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Journal

Kidney Medicine, 5(11)

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Publication Date

2023-11-01

DOI

10.1016/j.xkme.2023.100718

Peer reviewed

Kidney Medicine

Serial SARS-CoV-2 Antibody Titers in Vaccinated Dialysis Patients: Prevalence of Unrecognized Infection and Duration of Seroresponse

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Rationale & Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are likely underdiagnosed, but the degree of underdiagnosis among patients receiving maintenance dialysis is unknown. The durability of the immune response after the third vaccine dose in this population also remains uncertain. This descriptive study tracked antibody levels to (1) assess the rate of undiagnosed infections and (2) characterize seroresponse durability after the third dose.

Study Design: Retrospective observational study.

Setting & Participants: SARS-CoV-2-vaccinated patients receiving maintenance dialysis through a national dialysis provider. Immunoglobulin G spike antibodies [anti-spike immunoglobulin (Ig) G] titers were assessed monthly after vaccination.

Exposures: Two and 3 doses of SARS-CoV-2 vaccine.

Outcomes: Undiagnosed and diagnosed SARS-CoV-2 infections; anti-spike IgG titers over time.

Analytical Approach: Undiagnosed SARS-CoV-2 infections were identified as an increase in anti-spike IgG titer of ≥100 BAU/mL, not associated with receipt of vaccine or diagnosed SARS-CoV-2 infection (by polymerase chain reaction test or antigen test). In descriptive analyses, anti-spike IgG titers were followed over time.

Results: Among 2,703 patients without previous coronavirus disease 2019 (COVID-19) who received an initial 2-dose vaccine series, 271 had diagnosed SARS-CoV-2 infections (3.4 per 10,000 patient-days) and 129 had undiagnosed SARS-CoV-2 infections (1.6 per 10,000 patient-days). Among 1,894 patients without previous COVID-19 who received a third vaccine dose, 316 had diagnosed SARS-CoV-2 infections (7.0 per 10,000 patient-days) and 173 had undiagnosed SARS-CoV-2 infections (3.8 per 10,000 patient-days). In both cohorts, anti-spike IgG levels declined over time. Of the initial 2-dose cohort, 66% had a titer of ≥500 BAU/mL in the first month, with 24% maintaining a titer of ≥500 BAU/mL at 6 months. Of the third dose cohort, 95% had a titer of ≥500 BAU/mL in the first month after the third dose, with 77% maintaining a titer of ≥500 BAU/mL at 6 months.

Limitations: The assays used had upper limits.

Conclusions: Among patients receiving maintenance dialysis, about 1 in every 3 SARS-CoV-2 infections was undiagnosed. Given this population's vulnerability to COVID-19, ongoing infection control measures are needed. A 3-dose primary mRNA vaccine series optimizes seroresponse rate and durability.

Complete author and article information provided before references.

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Kidney Med. 5(11):100718. Published online August 25, 2023.

doi: 10.1016/j.xkme.2023.100718

Patients receiving maintenance dialysis are particularly vulnerable to poor outcomes from coronavirus disease 2019 (COVID-19), owing to their immunocompromised state, limited ability to physically distance themselves, and high comorbid burden.[1] Studies have shown that the majority of patients receiving dialysis mount a robust immune response to mRNA vaccines,[2,3] but this immune response is weaker and wanes more quickly than in the healthy adult population.[4-6] Additional doses of vaccine augment the immune response, including among those who failed to mount an immune response initially.[7,8] Higher antibody responses have been associated with a reduced incidence of breakthrough infections and reduced morbidity among those infected.[5,9,10]

Severe acute respiratory syndrome (SARS)-CoV-2 infections are likely underdiagnosed, potentially reflecting milder symptoms related to immunity induced by vaccines or previous infections and, potentially, less virulence in evolving strains.[11] The degree of underdiagnosis has not been investigated among patients receiving maintenance dialysis, a particularly unique population in both their risk for exposure and their opportunities for diagnosis given the frequency of contact with the health care system. In addition, the durability of the immune response after additional (third) doses and booster vaccine doses among patients receiving maintenance dialysis remains uncertain. The initial augmentation of the immune response by additional vaccine doses is well-established,[7,8] but longer-term studies have been limited by small sample sizes and infrequent monitoring.[12,13] In this descriptive study, we used serially collected antibody data to (1) identify

PLAIN-LANGUAGE SUMMARY

Patients receiving maintenance dialysis have been particularly vulnerable to COVID-19. Using serially measured antibodies, we found that a substantial proportion (about one-third) of SARS-CoV-2 infections among this population had been missed, both among those who had completed a 2-dose vaccine series and among those who had received a third vaccine dose. Such missed infections likely had only mild or minimal symptoms, but this failure to recognize all infections is concerning. Furthermore, vaccines have been effective among patients receiving dialysis, but our study additionally shows that the immune response wanes over time, even after a third dose. There is therefore a role for ongoing vigilance against this highly transmissible infection.

previously unrecognized SARS-CoV-2 infections based on an increase in titer and (2) characterize the trend of antibody titer levels over 6 months after additional vaccine doses.

