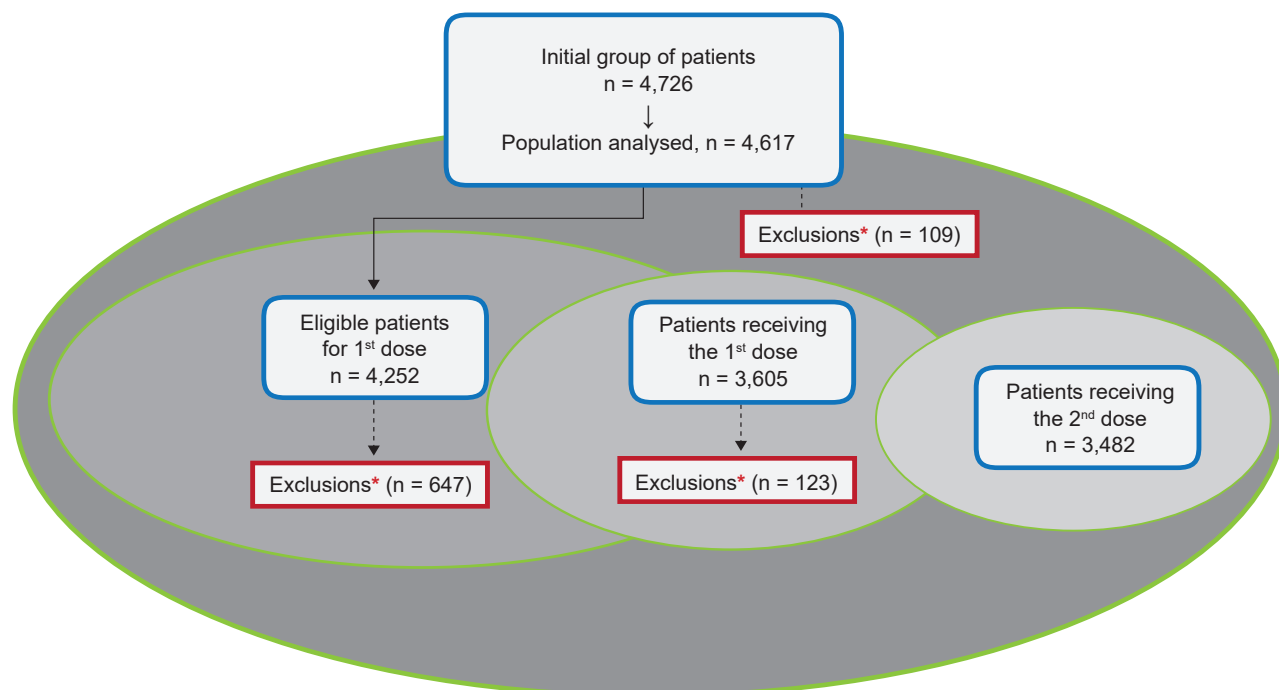
### Study design

This was an epidemiological, prospective and observational study involving all CKD-5D patients on regular haemodialysis programme and attending 38 NephroCare haemodialysis clinics in Portugal (Fresenius Medical Care - Portugal).

### Participants

The daily incidence rate of COVID-19 in HD patients (4,617 patients) and in general population were compared, assessing points of divergence between pre- and post-vaccination periods and understanding the influence of mass vaccination of a well-defined cohort of patients with 100% follow-up, on the emergence of new cases, within a short period of time (Fig. 1).

All patients previously diagnosed with COVID-19, those who refused the vaccination and those who were admitted to hospital within the period of administration of the vaccine were excluded from vaccination. All the remaining patients were considered eligible in compliance with *Direção Geral*



**Figure 1** – Study design. A total of 4,617 patients were analysed, from an initial group of 4,726 patients, upon exclusion of 109 patients (\* - death, hospital admission, patient refusal, clinical contraindication, previous SARS-CoV-2 infection); 4,252 patients were eligible for receiving a first dose, and 3,605 actually received it, upon 647 patients were excluded\*. A total of 3,482 patients received a second dose, upon 123 patients were excluded\*.

de Saúde (DGS) guidelines no. 021/2020 from 23/12/2020, updated on 01/03/2021 and no. 002/2021 from 30/01/2021 updated on 10/03/2021.<sup>6</sup>

### Procedures

Preventive measures were implemented in haemodialysis clinics aimed at minimising the incidence rate and impact of SARS-CoV-2 infection, including streamlined communication, the use of appropriate personal protective equipment (PPE), training and implementation of DGS standards and guidelines. Haemodialysis patients were included in the first phase of vaccination by the Ministry of Health task force, in compliance with DGS standard No. 002/2021 of 30/01/2021 updated on 10/03/2021.<sup>7</sup> Patients were vaccinated between 27 and 30 January (first dose) and between 17 and 20 February (second dose).

