Humoral response after the fourth dose of the SARS-CoV-2 vaccine in the CKD spectrum

SENCOVAC Collaborative Network; Quiroga, Borja; Soler, Maria Jose; Ortiz, Alberto; Mantecon, Carlos Jesus Jarava; Perez, Virginia Olinda Gomes; Bordils, Antoni; Lacueva, Jose; Franco, Antonio Jose Marin; Conde, Pablo Delgado

Published in:
Nephrology Dialysis Transplantation

DOI:
10.1093/ndt/gfac307

Publication date:
2023

Nephrol Dial Transplant (2023) 38: 969–981
https://doi.org/10.1093/ndt/gfac307
Advance Access publication date 24 November 2022

ORIGINAL ARTICLE

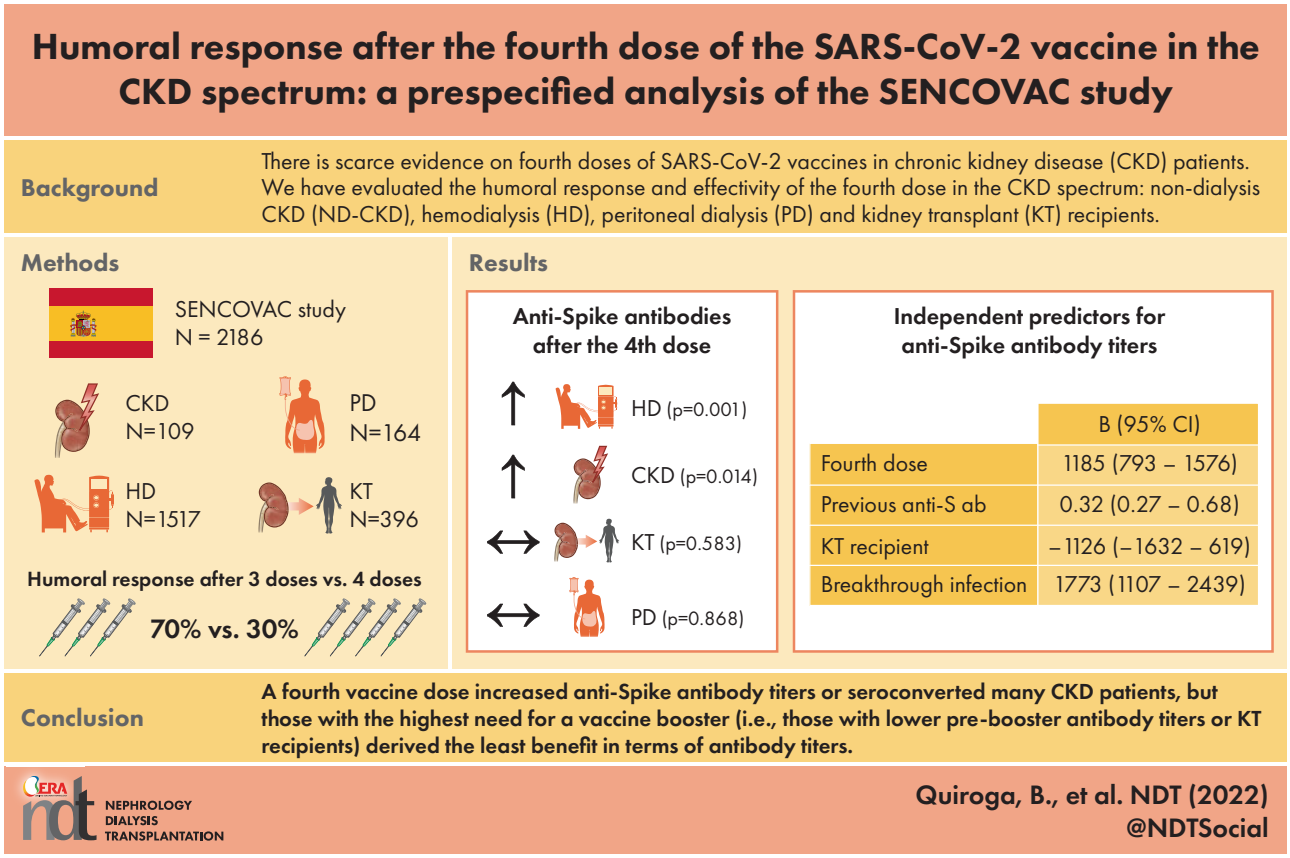
Humoral response after the fourth dose of the SARS-CoV-2 vaccine in the CKD spectrum: a prespecified analysis of the SENCOVAC study

Borja Quiroga[1], María José Soler[2,3], Alberto Ortiz[3,4], Carlos Jesús Jarava Mantecón[5], Virginia Olinda Gomes Pérez[5], Antoni Bordils[6], José Lacueva[6], Antonio José Marin Franco[7], Pablo Delgado Conde[8], Patricia Muñoz Ramos[9], Carmen Calderón González[10], Juan Manuel Cazorla López[11], Jinny Sanchez-Rodriguez[4], Ana Sánchez Horrillo[1], Tania Raquel Monzón Vázquez[12], Alba Leyva[13], José Rojas[13], Ron T. Gansevoort[14] and Patricia de Sequera[3,9]; on behalf of SENCOVAC collaborative network

[1]IIS-La Princesa. Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain, [2]Nephrology Department, Vall d'Hebrón University Hospital, Barcelona, Spain, , [3]RICORS2040 (Kidney Disease), [4]IIS-Fundación Jiménez Diaz, School of Medicine, Universidad Autónoma de Madrid, Fundación Renal Iñigo Álvarez de Toledo-IRSIN, REDinREN, Instituto de Investigación Carlos III, Madrid, Spain, [5]Diaverum Andalucía, Spain, [6]Diaverum Valencia, Spain, [7]Diaverum Castilla León-Galicia, Spain, [8]Diaverum Murcia–Alicante, Spain, [9]Nephrology Department, Hospital Universitario Infanta Leonor – Universidad Complutense de Madrid, Madrid, Spain, [10]Nephrology Department, Complejo Asistencial de Palencia, Palencia, Spain, [11]Nephrology Department, Hospital Universitario Puerta del Mar, Cádiz, Spain, [12]Nephrology Department, Hospital Universitario "Doctor Negrín" Las Palmas de Gran Canaria, Las Palmas, Spain, [13]R&D Department, VIRCELL SL, Granada, Spain and [14]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

*SENCOVAC collaborative network (see appendix).
Correspondence to: María José Soler; E-mail: mjsoler01@gmail.com; Twitter: @PepaSolerR; Alberto Ortiz; E-mail: aortiz@fjd.es

GRAPHICAL ABSTRACT



ABSTRACT

Background. There is scarce evidence on the fourth dose of severe acute respiratory syndrome coronavirus 2 vaccines in chronic kidney disease (CKD) patients. We evaluated the humoral response and effectivity of the fourth dose in the CKD spectrum: non-dialysis CKD (ND-CKD), haemodialysis (HD), peritoneal dialysis (PD) and kidney transplant (KT) recipients.
Methods. This is a prespecified analysis of the prospective, observational, multicentric SENCOVAC study. In patients with CKD who had received a complete initial vaccination and one or two boosters and had anti-Spike antibody determinations 6 and 12 months after the initial vaccination, we analysed factors associated with persistent negative humoral response and higher anti-Spike antibody titres as well as the efficacy of vaccination on coronavirus disease 2019 (COVID-19) severity.
Results. Of 2186 patients (18% KT, 8% PD, 69% HD and 5% ND-CKD), 30% had received a fourth dose. The fourth dose increased anti-Spike antibody titres in HD ($P = .001$) and ND-CKD ($P = .014$) patients and seroconverted 72% of previously negative patients. Higher anti-Spike antibody titres at 12 months were independently associated with repeated exposure to antigen (fourth dose, previous breakthrough infections), previous anti-Spike antibody titres and not being a KT recipient. Breakthrough COVID-19 was registered in 137 (6%) patients, 5% of whom required admission. Admitted patients had prior titres <620 UI/ml and median values were lower ($P = .020$) than in non-admitted patients.
Conclusions. A fourth vaccine dose increased anti-Spike antibody titres or seroconverted many CKD patients, but those with the highest need for a vaccine booster (i.e. those with lower pre-booster antibody titres or KT recipients) derived the least benefit in terms of antibody titres. Admission for breakthrough COVID-19 was associated with low anti-Spike antibody titres.