METHODS

Antibody Assessment

Dialysis Clinic, Inc (DCI) is a national not-for-profit dialysis provider that cared for ~15,000 patients at 260 outpatient dialysis clinics across 29 states at the onset of COVID-19. Previous work by this group on seroresponse after SARS-CoV-2 vaccination among patients receiving maintenance dialysis is summarized in Table S1. As previously described,[4] since January 2021, physicians at DCI facilities have had available an antibody monitoring protocol for patients, activated by physician order on documentation of receipt of a SARS-CoV-2 vaccine, regardless of the vaccine type or place of administration. Similar to the existing hepatitis B vaccine protocol, the SARS-CoV-2 vaccine protocol documents seroresponse to vaccination by measuring antibody titers as part of the monthly blood draws. The assay measures immunoglobulin G spike antibodies (anti-spike IgG) against the receptor-binding domain of the S1 subunit of SARS-CoV-2 spike antigen. The ADVIA Centaur XP/XPT COV2G assay was used from January 1, 2021 to September 30, 2021, and the manufacturer-updated ADVIA Centaur sCOVG assay was used from October 1, 2021, onward. Both are chemiluminescent semi-quantitative assays that report an index value established with calibrators. These index values were then converted to binding antibody units per mL (BAU/mL),[14] with the COV2G assay providing values between 0 and ≥837 BAU/mL and the sCOVG assay providing values between 0 and ≥1,781 BAU/mL. The manufacturer recommends a threshold equivalent to 45 BAU/mL as representing seropositivity. The handling of values at the upper limit of the assays is described throughout the specific analyses. Data were censored at transplant, kidney recovery, or December 31, 2022, whichever occurred first. If a patient had more than 1 titer assessed in a calendar month, only the first measurement was retained. The handling of missing values is described in the Supplemental Methods (Item S1).

This study was reviewed and approved by the WCG IRB Work Order 1-1456342-1. Statistical analyses were performed using R v4.0.2.

Population

Demographic and clinical data, vaccination dates, and anti-spike IgG titer results were obtained from the DCI electronic health record. This study includes adult patients (aged 18 years or older). Patients within the initial series cohort were included in the third dose subcohort upon receipt of a third dose of SARS-CoV-2 vaccine. The initial series cohort includes all patients who were fully vaccinated (≥14 days after 2 mRNA-1273/Moderna vaccine doses or 2 BNT162b2/Pfizer vaccine doses or 1 Ad26.COV2.S/Janssen vaccine dose) and had at least 1 anti-spike IgG titer assessment after full vaccination by this initial vaccine series and before any subsequent clinical COVID-19 diagnosis or receipt of a third dose. The third dose subcohort is the subset of the initial series cohort who received an additional vaccine dose and had at least 1 anti-spike IgG titer assessment after receipt of the additional vaccine dose and before any subsequent clinical COVID-19 diagnosis or receipt of a fourth dose. An additional vaccine dose is defined as a third monovalent dose for those who received a 2-dose Moderna or Pfizer series initially or as a second monovalent dose for those who received a Janssen dose initially; because the vast majority of included patients received either the Moderna or Pfizer vaccine series initially, we use the notation "third dose" for clarity. For patients who received a fourth dose of vaccine, the handling of these doses is described further in the analytic plan . Analyses were conducted in parallel on each of these cohorts.

Identification of SARS-CoV-2 Infections Based on an Increase in Titer

To minimize the effects of assay variability, a 3-month rolling average of the titers was used for these analyses. We defined undiagnosed SARS-CoV-2 infection as an increase of 100 BAU/mL or more from one rolling average to the next, not including any increase occurring after or up to 7 days before a diagnosed SARS-CoV-2 infection, defined as any positive polymerase chain reaction test or antigen test. This definition of undiagnosed SARS-CoV-2 infection also excludes any increase occurring within 60 days after completing an initial 2-dose mRNA vaccine series, within 90 days after an initial Janssen dose, or within 60 days after receiving an additional (third) vaccine dose. The selection of 100 BAU/mL as a threshold is described

in the Supplemental Methods (Item S1, Fig S1), with a 200 BAU/mL threshold used in sensitivity analyses.

Of note, all DCI patients are screened for COVID-19 symptoms and recent exposure on arrival to the dialysis facility for each hemodialysis treatment or for each peritoneal dialysis encounter, followed by SARS-CoV-2 testing if they screen positive. Positive SARS-CoV-2 tests were captured regardless of where the patient was tested (eg, in the dialysis clinic, at a testing center, at a hospital, or at home), and great care was taken to capture testing results at all sites as this information determines patients' need for isolation during dialysis treatment. Patients were assessed for the first of diagnosed SARS-CoV-2 infection or undiagnosed SARS-CoV-2 infection.

Analytic Plan

Study entry is defined by vaccination against SARS-CoV-2. Analyses were stratified by whether a patient had COVID-19 before receipt of vaccine. Previous COVID-19 status was defined by a positive SARS-CoV-2 polymerase chain reaction test at any time before the date of full vaccination or an anti-spike IgG titer ≥45 BAU/mL before or within 10 days after the first vaccine dose (representing likely undiagnosed COVID-19 at the time of initial vaccine receipt, as suggested by previous studies).[15,16] Analyses were further grouped by vaccine type. Patients were identified as developing diagnosed or undiagnosed SARS-CoV-2 infections during the post-vaccination period as described earlier.