Pre-vaccination analysis was performed from the period between the identification of the first case in Portugal (02/03/2020) and day 15 (13/02/2021) following the first dose. Post-inoculation variation analysis was performed at two different intervals, the first between day 16 (14/02/2021) following the first dose and day 7 (27/02/2021) following the second dose, and a second one starting on day 8 (28/02/2021) following the second dose up to 15/03/2021 (15-day follow-up, including seven days after what is considered as full vaccination).<sup>8</sup>

Given the highly variable daily incidence rate, related to the day of the week, in which a significant reduction is found on Saturday and Sunday, a way to normalise data was required and the calculation of the mean daily incidence rate for the previous seven days was considered. Since these samples were extremely variable, i.e., the Portuguese population [approximately 10,295,909 people, according to the census Portugal 2021, *Instituto Nacional de Estatística* (INE)]<sup>9</sup> and the group of HD patients attending NephroCare Portugal clinics (4,617 patients), the incidence rate was referred to 100,000 people. The infection by SARS-CoV-2 virus was considered as primary endpoint, confirmed by RT-PCR (reverse transcription-polymerase chain reaction).

Patients underwent RT-PCR-based testing in compliance with the DGS Standard 019/2020 of 26/10/2020 updated on 26/02/2021,<sup>10</sup> i.e., patients with suspected SARS-CoV-2 infection, in addition to the identification and diagnosis of high and low risk contacts.

The death of a CKD-5D patient related to SARS-CoV-2 infection was included as secondary endpoint.

The COVID-19 mortality rate in relation to the total number of patients and the case fatality rate (%) associated with the disease (COVID-19) for cases that already had an outcome - i.e., those who had recovered or were dead [deaths/(recovered cases + deaths) x 100], called post-outcome case fatality rate (CFR-O) were obtained, in assessment of the impact of SARS-CoV-2 infection on mortality in HD patients, and the results were compared to those found in general population.

### Statistical analysis

Data analysis was carried out by using SPSS, version 23 (IBM, Armonk, NY, USA) software. Absolute (n) and relative (%) frequencies were used to describe categorical variables, while means (M) and standard deviations (SD) were used in the case of continuous variables with symmetrical distribution; otherwise, medians and interquartile ranges were used. Symmetry was assessed by the asymmetry coefficient (symmetry when [-2; 2]) and completed with the observation of the histogram. Normality of the distributions was assessed by the Kolmogorov-Smirnov test. Mann-Whitney's U-test was used for testing the differences between the incidence rate of infection in CKD-5D patients and in the general population throughout the 3 study periods. For all comparisons, a significance level of  $p < 0.05$  was considered.

### Ethics

This study was approved by the Ethics Committee of Fresenius Medical Care, Portugal, according to the Helsinki declaration. Informed consent was waived by the same committee, since data were obtained centrally, anonymised and making reverse detection impossible; researchers were blinded to data.

### RESULTS

Data regarding 4,617 patients were analysed for this study (2,765 (59.9%) male patients), aged 19-97, mean age 69.37 (SD = 14.08) years, (IQR, 61 - 80) (Table 1). Multiple comorbidities were found, including 35.3% of patients diagnosed with diabetes, with a 4.11 (SD = 2.02) mean Charlson index.

From the total number of patients, 621 (13.45%) attended adult day care centres, including 345 (7.47%) living in nursing homes, and it is known that these settings were also severely affected by COVID-19, corresponding to an increased risk factor. Based on these considerations, a 14.92% COVID-19 incidence rate has been found in HD patients, with an 81.57% recovery rate, a 2.38% mortality rate and a 16.37% CFR-O.