Keywords: CKD, COVID-19, dialysis, kidney transplant, SARS-CoV-2, vaccines

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused severe morbidity and mortality in chronic kidney disease (CKD) patients [1]. Vaccine approval was expected to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2]. However, the initial vaccination schedule efficacy in patients with CKD, and especially in kidney transplant (KT) recipients, was suboptimal [3, 4]. The spontaneous loss of humoral immunity and the inherent or drug-induced immunosuppressive state of patients with CKD led some health authorities to approve a vaccine booster (i.e. a third dose in most cases) to improve protection against SARS-CoV-2. A previous prespecified analysis of the SENCOVAC study showed that a third vaccine dose seroconverted some patients with initial negative humoral response to the vaccine [5]. Humoral response was observed in most CKD and

KEY LEARNING POINTS

What is already known about this subject?

- The initial vaccination schedule efficacy in patients with chronic kidney disease (CKD), and especially in kidney transplant (KT) recipients, was suboptimal.
- The loss of humoral immunity and the inherent or drug-induced immunosuppressive state of patients with CKD led some health authorities to approve a vaccine booster to increase protection against severe acute respiratory syndrome coronavirus 2.
- A third vaccine dose helped in seroconverting patients with initial negative humoral response to the vaccine; however, in KT recipients the rates of response remained suboptimal.

What this study adds?

- A fourth vaccine dose increased anti-Spike antibody titres or seroconverted many CKD patients.
- Patients with lower pre-booster antibody titres or KT recipients derived the least benefit in terms of antibody titres.
- Patients with coronavirus disease 2019 (COVID-19) infection that required hospitalization had relatively low titres of anti-Spike antibodies.

What impact this may have on practice or policy?

- A fourth vaccine dose should be indicated in patients at risk for severe COVID-19, because it increases the effectivity in terms of increased anti-Spike antibody titres and the rate of seroconversion.
- KT recipients or patients with CKD and lower pre-booster antibody titres may benefit from antibody therapy for COVID-19.

dialysis patients, although KT recipients still had high rates of suboptimal protection [5].

To tackle the spontaneous fading of the humoral response and new SARS-CoV-2 variants (i.e. Omicron) and the low effectivity of the vaccines against them, health authorities in many countries recommended a new booster dose (i.e. a fourth dose) of SARS-CoV-2 vaccine in patients at high risk for severe COVID-19, such as those with CKD. In this regard, the scarce available evidence suggests that the fourth dose increases antibody titres in KT recipients but does not generally seroconvert patients with previous negative responses [6, 7]. In 46 dialysis patients, the fourth dose increased anti-Spike antibody titres, but there was no absolute reduction in further SARS-CoV-2 infections [8]. However, the optimal humoral response that protects from severe COVID-19 requiring hospitalization and allows individualization of SARS-CoV-2 booster vaccination is still unknown in patients with CKD.

The aim of the present prespecified analysis of the SENCOVAC study was to evaluate the impact of a new booster dose (i.e. fourth dose) of SARS-CoV-2 vaccine in the CKD spectrum, specifically on anti-Spike antibody titres and seroconversion rates and in severe COVID-19 cases.

MATERIALS AND METHODS

Study design

SENCOVAC is an observational, prospective and multicentric study promoted by the Spanish Society of Nephrology and open to all patients with CKD treated in Spain who have received SARS-CoV-2 vaccination. Following the national health authority's guidance, patients with non-dialysis CKD (ND-CKD), those on peritoneal dialysis (PD) or haemodialysis (HD) and KT recipients received BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca) or Ad26.COV.2 (Janssen) as an initial vaccination. The type of vaccine was mandated by regional health authorities depending on local availability at the time of vaccination and was not decided by SENCOVAC researchers. Third and fourth doses were only mRNA-based vaccines [BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna)] for all patients. Again, the type and timing of these booster doses was decided by health authorities external to SENCOVAC.

Population

This prespecified analysis included all patients with CKD who had completed the initial vaccination schedule and received at least one booster dose (third dose) and who had anti-Spike antibodies assessed at both 6 and 12 months after the initial vaccination schedule. We excluded patients with solid organ transplantation not kidney, active neoplasia, primary immunodeficiencies, human immunodeficiency virus and non-KT patients who had received immunosuppressive treatment within 6 months before vaccination [3–5]. Depending on protocols mandated by regional health authorities and on the speed at which individual hospitals fulfilled the regional health authority mandates, some patients had already received a fourth dose of SARS-CoV-2 vaccination before the 12-month anti-Spike assessment. The timing of the fourth dose was not decided by SENCOVAC investigators. In this analysis, we divided the cohort into two groups depending on the number (one or two) of received vaccine boosters at 12 months, allowing the evaluation of the humoral response to a fourth vaccine dose in the CKD spectrum in a real-world approach.

Objectives

The primary objective was to evaluate the humoral response after the fourth dose of SARS-CoV-2 vaccine in the

CKD spectrum. Secondary objectives included the effect of breakthrough infections on anti-Spike antibody development and the association between antibody titres and COVID-19 severity.

Variables and outcomes

Epidemiological data and comorbidities were registered at baseline. CKD aetiology, prescribed treatments (including immunosuppressive drugs in KT recipients), dialysis modality, baseline kidney function and vascular access were registered. Humoral immunity was assessed using a centralized anti-Spike antibody measurement for all centres 6 and 12 months after completing the initial vaccination schedule. Anti-Spike antibodies were tested by a CE-marked quantitative chemiluminescence immunoassay (CLIA; COVID-19 Spike Quantitative Virclia IgG Monotest, Vircell SL, Granada, Spain), with a sensitivity and specificity of 96% and 100%, respectively, that detects immunoglobulin G (IgG) antibodies against the SARS-CoV-2 Spike protein. This assay was calibrated against the First WHO International Standard for anti-SARS-CoV-2 human immunoglobulin (NIBSC code: 20/136) and results were expressed as IU/ml. According to performance studies by the manufacturer, titres ≤32 IU/ml were considered negative, those 32–36 IU/ml were equivocal and those >36 IU/ml were positive, reflecting the presence of anti-Spike IgG antibodies resulting from previous infection or vaccination. The highest titre that was measurable was 10 000 UI/ml. Thus a titre of 10 000 UI/ml means ≥10 000 UI/ml.

During follow-up, breakthrough infections were registered. A positive reverse transcription polymerase chain reaction or antigen test were required to confirm SARS-CoV-2 infection. Severity of infection was defined on a subjective scale: asymptomatic, mild (disease that allows a normal life), moderate (disease limiting activities of daily living) or severe (with pneumonia on chest X-ray). We also collected the need for admission due to infections.

Ethical concerns

The study was approved by the Ethical Committee of Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz (February 2021).

Statistics

Data are expressed as median [interquartile range (IQR)] or percentage. Categorical variables were compared using Fisher's test and continuous variables using the Mann–Whitney or Kruskal–Wallis test (depending on the groups being compared, i.e. dichotomous or non-dichotomous). Logistic regression analysis assessed variables associated with 12-month negative humoral response in adjusted models including confounders. Linear regression models were constructed to assess factors associated with higher anti-Spike antibody titres 12 months after initial vaccination completion. SPSS version 26.0 (IBM, Armonk, NY, USA) was used for statistics and GraphPad Prism version 9.02 (GraphPad Software, San Diego, CA, USA) was used for plotting.