Initial Series Cohort

Analyses of this cohort followed antibody titer levels after completion of the initial series. As a result, for most patients, these levels spanned the change in assay described earlier. To account for this change, analyses placed a limit at ≥837 BAU/mL, the upper limit of the COV2G assay, which was used initially. To assess trends over time, descriptive analyses compared titers by vaccine type. Anti-spike IgG titers were grouped by the month of assessment relative to the date of full vaccination (month 1, 2, etc). These analyses censored titers at the time of SARS-CoV-2 infection (whether diagnosed or undiagnosed) or at receipt of a third vaccine dose.

Third Dose Subcohort

Analyses were stratified by previous COVID-19 status and further grouped by the type of third (additional) vaccine dose received. Analyses of this cohort followed their antibody titer levels from receipt of the third vaccine dose. Because of the timing of the rollout of the third dose, nearly all titers after the third dose were collected after the assay change described above. Therefore, analyses are shown using the sCOVG assay's full range, from 0 to ≥1,781 BAU/mL. The titers at the upper limit of the COV2G assay were adjudicated with the upper limit of the sCOVG assay, ≥1,781 BAU/mL; the reasoning for this is provided in the Supplemental Methods (Item S1).

To assess antibody titer trends over time, descriptive analyses compared titers by type of third vaccine dose. Anti-spike IgG titers were grouped by the month of assessment relative to 14 days after receipt of a third dose (month 1, 2, etc). These analyses censored titers at SARS-CoV-2 infection (whether diagnosed or undiagnosed) or at receipt of a second additional (fourth) dose.

RESULTS

Among DCI patients receiving maintenance dialysis, 4,472 adults received a full SARS-CoV-2 vaccine series and had at

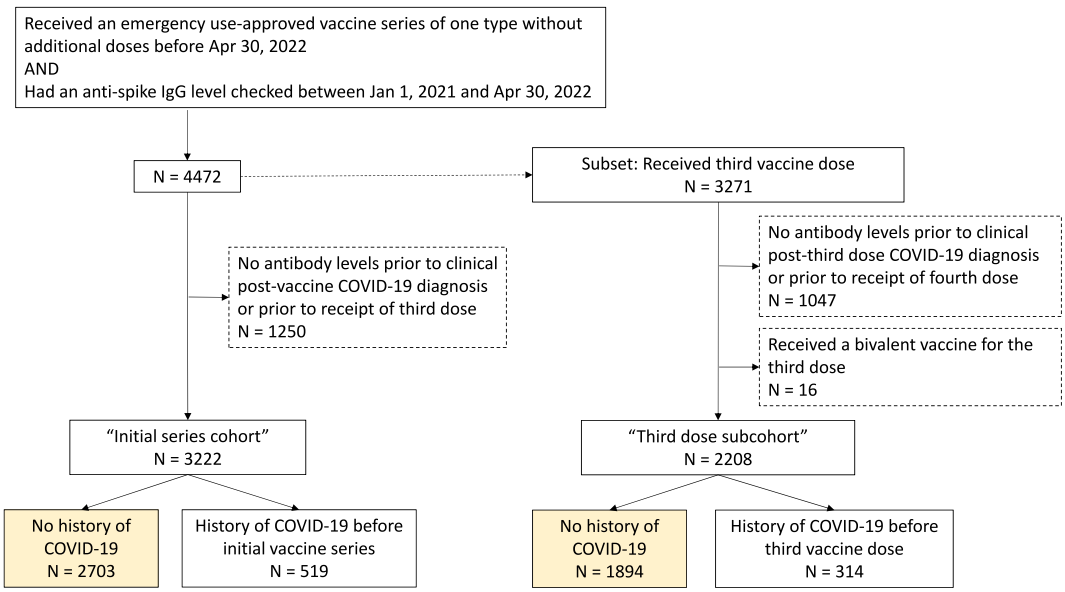


Figure 1. Consort diagram.