A 7.94% incidence rate, a 93.53% recovery rate, a 0.16% mortality rate and a 2.14% CFR-O were found in general population (data as of 16 March 2021).<sup>11</sup>

A significantly higher incidence rate per 100,000 people ( $p < 0.001$ ) has been found in HD patients, reaching peak incidence rates up to five times higher than in general population, when comparing the new cases per 100,000 people with HD patients attending NephroCare Portugal clinics (Fig. 2) within the period between the first reported case in Portugal and day 15 following the first dose of the vaccine, despite some fluctuations. In this period, a 41.39 mean daily incidence rate per 100,000 people was found in HD patients, compared to 22.42/100,000 in general population.

A 13.68 mean daily incidence rate /100,000 people was found in HD patients vs. and 14.09/100,000 in general

Table 1 – Demographic characteristics

Variable	Total (n = 4,617)
<b>Demographic</b>	
Male gender, n (%)	2,765 (59.9%)
Age (years), mean (SD)	69.37 (14.08)
Charlson Comorbidity Index, mean (SD)	4.11 (2.02)
Time on dialysis (months), mean (SD)	78.42 (79.10)
Diabetes, n (%)	1,632 (35.3%)
Institutionalised patients/nursing home residents	621 (13.45%)
<b>Vascular Access Type, n (%)</b>	
Arteriovenous fistula	3,203 (69.4%)
Arteriovenous graft	467 (10.1%)
Central venous catheter	947 (20.5%)

population, with no statistical significance ( $p = 0.541$ ), considering the period from day 16 following the first dose and day 7 following the second dose of the vaccine.

The trend towards dissociation of the incidence rate curves, which was found from day 16 following the first dose, would increase on day 8 following the second dose (full vaccination). A 1.33/100,000 mean daily incidence rate within the previous seven days was found in HD patients from day 7 following the second dose (full vaccination), while a 6.65/100,000 rate was found in general population. In this period, a significant reduction in the incidence rate was found in the CKD-5D population when compared with the general population ( $p < 0.001$ ) (Fig. 3).

A significant asymmetry in mortality and CFR-O has also been found in HD patients vs. general population, mainly affecting HD patients. A 2.38% mortality rate related to COVID-19 was found in CKD-5D patients when compared to 0.16% in general population ( $p < 0.001$ ) and CFR-O of 16.37% vs. 2.14%, respectively. A mean time of 13.29 days (SD 10.92; IQR 6-17) from diagnosis to death was found in CKD-5D patients, ranging between 1 and 52 days.

## DISCUSSION

A high incidence rate of SARS-CoV-2 infection has been found in patients diagnosed with CKD-5D, aggravated not only by age,<sup>12,13</sup> multiple comorbidities<sup>4</sup> and diabetes,<sup>14,15</sup> but also by poor socio-demographic conditions. The fact that 13.45% of patients lived in or attended elderly care facilities represented a significant risk factor according to the study by Caroline M. Hsu.<sup>14</sup> The significant mortality and lethality rates when compared to general population were certainly explained by the high institutional exposure of HD patients and the combination of the remaining factors.<sup>14</sup>

According to the results obtained in these comparisons, a significantly higher incidence rate has been found in HD patients, mainly during the third wave, despite potential biases related to the different testing strategies that were considered in the different population groups, even considering the significant testing numbers found in Portugal. However, there was a reduction in the mean incidence rate following the first dose of the vaccine, a trend that increased following the second dose. A lower mean incidence rate was also found in HD patients within the 15-day period starting on