RESULTS

Baseline characteristics

Among the 4250 screened patients, 4079 were included as the safety population and 2439 had an anti-Spike antibody assessment 12 months after completing the initial vaccination schedule. Of these, 2186 patients (89%) [median age 66 years (IQR 18–92), 63.4% males] had completed a full initial vaccination schedule with one booster dose and had anti-Spike antibody assessments at 6 and 12 months (Fig. 1): 396 (18%) were KT recipients, 164 (8%) on PD, 1517 (69%) on HD and 109 (5%) had ND-CKD (Table 1).

Vaccination status

Among the 2186 included patients, 1532 (70%) had received only three doses and 654 (30%) had received an additional fourth dose. Vaccines for third and fourth doses were mRNA-based, and mRNA-1273 was more common than BNT162b2 (60.1% and 52.7%, respectively; Table 1). The distribution of the type of fourth dose differed across the CKD spectrum (Table 1). KT recipients and patients on PD or HD more frequently received a fourth dose than patients with ND-CKD (29.3%, 32.9% and 30.9% versus 11.9%) ($P = .001$). BNT162b2 was the most common vaccine for ND-CKD in the third dose and for HD patients in the fourth dose.

Impact of vaccination on anti-Spike antibody titres

At 12 months, patients who had received only three doses had significantly lower anti-Spike antibody titres than patients who had received a fourth dose [3146 UI/ml (IQR 582–10 000) versus 10 000 UI/ml (IQR 1716–10 000), $P < .001$]. The impact of the fourth dose was different across the CKD spectrum, as anti-Spike antibody titres were significantly higher than titres for three-dose-only patients in the HD and ND-CKD cohorts ($P < .001$ and $P = .037$, respectively) but not in the KT and PD cohorts ($P = .583$ and $P = .868$) (Fig. 2). Lower patient numbers and lower rates of SARS-CoV-2 infections prior to the 12-month assessment (1.2%) may have contributed to the lack of statistically significant differences in PD patients [three doses 2287 UI/ml (IQR 560–10 000) versus four doses 2647 UI/ml (IQR 827–10 000)]. In KT patients, the fourth dose was associated with numerically lower values of anti-Spike antibody titres [three doses 2110 UI/ml (IQR 143–10 000) versus four doses 1620 UI/ml (IQR 433–10 000); Fig. 2]. Immunosuppressive drugs impacted negatively on anti-Spike antibody titres in KT patients. Steroids and mycophenolate mofetil were both associated with lower anti-Spike antibody titres ($P = .030$ and $P = .004$, respectively; Fig. 3). When patients with SARS-CoV-2 infections before anti-Spike assessment [$n = 150$ (6%)] were excluded, results were similar across the different cohorts.

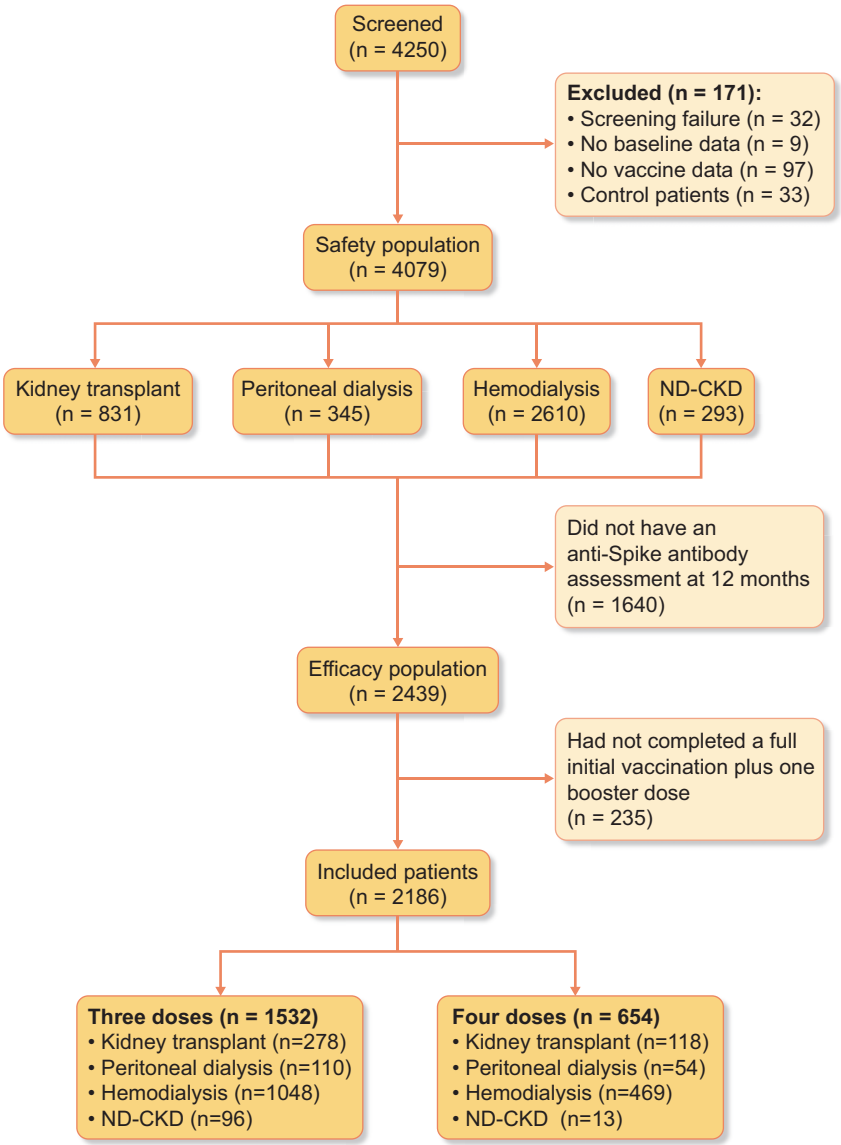


Figure 1: Flow chart.

Breakthrough infection increases anti-Spike antibody titres

During follow-up, 164 (7%) patients developed a SARS-CoV-2 breakthrough infection [median time from last vaccine dose 96 days (IQR 71–130)]. The infection rate differed across the cohorts (1.2% in PD, 3.7% in ND-CKD, 8.4% in HD and 7.6% in KT) ($P = .004$). Of SARS-CoV-2-infected patients, 27 (16%) were infected before the third dose, 123 (75%) between the third and fourth dose and 14 (9%) after the fourth dose. Anti-Spike antibody titres at 12 months differed between these three groups (Fig. 4). Specifically, patients with three vaccine doses and breakthrough infections had higher subsequent anti-Spike antibody titres at 12 months than patients with three doses without infection [10 000 UI/ml (IQR 3580–10 000) versus 3125 UI/ml (IQR 582–10 000), $P < .001$]. However, patients who had received the fourth dose already had median antibody titres in the upper limit of the assay and no differences were observed between patients with or without breakthrough infection [10 000 UI/ml (IQR 4500–10 000) versus 10 000 UI/ml (IQR 1689–10 000), $P = .188$]. Interestingly, a trend (i.e. a P-value close to $<.05$) for higher anti-Spike antibody titres was observed in patients with a third dose who had suffered a breakthrough infection compared with those with the fourth dose but without infections, mainly

Table 1: Baseline characteristics of included patients.