Table 1. Baseline Characteristics of Those Without Previous COVID-19

Characteristic	Initial Series Cohort n = 2,703	Third Dose Subcohort n = 1,894
Age, y	64.0 ± 14.1	64.6 ± 13.3
Male sex	1,563 (57.8)	1,135 (59.9)
Race		
Native American	179 (6.6)	130 (6.9)
Asian/Pacific Islander	122 (4.5)	89 (4.7)
Black	640 (23.7)	411 (21.7)
Unknown/Other	306 (11.3)	241 (12.7)
White	1,456 (53.9)	1,023 (54.0)
Hispanic ethnicity	282 (10.4)	252 (13.3)
Dialysis vintage, mo	29.9 (9.1-62.4)	26.4 (5.3-59.6)
Body mass index, kg/m^2	28.8 ± 7.1	29.1 ± 7.2
Diabetes	1,375 (50.9)	975 (51.5)
Long-term care facility	86 (3.2)	45 (2.4)
Modality		
Home hemodialysis	56 (2.1)	43 (2.3)
In-center hemodialysis	2,291 (84.8)	1,594 (84.2)
Peritoneal dialysis	354 (13.1)	255 (13.5)
Unknown	2 (0.1)	—
Albumin, g/dL	3.9 ± 0.4	3.9 ± 0.4
HBsAb ≥10 mIU/mL[a]	1,577 (58.3)	1,041 (55.0)
History of transplantation	144 (5.3)	119 (6.3)
Immunodeficiency[b]	90 (3.3)	68 (3.6)
Immunomodulating medication[c]	227 (8.4)	152 (8.0)
Congestive heart failure	533 (19.7)	364 (19.2)
Peripheral vascular disease	178 (6.6)	108 (5.7)
Cerebrovascular disease	192 (7.1)	137 (7.2)
Chronic obstructive pulmonary disease	203 (7.5)	117 (6.2)
History of cancer	187 (6.9)	139 (7.3)
Duration of follow-up, d	270 (187-454)	259 (175-370)
Time between initial vaccine series and third dose, d	—	178 (143-211)

Note: Vintage and duration of follow-up are reported as median (IQR). All other data are reported as mean ± SD or %. Data on baseline patient characteristics were complete.
[a]HBsAb ≥10 mIU/mL signifies hepatitis B seroimmunity.
[b]Immunodeficiency includes primary immunodeficiency disorders, certain rheumatologic diseases, neoplastic disease, and history of transplantation, as identified by ICD-10 codes.
[c]Immunomodulating medications include anti-inflammatory medications, anti-neoplastic agents, corticosteroids, and certain anti-infective medications.

least 1 anti-spike IgG titer assessment. Of these, 3,222 (72%) had at least 1 anti-spike IgG titer assessment after receipt of an initial vaccine series and before any subsequent COVID-19 diagnosis or receipt of a third dose. Of the 4,472 patients who received a full, 2-dose SARS-CoV-2 vaccine series (or a single dose of the Janssen vaccine), 3,271 (73%) received a third dose. Of these, 2,208 (68%) had at least 1 anti-spike IgG titer assessment after their third dose and before any subsequent COVID-19 diagnosis or receipt of a fourth vaccine dose (Fig 1).

Initial Vaccine Series Cohort

Among the 3,222 patients who completed an initial vaccine series, the mean age was 63 ± 14 years, 1,863 (58%) were male, and 147 (5%) resided in a long-term care facility. (Tables 1 and S2) Among the 519 (16%) patients who had COVID-19 before full immunization by the initial vaccine series, titers largely remained at the upper limit of the assay (Fig S2). For this reason, identification of infection by increase in antibody titer could not be conducted among those with previous COVID-19.

Among the 2,703 patients without a previous history of COVID-19, 271 had clinically diagnosed SARS-CoV-2 infections (3.4 per 10,000 patient-days), and 129 had clinically undiagnosed infections that were identified only by an increase in antibody titer (1.6 per 10,000 patient-days). A greater number of undiagnosed infections occurred in the summer of 2021 and the winter of 2021-2022, overlapping with the Delta and Omicron waves in the United States, respectively (Fig 2).[17] The association of vaccine type with diagnosed and undiagnosed SARS-CoV-2 infections is shown in Table 2. Janssen vaccine recipients had the highest rate of total SARS-CoV-2 infections. Moderna and Pfizer vaccine recipients had

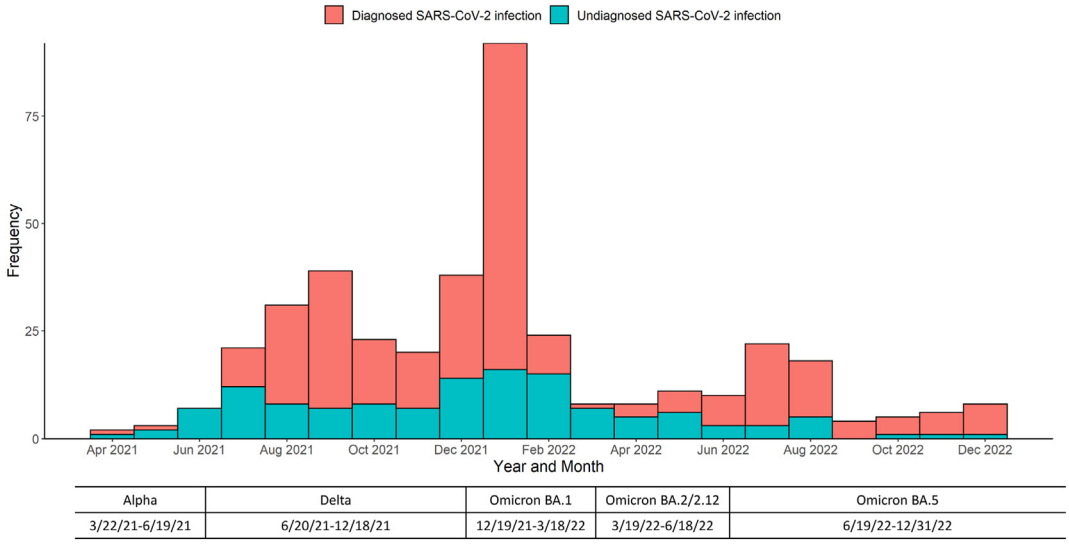


Figure 2. Timing of titer-identified SARS-CoV-2 infections, initial series cohort.

similar rates of total SARS-CoV-2 infections, but Pfizer vaccine recipients had a higher rate of diagnosed infections. In sensitivity analyses using a threshold of an increase of 200 BAU/mL, there were 96 undiagnosed infections identified, a reduction of 33 compared with using the 100 BAU/mL threshold (Table S3).