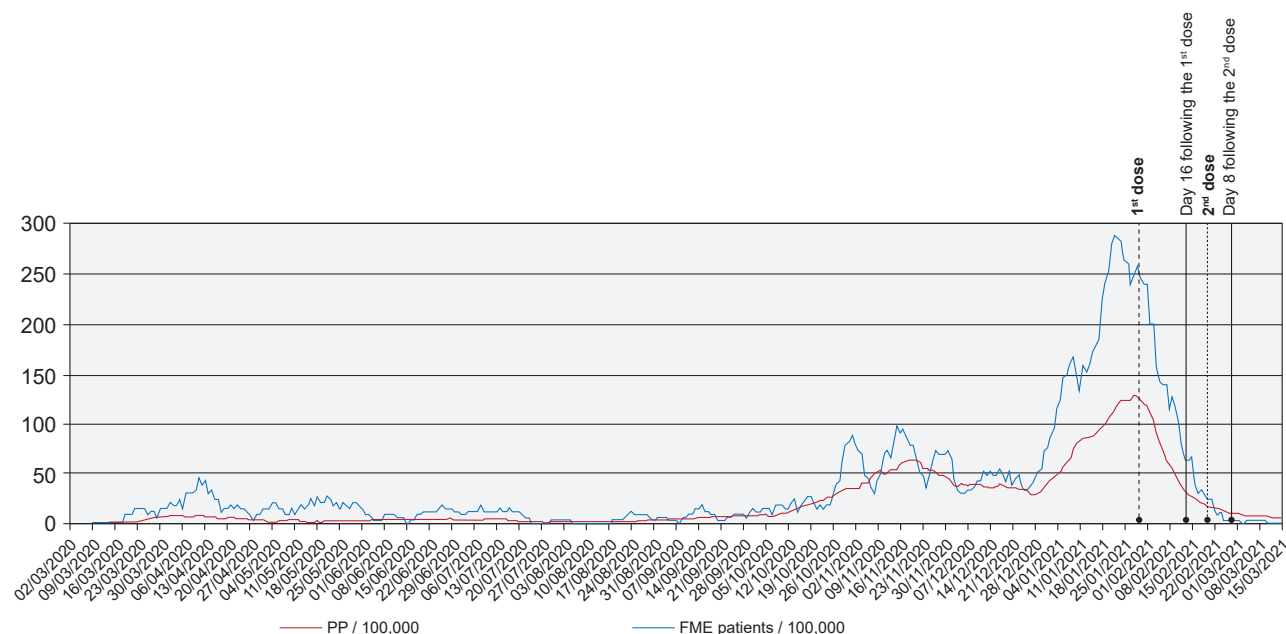
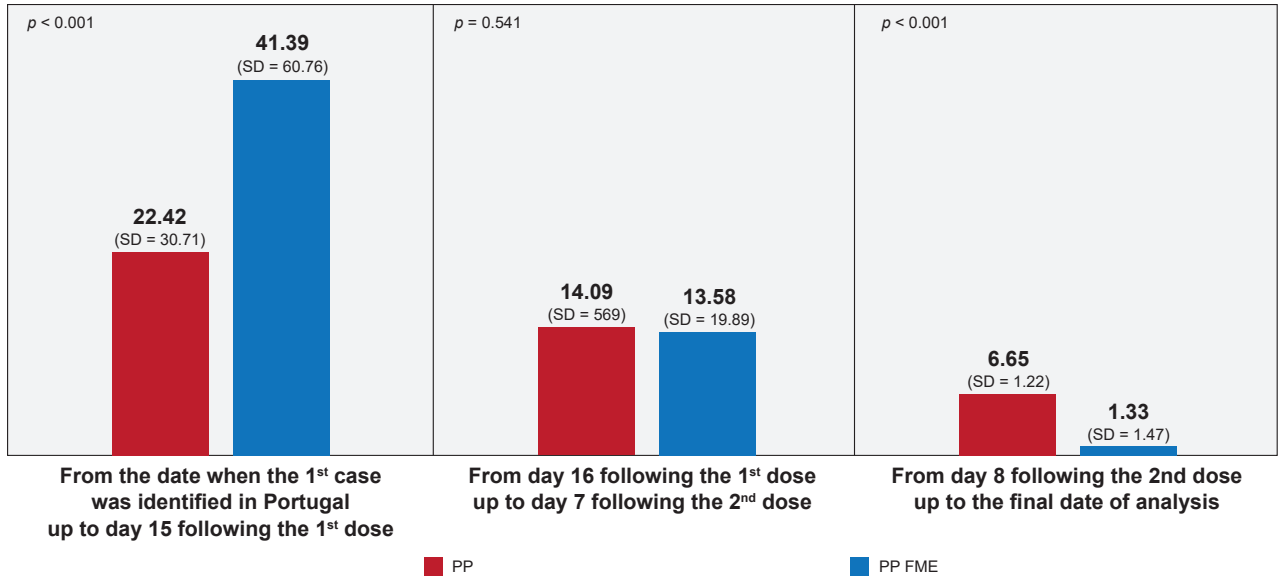


Figure 2 – Chart representing the daily mean incidence rate throughout the study period for both groups of patients.