Characteristics	Total ($N = 2186$)	KT ($n = 396$)	PD ($n = 164$)	HD ($n = 1517$)	ND-CKD ($n = 109$)	*P*-value
Male, *n* (%)	1386 (63.4)	250 (63.1)	113 (68.9)	960 (63.3)	63 (57.8)	.306
Age (years), median (range)	66.5 (18–92)	57.6 (18–80)	64.2 (24–85)	68.8 (20–92)	70.3 (25–88)	.001
Diabetic kidney disease, *n* (%)	460 (21.0)	20 (5.1)	31 (18.9)	376 (24.8)	33 (30.3)	.001
HD technique, *n* (%)						
HFHD				697 (46.0)		
HDx				74 (4.9)		
OL-HDF				744 (49.1)		
Vascular access, *n* (%)						
AVF				988 (66.4)		
Catheter				501 (33.6)		
Immunosuppression, *n* (%)						
Steroids		256 (64.6)				
Calcineurin inhibitors		317 (80.1)				
Mycophenolate mofetil		268 (67.7)				
mTORi		68 (17.2)				
Azathioprine		11 (2.8)				
Anticoagulants, *n* (%)	347 (15.9)	37 (9.3)	29 (17.7)	261 (17.2)	20 (18.3)	.002
Antiplatelet agents, *n* (%)	801 (36.6)	115 (29.0)	45 (27.4)	597 (39.4)	44 (40.4)	.001
RAASi, *n* (%)	813 (37.2)	183 (46.2)	101 (61.6)	483 (31.8)	46 (42.2)	.001
ESA, *n* (%)	1454 (66.5)	66 (16.7)	107 (65.2)	1213 (80.0)	68 (62.4)	.001
Pre-vaccination COVID-19, *n* (%)	193 (8.8)	22 (5.6)	15 (9.1)	147 (9.7)	9 (8.3)	.087
Baseline anti-Spike Ab+, *n* (%)	142 (6.5)	24 (6.1)	15 (9.1)	98 (6.5)	5 (4.6)	.450
Influenza vaccine, *n* (%)	1614 (73.8)	311 (78.5)	125 (76.2)	1111 (73.2)	67 (61.5)	.003
Anti-HBs Ab+, *n* (%)	937 (42.9)	128 (32.3)	59 (36.0)	720 (47.5)	30 (27.5)	.001
Vaccine (1st/2nd doses) , *n* (%)						.001
BNT162b2	877 (40.1)	139 (35.1)	41 (25.0)	626 (41.3)	71 (65.1)	
mRNA-1273	1295 (59.2)	256 (64.6)	123 (75.0)	880 (58.0)	36 (33.0)	
ChAdOx1-S	10 (0.5)	1 (0.3)	0 (0.0)	7 (0.5)	2 (1.8)	
Ad26.COV.2	4 (0.2)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)	
Vaccine (3rd dose) , *n* (%)		141 (35.6)	31 (18.9)	638 (42.1)	62 (56.9)	.001
BNT162b2	872 (39.9)	255 (64.4)	133 (81.1)	879 (57.9)	47 (43.1)	
mRNA-1273	1314 (60.1)					
Vaccine (4th dose) , *n* (%)	654 (29.8)[a]	116 (29.3)	54 (32.9)	468 (30.9)	13 (11.9)	.001
BNT162b2	309 (47.2)	21 (18.1)	23 (42.6)	261 (55.8)	3 (23.1)	.001
mRNA-1273	343 (52.4)	95 (81.9)	31 (57.4)	207 (44.2)	10 (76.9)	

HFHD: high-flux haemodialysis; HDx: expanded haemodialysis therapy; OL-HDF: online haemodiafiltration; AVF: arteriovenous fistula; mTORi: mammalian target of rapamycin inhibitor; RAASi: renin–angiotensin–aldosterone inhibitor; eGFR: estimated glomerular filtration rate; Ab: antibody; SD: standard deviation.
[a]Two patients had received an unknown mRNA fourth dose.

reflected in lower Q3 values (10 000 UI/ml (IQR 4500–10 000) versus 10 000 UI/ml (IQR 1689–10 000), $P = .057$].

In univariate analysis, higher anti-Spike antibody titres were associated with previous anti-Spike antibody titres ($P < .001$), not being a KT recipient ($P < .001$), having received a fourth dose ($P < .001$), having presented a breakthrough infection ($P < .001$) and having an mRNA-1273-based third dose ($P = .003$). An adjusted logistic regression analysis showed that a fourth dose, previous anti-Spike antibody titre, not being a KT recipient and previous breakthrough infections were associated with higher anti-Spike antibody titres at 12 months (Table 2).

Factors associated to negative humoral response

At 12 months, 93 (4%) patients presented a negative humoral response, i.e. antibody titres ≤32 IU/ml. They represented 17/654 (3%) of patients with four vaccine doses and 76/1532 (5%) of patients with three vaccine doses ($P = .011$). After the fourth dose, 34/47 (72%) patients that were previously negative or uncertain achieved seroconversion. Patients that did not seroconvert after the fourth dose were more frequently KT recipients (9/13) than patients on HD (3/13) or PD (1/13) ($P = .017$).

In univariate analysis, a negative humoral response at 12 months was associated with being a KT recipient ($P < .001$), negative humoral response at 6 months ($P < .001$) and having only received three vaccine doses ($P = .038$). BNT162b2 was associated with a numerical, but not statistically significant, higher rate of negative humoral response (4.8% versus 3.2%; $P = .069$). An adjusted logistic regression showed that a negative humoral response at 6 months and being a KT recipient were independent predictors of negative humoral response at 12 months (Tables 3 and S1).

Booster dose and breakthrough infections in the CKD spectrum

Breakthrough SARS-CoV-2 infections developed in 137 (6%) patients after receiving the third dose. Among infected

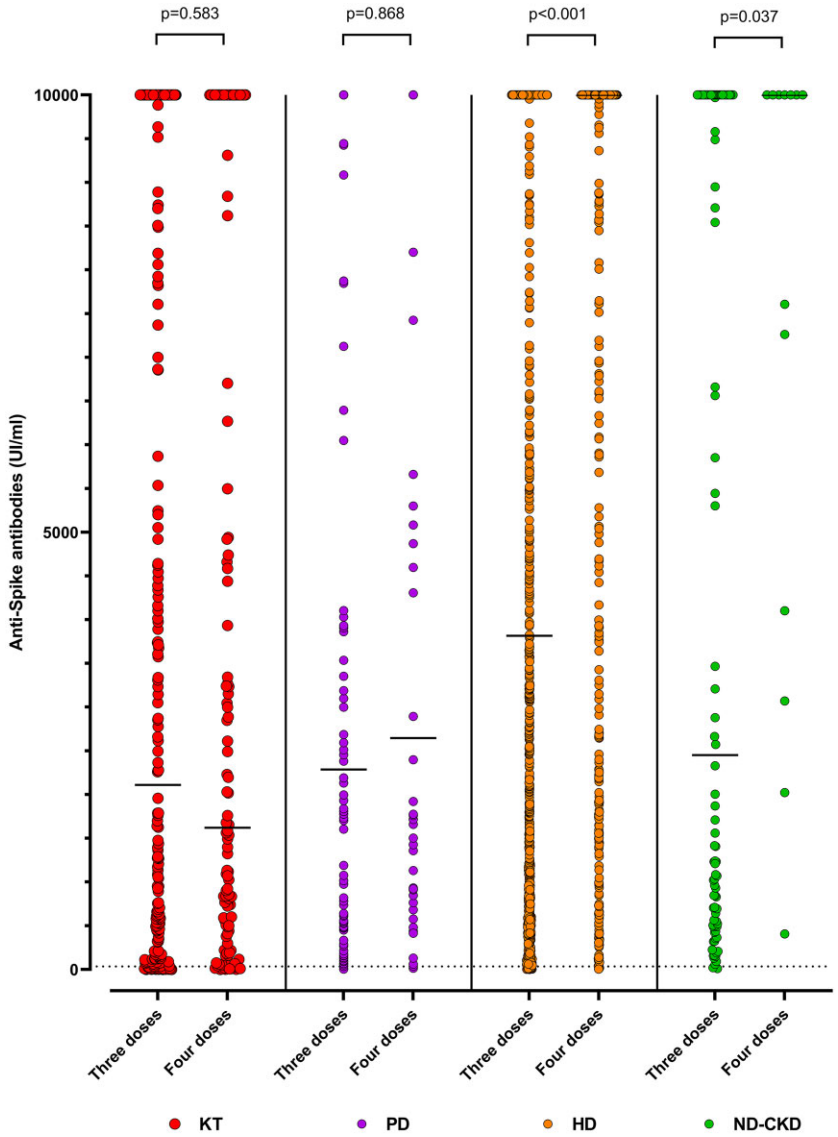


Figure 2: Anti-Spike antibodies at 12 months by number of vaccine doses received and patient cohort.

patients, 4 (3%) remained asymptomatic, 120 (90%) presented mild symptoms, 6 (4%) presented moderate symptoms and 4 (3%) presented pneumonia. One death was recorded. Three patients presented an unknown course. Numerical but not statistically significant differences were detected in anti-Spike antibody titres (in the last available titre prior to infection) regarding the clinical spectrum of SARS-CoV-2 infections (Fig. 5).