Antibody titers were tracked over time. Among mRNA vaccine recipients, titers waned over time among those without a previous history of COVID-19 (Fig 3). Among Moderna vaccine recipients, median (IQR) titers were ≥837 (≥837-≥837) in month 1, 279 (118-≥837) in month 6, and 206 (76-≥837) in month 12. Among Pfizer vaccine recipients, median (IQR) titers were ≥837 (384-≥837) in month 1, 122 (46-256) in month 6, and 81 (0-600) in month 12. Only 34% of Moderna vaccine recipients and 16% of Pfizer vaccine recipients still had a titer of at least 500 BAU/mL at 6 months after the initial series in the absence of infection.

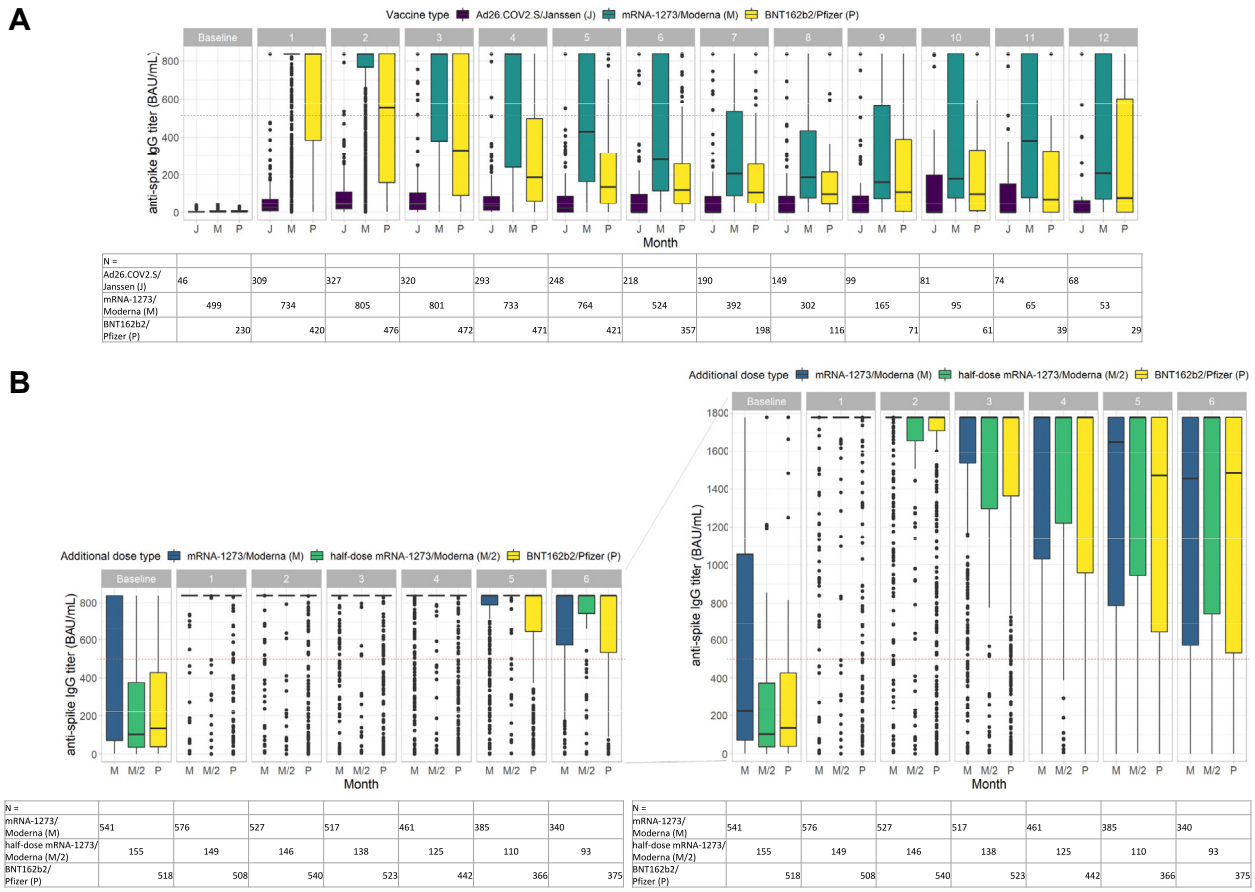
Third (additional) dose cohort

Among 2,208 patients who received a third (additional) vaccine dose, the average age was 64 ± 13 years, 1,314 (60%) were male, and 85 (4%) lived in a long-term care facility (Tables 1 and S2). The breakdown of vaccine type received by initial vaccine series and by third dose is shown in Table S4. Among the 314 (14%) patients who had COVID-19 before the third dose, the 7 recipients of the Janssen vaccine as a third dose and the 21 recipients of the half-dose Moderna vaccine as a third vaccine dose were excluded from analysis because of small sample size. Among the remaining 286 patients, titers largely remained at the upper limit of the assay (Fig S3); accordingly, identification of infection by increase in antibody titer could not be conducted among those with previous COVID-19.