PP: Portuguese population; FME patients: patients attending Fresenius Medical Care facilities

## Mean daily incidence rate / 100,000 people



**Figure 3** – – Chart representing the daily mean incidence rate of SARS-CoV-2 infection / 100,000 people. The first period started on the date when a first case was identified in Portugal up to day 15 following the first dose of the Cominarty<sup>®</sup> vaccine (Pfizer-BioNTech). The second period started on the day following the first dose up to day 7 following the second dose (full vaccination). The third period started on day 8 following the full vaccination regimen up to 15 March 2021 (study closure).

PP: Portuguese population; FME patients: patients on follow-up at Fresenius Medical Care facilities

day 8 following the second dose, when compared to the general population.

An increased attention and care, in addition to significant support during the pandemic are required by this group of patients, according to our results, while benefiting from an important advantage associated with timely and mass vaccination. Although there are currently no publications on this subject, we believe that further studies will confirm these conclusions, including the rate of seroconversion and sustainability of the immune response over time. COVID-19 vaccination of HD patients proved to be an extremely promising measure, with a relevant reduction in new infections as well as morbidity and mortality associated to this specific group of patients. We believe that our experience can be extrapolated to the general population, suggesting the added benefit of mass vaccination of large groups of individuals maximising the reduction of new cases and controlling transmission in confined communities.

The outset of this vaccination campaign matched the peak incidence of new cases of the disease in our network of clinics and simultaneously in the community. There was a reduction in the incidence of COVID-19 in the community throughout the observation period between vaccination doses and post-vaccination, probably associated with the declaration of a state of emergency and subsequent containment measures, which may have impaired the understanding of the real benefits of the vaccine. Both concomitant effects should therefore be differentiated.

The CFR that was found in the CKD-5D group of patients (secondary outcome) was considered significantly lower than the one found in Mabel Aoun's study,<sup>4</sup> as well as

the 25% found in the ERACODA study<sup>12</sup> carried out in different European countries.

A 13.29-day average time from diagnosis to death was found in our group of patients, compared with heterogeneous results found in different studies, ranging from an average of six days in the Lebanese study<sup>4</sup> to an average of 18.5 days in the study by Fei Zhou *et al.*<sup>16</sup> Further studies will be required to assess the influence of vaccination on mortality reduction.

A bias in data must be considered as a limitation, since the patients in our group (HD patients) are also part of the general population, even though only in a residual way (< 0.05). Patients with a previous history of SARS-CoV-2 infection and patients with contraindications or who refused vaccination were also included in the incidence analysis following full vaccination.

Despite the limitations, different characteristics make this study unique, namely the results coming from a robust database with ensured full adherence - EuCliD-5 - and the sample size.

## CONCLUSION

In this network of clinics, based on a mass vaccination operation involving almost the entire population at risk, we were able to achieve a significant degree of immunity over a short period of time, which is difficult to reproduce in the community within a similar period. Even though involving a population whose immune response to vaccination may be compromised, this pilot experience will represent a model for the benefits to be expected within the short and medium term for a universal vaccination policy based on subgroups.

According to data, vaccination has contributed to a reduction in the emergence of new cases among CKD-5D patients.

A significant reduction in the number of deaths from COVID-19 can be expected due to the reduction in new cases, resulting from subgroup immunity.

The reproducibility of this methodology may contribute to the implementation of future vaccination campaigns in specific subgroups of patients.

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## AUTHOR CONTRIBUTION

JFM: Study design, data analysis and interpretation, writing of the manuscript, final version review and approval.

RP: Study design, data analysis and interpretation, writing of the manuscript.

CF, BP: Data analysis and interpretation, writing of the manuscript.

PP: Data analysis and interpretation, writing of the manuscript, final version review and approval.

## HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

## CONFLICTS OF INTEREST

All the authors work for NephroCare Portugal.

## FINANCIAL SUPPORT

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