Only seven patients (5%) required hospital admission (three KT recipients and four patients on HD). Patients with breakthrough infections admitted into the hospital had lower anti-Spike antibody titres prior to infection than those infected but not admitted [126 UI/ml (IQR 6–428) versus 747 UI/ml (IQR 66–3262), $P = .020$; Fig. 5]. All admitted patients had anti-Spike antibody titres <613 UI/ml in the last assessment before the infection that required admission. The last available anti-Spike antibody titre before breakthrough COVID-19 was 3 UI/ml (negative humoral response) in the KT recipient who died.

DISCUSSION

The key findings of the present prespecified analysis of SENCOVAC include that a fourth vaccine dose achieved seroconversion in almost 75% of previously antibody-negative CKD patients and increased anti-Spike antibody titres in HD and ND-CKD patients. Achieving higher antibody titres was associated with prior repeated exposure, either as a fourth vaccine dose or breakthrough infection, the previous anti-Spike antibody titre and not being a KT recipient. In this regard, breakthrough infections could enhance humoral response at least as much as subsequent booster doses of SARS-CoV-2 vaccination. Additionally, adequate anti-Spike antibody titres could protect against the more severe COVID-19 forms, as the only reported death in >100 patients with breakthrough infection had a negative humoral response and all patients admitted for COVID-19 had anti-Spike antibody titres <620 UI/ml in the last assessment prior to infection. In this regard, neutralizing antibodies correlate with improved outcomes in infected patients [9]. Our study

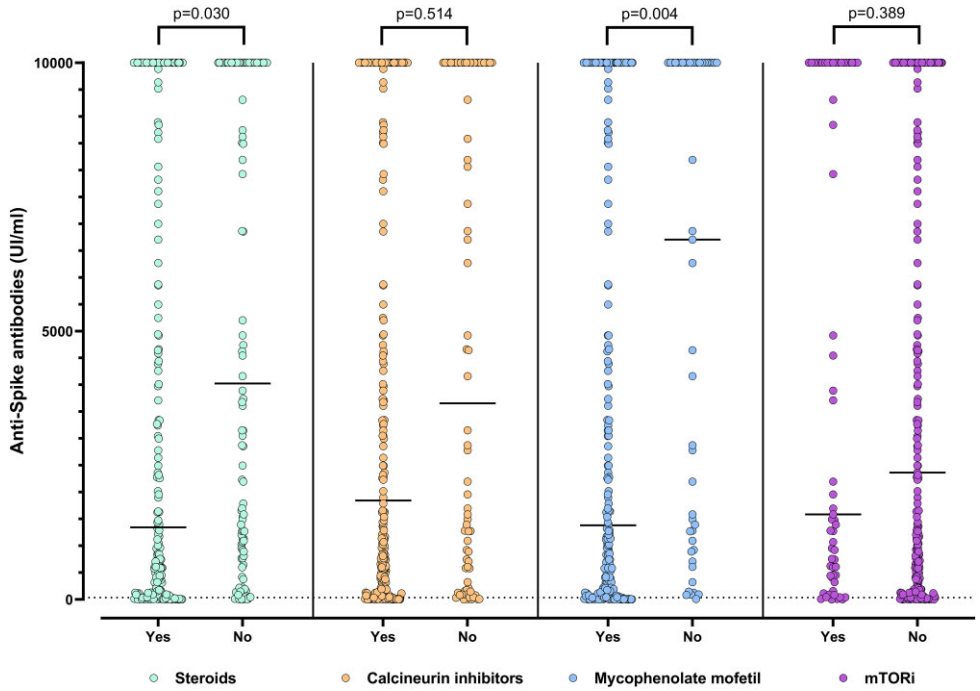


Figure 3: Anti-Spike antibody titres at 12 months by immunosuppressive drugs among KT recipients. mTORi: mammalian target of rapamycin inhibitor.

demonstrates that in patients with CKD, higher titres are also related to better outcomes. The antibody titre cut-off point could differ from the general population and also change over time as the virus evolves. However, as a note of caution, those CKD patients with the highest need for a vaccine booster (i.e. those with lower pre-booster antibody titres or KT recipients) derived the least benefit from a fourth dose in terms of antibody titres.

The impact of a fourth dose of SARS-CoV-2 vaccine was uneven across the CKD spectrum. On one hand, in non-KT recipients, anti-Spike antibody titres increased after the new booster. However, in KT recipients, the fourth dose did not increase anti-Spike antibody titres, which is worrisome because KT patients had the worst response to the initial vaccination protocol. These data from a nationwide study are consistent with some small prior reports [6]. Indeed, the results of a fourth booster were clearly suboptimal in patients that did not respond to prior vaccine doses, as 25% did not seroconvert and antibody titres in those who seroconverted were low, showing that additional protective strategies should be implemented for these patients.

Regarding the effectivity of SARS-CoV-2 vaccines, until now, public policy called for prescribing boosters independent of the anti-Spike antibody titre. However, as shown in our data, anti-Spike antibody titres are related to hospital admissions due to COVID-19. Consequently, it should be more efficient to identify cut-off values for anti-Spike antibody titres that increase the risk of infection, or of severe disease, and develop individualized recommendations for SARS-CoV-2 vaccine booster doses in the CKD spectrum, in a manner similar to current practice for hepatitis virus B vaccination [10]. As a starting point, all CKD patients in SENCOVAC who required hospital admission in the context of breakthrough COVID-19 had anti-Spike antibody titres <613 UI/ml. In addition, the neutralizing effect of vaccines against emerging variants should be considered. To our knowledge, the effectivity of vaccine boosters in CKD patients has not yet been tested in the Omicron era. In the general population, the administration of a fourth dose was associated with lower severity of COVID-19 but not with a reduced incidence of infections and there was a significant reduction in the neutralization of the Omicron variant of SARS-CoV-2 [11–13].

With these data, some difficulties arise for the optimal management of patients with CKD in terms of preventing SARS-CoV-2 infection. It is likely that periodic vaccination, especially in previous responders who have lost the humoral response, in combination with new monoclonal antibodies (for non-responders) could improve outcomes. However, there is suboptimal evidence on the effectivity of monoclonal antibodies across the CKD spectrum and this effectivity may change over time as the virus mutates [14].