Among the 1,894 patients without a previous history of COVID-19, 316 had clinically diagnosed SARS-CoV-2 infections (7.0 per 10,000 patient-days) and 173 had clinically undiagnosed infections that were identified only by an increase in antibody titer (3.8 per 10,000 patient-days). Many of the otherwise unexplained increases in antibody titer levels occurred from late 2021 into the spring of 2022, coinciding with the Omicron wave in the United States (Fig 4).[17] The association of vaccine type (type of initial series and type of third dose) with diagnosed and undiagnosed infections is shown in Tables 3 and 4, and there was little difference by vaccine type. Although recipients of Janssen vaccine as a third dose had the highest rate of total SARS-CoV-2 infections, there were only 23

Table 2. Association of Vaccine Type With Diagnosed and Undiagnosed SARS-CoV-2 Infections Within the Initial Vaccine Series Cohort, Among Those Without History of COVID-19

Infections	Total (N = 2703)	Ad26.COV2.S/ Janssen (n = 402)	mRNA-1273/ Moderna (n = 1,468)	BNT162b2/ Pfizer (n = 833)
No. of infections				
Diagnosed SARS-CoV-2 infection	271	71	113	87
Undiagnosed SARS-CoV-2 infection	129	36	65	28
Infections per 10,000 patient-d				
Diagnosed SARS-CoV-2 infection	3.4	6.3	2.6	3.5
Undiagnosed SARS-CoV-2 infection	1.6	3.2	1.5	1.1



N =													
Ad26.COV2.S/ Janssen (J)	46	309	327	320	293	248	218	190	149	99	81	74	68
mRNA-1273/ Moderna (M)	499	734	805	801	733	764	524	392	302	165	95	65	53
BNT162b2/ Pfizer (P)	230	420	476	472	471	421	357	198	116	71	61	39	29

N =							
mRNA-1273/ Moderna (M)	541	576	527	517	461	385	340
half-dose mRNA-1273/ Moderna (M/2)	155	149	146	138	125	110	93
BNT162b2/ Pfizer (P)	518	508	540	523	442	366	375

N =							
mRNA-1273/ Moderna (M)	541	576	527	517	461	385	340
half-dose mRNA-1273/ Moderna (M/2)	155	149	146	138	125	110	93
BNT162b2/ Pfizer (P)	518	508	540	523	442	366	375

Figure 3. Anti-spike IgG titers versus months. (A) After date of full immunization by initial vaccine series. (B) After date of full immunization by third vaccine dose, among patients without previous COVID-19. The boxplots shown here are bounded by the upper and lower limits of the assay used. For example, in (A), among the mRNA-1273/Moderna recipients, the median (IQR) titer was ≥837 (≥837-≥837) in month 1 and ≥837 (379-≥837) in month 3. In (B), among the mRNA-1273/Moderna recipients, the median (IQR) titer was ≥1,781 (≥1,781-≥1,781) in month 1 and ≥1,781 (1,534-≥1,781) in month 3; this is shown on the left capped at ≥837 to enable comparison with (A), and it is shown on the right with the updated assay's full range. The dots represent the outliers, defined as greater than 1.5*IQR above the third quartile or less than 1.5*IQR below the first quartile. The tables of n show the number of titers for each month, by vaccine type.

Janssen vaccine recipients in total, compared with 1,871 mRNA vaccine recipients in total. In sensitivity analyses using a threshold of an increase of 200 BAU/mL, there were 119 undiagnosed infections identified, a reduction of 54 compared with using the 100 BAU/mL threshold (Table S3).

Antibody titers were tracked over time after the third vaccine dose. Patients who received the Janssen vaccine as the third dose were excluded because of small sample size (n = 23). Antibody titers waned over time among those without a previous history of COVID-19 (Fig 3B). At least 75% of patients had antibody titers at the assay's upper limit of ≥1,781 BAU/mL during the first month after receiving the third vaccine dose, regardless of vaccine type. By month 6, median (IQR) titer levels had waned to 1,454 (571-≥1781) among Moderna vaccine recipients and 1,483 (532-≥1,781) among Pfizer vaccine recipients. This trend did not notably differ across types. Of note, the waning is only observable because of the increased assay upper limit, and 77% of patients still have an antibody titer of at least 500 BAU/mL at 6 months after the third dose.

DISCUSSION

In this study of patients receiving maintenance dialysis, the first major finding is that a substantial proportion of patients had undiagnosed SARS-CoV-2 infection, comprising about one-third of all SARS-CoV-2 infections, respectively, in the initial vaccine series cohort and the third (additional) dose subcohort, among patients without history of COVID-19 before vaccination. The second major finding of this study is that anti-spike IgG antibody titers were higher and waned more slowly after a third vaccine dose than after an initial vaccine series; after an initial vaccine series, 76% of IgG titer levels had waned to ≤500 BAU/mL by 6 months; by contrast, among those who received a third dose, only 23% of titer levels were ≤500 BAU/mL at 6 months.