Some limitations should be acknowledged. First, this is an observational study with some missing data. However, real-world studies with a prospective design are clinically useful, as they include all kinds of patients and it is easier to extrapolate conclusions to a wider population. Second, cellular immunity was not assessed. As this study is multicentric, measuring cellular immunity posed insurmountable logistical difficulties. In addition, for daily practice, humoral immunity is easier to assess and appears to provide information on the protective effects of vaccines. Third, as the number of infections was low, we did not have a large enough sample size to definitely establish a cut-off value for anti-Spike antibodies that is associated with the risk of severe COVID-19. However, providing an

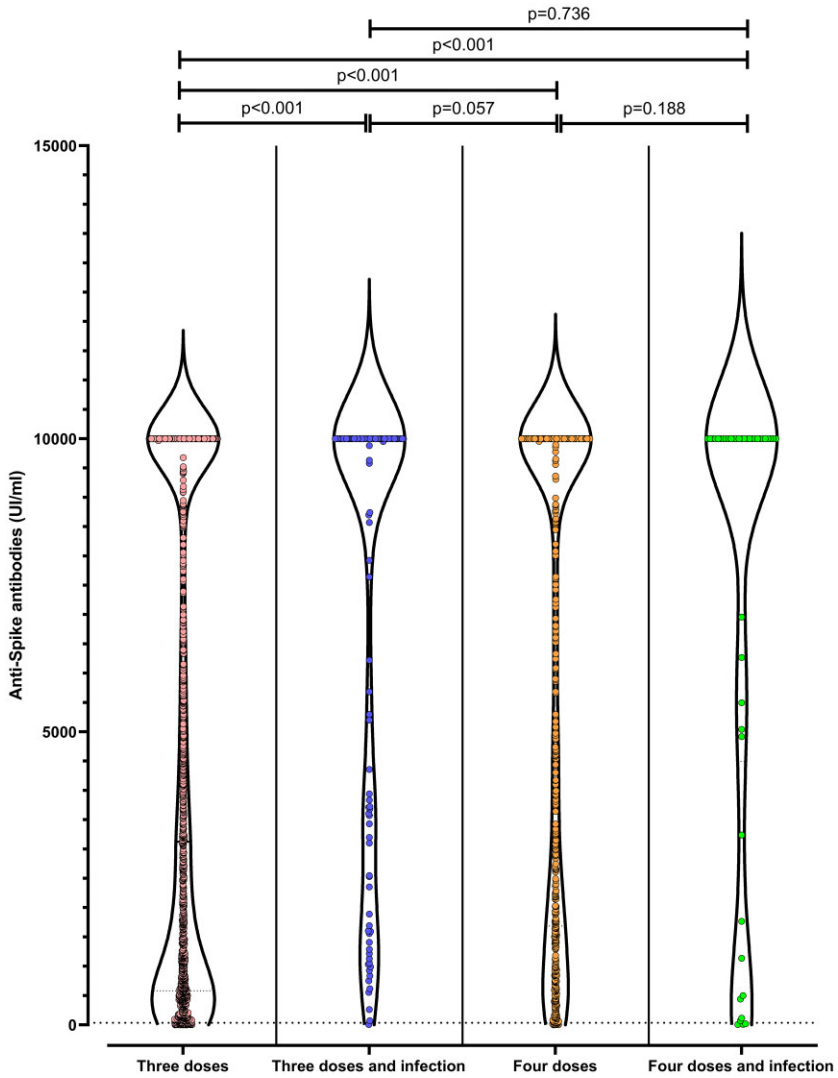


Figure 4: Effect of the number of doses of SARS-CoV-2 vaccines and breakthrough infections prior to 12 months on anti-Spike antibody titres at 12 months.

Table 2: Linear regression of independent predictors for anti-Spike antibody titres at 12 months.

Predictors	B (95% CI)	*P*-value
Fourth dose (yes)	1185 (793–1576)	<.001
Previous anti-Spike antibody titre (per unit)	0.32 (0.27–0.68)	<.001
KT recipient (versus others)	−1126 (−1632–619)	<.001
Breakthrough infection (yes)	1773 (1107–2439)	<.001

Linear regression adjusted for type of third dose vaccine, age and sex.
B (95% CI): beta coefficient (95% confidence interval).

Table 3: Logistic regression for independent predictors for negative humoral response at 12 months.

Predictors	OR (95% CI)	*P*-value
Previous negative humoral response (yes)	39.1 (18.5–82.5)	<.001
KT recipient (versus others)	7.8 (4.0–15.1)	<.001

Logistic regression adjusted for age, breakthrough infections, type of third dose vaccine and fourth dose.
OR (95% CI): odds ratio (95% confidence interval).

initial estimate may facilitate the design of larger, more focused studies. Also, asymptomatic SARS-CoV-2 infections may have gone unnoticed, as screening of asymptomatic persons was not routinely performed in many centres. Finally, the assay used for measuring anti-Spike antibodies had a maximum value of 10 000 UI/ml, so patients with higher titres were codified as this maximum value.

In conclusion, booster doses and breakthrough infections generate similar increases in anti-Spike antibody titres and a fourth vaccine dose seroconverted a significant percentage of CKD patients with negative antibody titres. However, patients most in need of boosting the humoral response, including KT recipients and those with previous negative humoral response, derived the least benefit in terms of anti-Spike antibody titres from a fourth booster dose. Finally, patients with breakthrough infection who required hospitalization had relatively low titres of anti-Spike antibodies, setting the stage for the definition of 'protective anti-Spike antibody titres' as opposed to the current

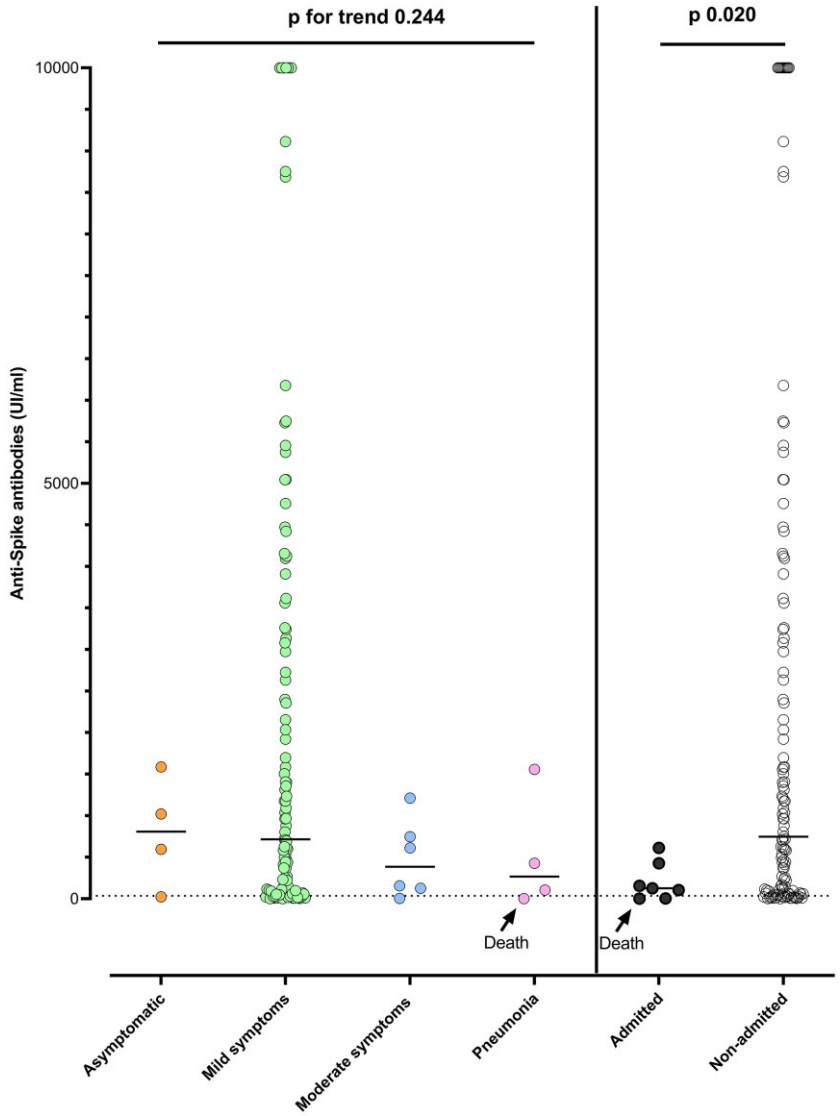


Figure 5: Anti-Spike antibody titres during the study (i.e. last available titre prior to infection) across the different clinical presentations of SARS-CoV-2 infections.

definition of positive anti-Spike antibody titres, which is based on evidence of prior exposure to the antigen that differentiates exposed from unexposed individuals.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We thank all the involved centres and healthcare workers, especially the nurse team, for their help with this project. In addition, we want to thank the Sociedad Española de Enfermería Nefrológica (SEDEN), Organización Nacional de Trasplantes (ONT) and Sociedad Española de Trasplante (SET) for their support.