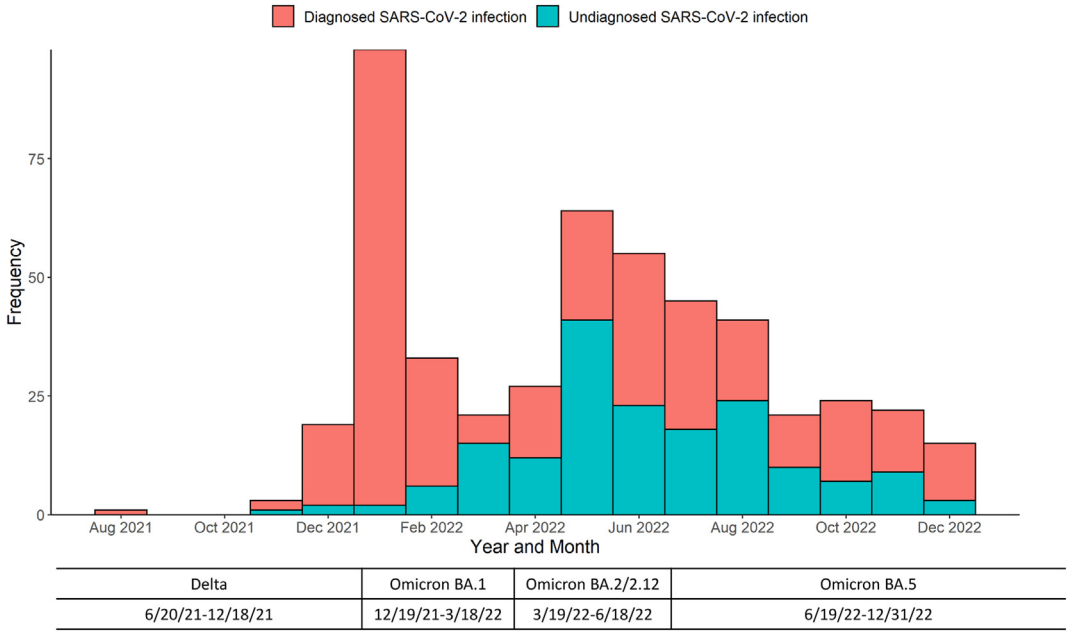


Figure 4. Timing of titer-identified SARS-CoV-2 infections, third dose cohort.

It is notable that, even among a population of patients with frequent health care contact and high utilization, 1 out of every 3 SARS-CoV-2 infections was undiagnosed. Such missed infections likely had only minimal or mild symptoms, and the ability of vaccines to prevent severe COVID-19 (defined by hospitalization for COVID-19 or death) is critical to highlight. At the same time, failure to recognize all SARS-CoV-2 infections remains concerning for patients receiving maintenance dialysis. As medically vulnerable patients who frequently receive care in mandatory congregate settings with high utilization of shared transportation and a high prevalence of long-term care facility residence, the dialysis population is vulnerable to this highly transmissible infection. Other studies on unrecognized SARS-CoV-2 infections either used data from before widespread vaccination of patients receiving maintenance dialysis[18-20] or were conducted in other populations with different risk factors.[21-23] These findings highlight the need for ongoing vigilance against COVID-19 and maintenance of sensible precautions, such as mask utilization and prompt testing in dialysis facilities, particularly during times of high transmission risk.[24]

Antibody levels were higher among recipients of the third vaccine dose beyond the initial series, reinforcing the finding that additional vaccine doses bolster the immune response among patients receiving maintenance dialysis.[7,8,16,25] However, longer-term studies after the immune response after third doses have so far been limited by sample size and infrequent assessment.[12,13] This study used 6 months of post-third dose data to show that third doses also improved the durability of the immune response. In particular, among those without history of COVID-19, median (IQR) titer was 150 (44-477) BAU/mL at 6 months in the initial series cohort, similar to our previous findings,[4,14] but 1,530 (566-≥1,781) BAU/mL at 6 months in the third dose cohort. Thus, a 3-dose mRNA vaccine series appears superior to a 2-dose mRNA vaccine series as a primary vaccine series for patients receiving maintenance dialysis. Although the CDC has recommended a 3-dose initial series for immunocompromised patients,

Table 3. Association of Initial Vaccine Series Type With Diagnosed And Undiagnosed SARS-CoV-2 Infections Within the Third Dose Cohort Among Those Without History of COVID-19

Infections	Total (N = 1,894)	Ad26.COV2.S/ Janssen (n = 138)	mRNA-1273/ Moderna (n = 1,070)	BNT162b2/ Pfizer (n = 686)
No. of infections				
Diagnosed SARS-CoV-2 infection	316	19	184	113
Undiagnosed SARS-CoV-2 infection	173	23	96	54
Infections per 10,000 patient-d				
Diagnosed SARS-CoV-2 infection	7.0	6.2	7.1	7.0
Undiagnosed SARS-CoV-2 infection	3.8	7.5	3.7	3.4

Table 4. Association of Third Vaccine Dose Type With Diagnosed and Undiagnosed SARS-CoV-2 Infections Within the Third Dose Cohort Among Those Without History of COVID-19

Infections	Total (N = 1,894)	Ad26.COV2.S/ Janssen (n = 23)	mRNA-1273/ Moderna (n = 807)	Half-Dose mRNA-1273/ Moderna (n = 215)	BNT162b2/ Pfizer (n = 849)
No. of infections					
Diagnosed SARS-CoV-2 infection	316	9	136	33	138
Undiagnosed SARS-CoV-2 infection	173	2	80	25	66
Infections per 10,000 patient-d					
Diagnosed SARS-CoV-2 infection	7.0	16.8	7.0	7.0	6.8
Undiagnosed SARS-CoV-2 infection	3.8	3.7	4.1	5.3	3.2

patients receiving dialysis are not clearly categorized as immunocompromised.

However, anti-spike IgG antibody titers waned over time, even after an additional vaccine dose, suggesting a need for subsequent administration of boosters. Serial antibody monitoring among patients receiving dialysis could be explored, both to identify high risk patients who may benefit from additional antiviral strategies for COVID-19 and to optimally time future vaccine doses.[25] Indeed, studies have shown that fourth doses additionally increase the immune response.[26-28]

This study has several limitations. First of all, because of the assays having upper limits that changed during the study, we focused on descriptive analyses, since even sophisticated statistical modeling could not adjust for this limitation in the data collection. The assays had upper limits that varied during the study. However, we used multiple methods, including sensitivity analyses, to address this limitation. Second, increases in antibody titer may have occurred because of a delayed response to a vaccine dose or a lab error. We attempted to account for these by excluding increases around the time of vaccine administration and by using a 3-month rolling average, a strategy that does increase the risk of underestimating the number of undiagnosed SARS-CoV-2 infections. We are also unable to identify those with an increase in titer occurring above the assay's limit of detection, potentially underestimating undiagnosed infections. The undiagnosed infections identified in this study occurred during the Delta and Omicron dominant periods, but subsequent patterns of testing and newer Omicron subvariants may affect the future applicability of these results. Finally, the differences by vaccine type are primarily hypothesis-generating because there may have been confounding by geographic distribution.

In conclusion, among patients receiving maintenance dialysis, there was a high rate of undiagnosed SARS-CoV-2 infections, which supports the role of ongoing common sense precautions, such as mask utilization and prompt testing in dialysis facilities, particularly during times of high transmission rates. Higher titer levels and greater durability of titers after a third dose indicate that, among patients receiving maintenance dialysis, a 3-dose mRNA series is likely the optimal primary series. Moreover, we observed that even after an additional vaccine dose, titers still wane over time, and serial redosing of vaccine is likely needed in this vulnerable population.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Distribution of the increase in 3-month rolling antibody level associated with a test-diagnosed SARS-CoV-2 infection.

Figure S2. Anti-spike IgG titers vs months after date of full immunization, comparing by vaccine type, among patients with previous COVID-19 in the initial series cohort.

Figure S3. Anti-spike IgG titers versus months after date of full immunization by third vaccine dose, comparing by vaccine type, among patients with previous COVID-19 in the third dose cohort.

Item S1. Supplemental Methods.

Table S1. Papers by Tufts/DCI Collaboration on Seroresponse After SARS-CoV-2 Vaccination Among Patients Receiving Maintenance Dialysis.

Table S2. Baseline Characteristics of Those With Previous COVID-19.

Table S3. Identification of Undiagnosed SARS-CoV-2 Infections by Increase in Anti-Spike IgG Titer.

Table S4. Among Those Who Received a Third (Additional) Vaccine Dose, the Breakdown of Vaccine Type Received, by Initial Vaccine Series and by Third Dose.

ARTICLE INFORMATION

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Support: This report was supported by Dialysis Clinic, Inc. Dr Hsu has received support from ASN KidneyCure's Ben J. Lipps Research fellowship and from NIH/NCATS grants KL2TR002545 and 1K12TR004384. Dr Hsu's funders had no role in study design, data collection, reporting, or the decision to submit.

Financial Disclosure: Dr Manley, Mr Sanders, Mr Ladik, Dr Frament, Dr Johnson and Dr Lacson Jr are all employees of DCI, where Dr Johnson is vice chair of the board. Dr Hsu, Dr Weiner, Dr Miskulin, Dr Harford, Dr Argyropoulos, Dr Abreo, Dr Chin, Dr Gladish, and Dr Salman receive salary support to their institution from DCI.

Peer Review: Received January 28, 2023 Evaluated by 1 external peer reviewer and an external statistician, with editorial input from an Acting Editor-in-Chief (Editorial Board Member Jordana B. Cohen, MD, MSCE). Accepted in revised form July 31, 2023. The involvement of an Acting Editor-in-Chief to handle the peer-review and decision-making processes was to comply with Kidney Medicine's procedures for potential conflicts of interest for editors, described in the information for authors and journal policies.

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