FUNDING

This project has been supported by Diaverum, Vifor Pharma, Vircell, Fundación Renal Iñigo Álvarez de Toledo and ISCIII FEDER funds RICORS2040 (RD21/0005).

AUTHORS' CONTRIBUTIONS

B.Q., M.J.S., A.O., R.T.G. and P.S. were responsible for the research idea and study design and supervision or mentorship. C.J.J.M., V.O.G.P., A.B., J.L., A.J.M.F., P.D.C., P.M.R., C.C.G., J.M.C.L., J.S., A.S.H. and T.R.M.V. were responsible for data acquisition. B.Q., M.J.S., A.O., A.L., J.L. and P.S. were responsible for data analysis/interpretation. B.Q., M.J.S., A.O. and P.S. were responsible for statistical analysis. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for

the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the Spanish Society of Nephrology under licence/by permission. Data will be shared upon request to the corresponding author with permission of the Spanish Society of Nephrology.

CONFLICT OF INTEREST STATEMENT

B.Q. has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme and Otsuka. M.J.S. reports honorarium for conferences, consulting fees and advisory boards from AstraZeneca, Novo Nordisk, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, ICU Medical and Boehringer Ingelheim. A.O. has received consultancy or speaker fees or travel support from Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Otsuka and Vifor Fresenius Medical Care Renal Pharma and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes. C.J.J.M. has received honoraria for one conference from Vifor-Pharma. P.d.S. reports honorarium for conferences, consulting fees and advisory boards from Amgen, Astellas, AstraZeneca, Baxter, Braun, Fresenius Medical Care, GlaxoSmithKline, Nipro, Otsuka, Sandoz, Nipro and Vifor-Pharma. She is the present president of the Spanish Society of Nephrology. The remaining authors have no conflicts to declare.

APPENDIX

SENCOVAC collaborative network:

María Teresa Jaldo Rodríguez, Rafael Lucena Valverde, Marta Puerta Carretero, Mayra Ortega Díaz, Daniel Gaitán Tocora, Esther Rodriguez Suárez, Alfredo José Sáenz Santolaya, Patricia Arribas Cobo, Tamar Talavan, Raquel Cerrajero Calero (Hospital Universitario Infanta Leonor);

Carolina Gracia-Iguacel, Emilio González-Parra, Mónica Pereira, Catalina Martin-Cleary, Ana Ramos-Verde (Hospital Fundación Jiménez Díaz);

Martín Giorgi, Carmen Sánchez, Yohana Gil Giraldo, Ana Sánchez Horrillo, Pablo Ruano Suárez, Antonio Fernández Perpén, Andrés Fernández Ramos, Laura Salanova Villanueva, Alejandra Cortiñas, Pablo A. Díez Arias, Alicia Cabrera Cárdenas, Antonio de Santos, Almudena Núñez, Guillermina Barril Cuadrado, Loreto Mariscal de Gante, Raquel Repollet, Concepción Redondo Polo (Hospital Universitario de la Princesa);

Francesc Moreso, María Antonieta Azancot, Natalia Ramos, Oriol Bestard Nestor Toapanta, Ignacio Cidraque, Sheila Bermejo, Irene Agraz, Oreto Prat, Carlota Medina, Emma Pardo, Oreto Prat, Alejandro Saiz (Hospital Vall D'Hebrón);

Maria Antònia Munar Vila (Hospital Son Espases);

Secundino Cigarrán Guldris, Nicolás Menéndez Granados, María Jesús Corton Cabo, Walter López Alarcón (Hospital Da Mariña);

Soledad Pizarro Sánchez, Simona Alexandru, Laura García Puente Suarez, Saul Pampa Saico, Marisol Poma Tapia (Hospital Rey Juan Carlos);

Rocío Zamora, Rosa Sánchez Hernández, Laura Rodríguez Osorio (Hospital Universitario de Villalba);

Nuria García-Fernández, Paloma Leticia Martin Moreno, Noelia Ania González, Ana Sabalza Ortiz, María Nieves Bastida Iñarrea (Clínica Universidad de Navarra);

Sagrario Soriano Cabrera, Raquel Ojeda López, Cayetana Moyano Peregrí, Maria Luisa Agüera Morales, Maria Dolores Navarro Cabello (Hospital Reina Sofía de Córdoba);

Auxiliadora Mazuecos, Teresa García, Carlos Narváez, Cristhian Orellana (Hospital Universitario Puerta del Mar);

María Gabriela Sánchez Márquez, Carolina Lancho Novillo, Pedro Luis Quirós Ganga, Fernando Vallejo Carrión, Antonio Luis García Herrera (Hospital Universitario Puerto Real);

Natalia Blanco Castro (Hospital Quirón Salud A Coruña);

Rosa María Ruiz-Calero Cendrero, María Victoria Martín Hidalgo-Barquero, Román Hernández Gallego, Álvaro Alvarez, Eva Vázquez Leo (Hospital Universitario de Badajoz);

José Luis Pizarro León, Manuel Antonio Martínez García, Benaldina García Jiménez, Virginia Olinda Gómez Pérez, Juan de Dios Ramiro Moya, Diana López Espinosa, Alejandro Jiménez Herrador, Manuel Navarro Zurita, Leonardo Díaz Álvarez, Álvaro González Martínez, Sandra Báez Arroyo, Raquel Reina Fernández, Marlyn Janella Suárez Vargas, Rocío Calurano Casero (Diaverum Andalucía);

Gustavo Useche, Amparo Bernat García, Ana Beatriz Muñoz Díaz, Carmen Santamaría de Miguel, Ángel Palacios, Brenda Henningsmeyer, Esther Orero Calve, José Lacueva Moya, Yurika Sato, Marta Serra Marín, Sandra Tejedor (Diaverum Valencia);

Shaida Martínez Vaquera, Manuel Carnerero di Riso, Irene Torres, Georgina Alfaro, Olga Halauko, Fouad El Rifai, Ana Dolores Martínez (Diaverum Murcia-Alicante);

Pablo Justo Ávila (Diaverum Baleares);

Christian Alfaro Sánchez (Diaverum Galicia–Castilla y León);

Marta Sanz Sainz (Diaverum Madrid);

José María Baltar Martín, Laura del Río García, José Luis Pérez Canga, Paola Milena Villabón Ochoa (Hospital Universitario San Agustín);

Laura Muñiz Pacios, Lina León Machado (Hospital Infanta Cristina);

Augusto Quiroz Morales, Ignacio Manzur Cavalotti, Itziar Navarro Zorita, Sol Otero López, Sara Outon González, Carlos Soto Montañez (Consorci Sanitari Alt Penedès);

Auxiliadora Bajo Rubio, Gloria Del Peso Gilsanz, Marta Ossorio Gonzalez, Rafael Sánchez Villanueva, Maria Ovidia Lopez Oliva (Hospital Universitario de la Paz);

Jesús Calviño Varela, Alba García Enríquez, Carmen Cobelo Casas, Pablo Otero Alonso, Lourdes González Tabares (Hospital Lucus Augusti);

José María Lamas Barreiro, Luisa Palomares Solla, Arginino Gándara, Walfred Nájera de la Garza, Francisco Fernández Fleming, María Gloria Rodríguez Goyanes, Cintia Caramés Feijoo, María Mercedes Moreiras Plaza, Cristina Bayón Juan (Complejo Hospitalario Universitario de Vigo);

Gabriel de Arriba de la Fuente, Katia Pérez del Valle (Hospital Universitario de Guadalajara);

Francisco Javier Pérez Contreras, Noelia Balibrea Lara, Dioné González Ferri, Eduardo Muñoz de Bustillo Llorente (Hospital General de Alicante);

Enriqueta González Rodríguez (Hospital Cruz Roja de Gijón);

Virginia Lopez De La Manzanara Perez, Marta Calvo Arevalo, Jose Antonio Herrero Calvo (Hospital Clínico San Carlos);

María Rosario Llópez Carratalá, Leyre María Martin Rodríguez, Marisa Serrano Salazar, Begoña Bravo Prieto, José María Portolés Pérez (Hospital Universitario Puerta de Hierro);

Antonio Gil Paraíso, Emma Huarte, M. Lanau (Hospital San Pedro);

Rodrigo Avellaneda Campos, José Manuel Ubé (Fundación Hospital Calahorra);

Isabel Berdud Godoy, Esther Torres Aguilera, Rolando Tello Alea, Margie Soledad Del Rosario Saldaña (FMC San Rafael);

Mercedes Salgueira, Nuria Aresté, María de los Ángeles Rodríguez, Rocío Collantes, Ana Isabel Martínez, María Jesús Moyano, Elena Jiménez Víbora (Hospital Virgen Macarena de Sevilla);

Sandra Castellano Gash, Lara Ruíz Martínez (FMC Madrid-Dialcentro);

María Cinta Aguilar Cervera, María Teresa Rodrigo De Tomas, Beatriz Azcue Prieto, Carmen Toyos, José Molina Del Rio, Adriana Restrepo Acosta, Amagoia Celayeta Zamacona (Hospital Universitario de Donosti);

Mª Isabel Jimeno Martin, Saioa Bilbao Ortega, Mª Isabel Gallardo Ruiz, Ainhoa Hernando Rubio, Paula Garcia Ledesma, Alvaro Goyoaga Alvarez (Hospital de Galdakao);

Esteban Poch, David Cucchiari, José Broseta Monzo (Hospital Clinic de Barcelona);

Beatriz Escamilla Cabrera, Aurelio Pastor Rodríguez Hernández, María Sagrario García Rebollo, Juana Margarita Rufino Hernández (Hospital Universitario de Canarias);

Alejandra Yugueros González, Juan Carlos Alonso, Amparo Martínez Más, Manuel Calvé, Marina Garces Cardona, Vanesa Canto Balaguer (Hospital Lluis Alcanyis);

José Ignacio Minguela Pesquera (Hospital de Basurto);

Eva Cotilla de la Rosa, David Rodríguez Santarelli, Alba Santos Garcia, Antonio Cabezas Martin-Caro, Inmaculada Martinez Santamaria (Hospital de Vinalopó);

Michal Cervienka. Ana María Urraca de la Pisa, Lidia Sendino Monzon, Karina Ampuero Anachuri, Esther Hernández Garcia, Victoria Oviedo Gomez (CAU Palencia);

Raquel Santana Estupiñán, Francisco Valga Amado, Patricia Pérez Borges (Hospital Universitario Doctor Negrín);

Marta Durán Beloso, Fernanda Arroyo Alonso, Noemí Pérez Felpete, Ana Meizoso Ameneiro, Mónica Cunha Mera (Hospital Arquitecto Marcide);

Beatriz Gil Casares (Hospital Universitario del Sureste);

Sofía Zarraga Larrondo, Naroa Maruki Kareaga, Ainhoa Inza San Salvador del Valle, Ana Rosa Muñoz García (Hospital de Cruces);

Blanca Villacorta Linaza, Nuria del Toro Espinosa, Paola Estupiñan Perico, José Manuel Sánchez Oliva (Clínica Santa Isabel);

Joaquín Manrique, Itziar Castaño, Carolina Purroi; Nerea Gómez, Cristina Mansilla, Ane Utzurrum (Complejo Hospitalario de Navarra);

Manuel Ramírez de Arellano Serna (Consorci Sanitari de Terrasa);

Luis Guirado Perich (Fundación Puigvert);

María Muñiz Rincón, Virginia Lopez De La Manzanara Perez, Marta Calvo Arevalo, Jose Antonio Herrero Calvo (Hospital Clínico San Carlos);

Jesús Grande Villoria (Complejo Hospitalario de Zamora);

Alfonso Pobes Martínez De Salinas (Hospital Álvarez Buylla de Mieres).

REFERENCES

1. Ortiz A, Cozzolino M, Fliser D *et al.* Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant* 2021;**36**:87–94. https://pubmed.ncbi.nlm.nih.gov/33340043/
2. Soler MJ, Jacobs-Cachá C. The COVID-19 pandemic: progress in nephrology. *Nat Rev Nephrol* 2022;**18**:80–1. https://pubmed.ncbi.nlm.nih.gov/34873314/
3. Quiroga B, Soler MJ, Ortiz A *et al.* Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study. *Nephrol Dial Transplant* 2021;**37**:1868–78. https://pubmed.ncbi.nlm.nih.gov/34788858/
4. Quiroga B, Soler MJ, Ortiz A *et al.* Loss of humoral response 3 months after SARS-CoV-2 vaccination in the CKD spectrum: the multicentric SENCOVAC study. *Nephrol Dial Transplant* 2022;**37**:994–9. https://pubmed.ncbi.nlm.nih.gov/35022757/
5. Quiroga B, Soler MJ, Ortiz A *et al.* Humoral response to third dose of SARS-CoV-2 vaccines in the CKD spectrum. *Clin J Am Soc Nephrol* 2022;**17**:872–6. https://pubmed.ncbi.nlm.nih.gov/35551070/
6. Midtvedt K, Vaage JT, Heldal K *et al.* Fourth dose of the SARS-CoV-2 vaccine in kidney transplant recipients with previously impaired humoral antibody response. *Am J Transplant* 2022;**22**:2704–6. https://pubmed.ncbi.nlm.nih.gov/35533010/
7. Cristelli MP, Nakamura MR, Viana LA *et al.* The fourth dose of CoronaVac vaccine results in a small increase of seroconversion and antibody values among kidney transplant recipients. *Transplantation* 2022;**106**:e420–1. https://pubmed.ncbi.nlm.nih.gov/35698262/
8. Einbinder Y, Perl J, Nacasch N *et al.* Humoral response and SARS-CoV-2 infection risk following the third and fourth doses of the BNT162b2 vaccine in dialysis patients. *Am J Nephrol* 2022;**53**:586–90. https://pubmed.ncbi.nlm.nih.gov/35850101/
9. Bates TA, Leier HC, Lyski ZL *et al.* Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. *Nat Commun* 2021;**12**:5135. https://pubmed.ncbi.nlm.nih.gov/34446720/
10. Caillard S, Thaunat O, Benotmane I *et al.* Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. *Ann Intern Med* 2022;**175**:455–6. https://pubmed.ncbi.nlm.nih.gov/35007148/
11. Bar-On YM, Goldberg Y, Mandel M *et al.* Protection by a fourth dose of BNT162b2 against Omicron in Israel. *N Engl J Med* 2022;**386**:1712–20. https://pubmed.ncbi.nlm.nih.gov/35381126/

12. Guo Y, Han J, Zhang Y *et al.* SARS-CoV-2 Omicron variant: epidemiological features, biological characteristics, and clinical significance. *Front Immunol* 2022;**13**:877101. https://pubmed.ncbi.nlm.nih.gov/35572518/
13. Muhsen K, Maimon N, Mizrahi AY *et al.* Association of receipt of the fourth BNT162b2 dose with Omicron infection and COVID-19 hospitalizations among residents of long-term care facilities. *JAMA Intern Med* 2022;**182**:859–67. https://pubmed.ncbi.nlm.nih.gov/35737368/
14. Benotmane I, Velay A, Gautier-Vargas G *et al.* Pre-exposure prophylaxis with 300 mg Evusheld elicits limited neutralizing activity against the Omicron variant. *Kidney Int* 2022;**102**:442–4. https://pubmed.ncbi.nlm.nih.gov/35618094/

Received: 3.9.2022; Editorial decision: 27.10.2022