**Antibody Response to COVID-19 vaccination in Patients on Dialysis**

**Table of Contents**

**Supplemental Methods**  p2

**Supplemental Table 1** Participant characteristics according to SARS-CoV-2 spike protein receptor binding domain antibody status prior to vaccination p5

**Supplemental Table 2** Prevalence of absent or attenuated response among fully vaccinated individuals overall and by age group, at least 14 days after completion of vaccine p7

**Supplemental Table 3** Prevalence of absent or attenuated response among fully vaccinated individuals overall and by age group, at least 28 days after completion of vaccine p8

**Supplemental Table 4** Risk factors for absent or attenuated response to SARS-CoV-2 vaccination in fully vaccinated patients receiving dialysis p9

**Supplemental Table 5** Prevalence of absent or attenuated response among fully vaccinated individuals by vaccine type, at least 14 days after completion of vaccine\* p10

**Supplemental Figure 1** Study flowchart of participants p11

**Supplemental Figure 2a&b** Semiquantitative IgG values in patients receiving Moderna (a) or Pfizer (b)

 p12

**Supplemental Methods**

Our study was conducted in partnership with the dialysis network US Renal Care and Ascend Clinical Laboratory. Ascend Clinical tested remainder plasma of patients for SARS-CoV-2 antibody, and anonymized all patient demographic, comorbidity, and laboratory data prior to transfer to Stanford University. The Institutional Review Board at Stanford University reviewed and approved the study.

*Sample size*

We selected 4,348 patients on follow from the 17,390 patients on dialysis without prior evidence of SARS-CoV-2 infection (as of January 2021) in US Renal Care network. To estimate sample size, we used previously published data on hepatitis B vaccination non-response, as available by age strata from Bruguera et al.1, who evaluated immune response in 270 patients. In this study, the rate of non-response among persons age 20-40, 40-60, and >60 years was 7%, 13%, and 35% respectively. Correspondingly, our estimates of non-response among persons age 18-44, 45-64, ≥65 years was 5%, 15%, and 30% respectively. Estimating these proportions of non-response with an absolute precision of 2%, and oversampling by 15%, resulted in a sample size estimate of 4222 (see Table).

Population and subpopulation sizes by age and number of patients required to obtain a prevalence estimate with the specified absolute precision assuming and the specified proportion of non-response to the vaccine.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age group** | **Proportion of non-response to vaccine** | **Absolute precision** | **USRDS Population count** | **US Renal Care Population size** | **Sample size required** | **Over sample (15%)** |
| 18 to 44 | 5% | 2% | 60,540 | 2,871 | 453 | 521 |
| 45 to 64 | 15% | 2% | 207,022 | 10,605 | 1,218 | 1,401 |
| ≥ 65 | 30% | 2% | 231,588 | 12,777 | 2,000 | 2,300 |
| Total |  |  | 499,150 | 26,253 | 3,671 | 4,222 |

We used systematic sampling with fractional intervals. In systematic sampling the patients are selected from the list using a fixed selection interval, calculated by dividing the total number of patients in the list by the desired number (i.e., 17390/4222 = 4.1). We thus randomly selected one number between 1 and 4 and then selected every 4th patient in the sampling frame sorted by zip code, age, sex and race. This resulted in a sample size of 4348 patients on dialysis; however two sampled patients seroconverted prior to vaccination, thus we followed 4346 patients from January 2021. This cohort comprised the seronegative prior to vaccination cohort (see Supplemental Figure 1).

In addition, since August 2020, we have followed 6551 patients among whom a subset seroconverted prior to vaccination (i.e., developed evidence of natural infection). All 540 patients seropositive as of January 2021, and any additional patients who seroconverted prior to vaccination comprised the “seropositive prior to vaccination cohort” (see Supplemental Figure 1).

**Assay Characteristics:** We tested remainder samples using the Siemens’ total RBD Ig assay, which measures IgG and IgM antibodies, in January 2021 and monthly thereafter in the seronegative prior to vaccination cohort. This assay is reported by the manufacture to have 100% sensitivity and 99.8% specificity for tests performed ≥14 days after a positive reverse transcriptase polymerase chain reaction test2; it has been validated independently with similar performance characteristics3,4. Subsequent to a positive total RBD Ig result in the seronegative and among all patients in the seropositive prior to vaccination cohorts, we tested samples only using a semiquantitative Siemens RBD IgG assay monthly. The Siemens RBD IgG assay is semiquantitative two-step sandwich indirect chemiluminescent assay with a manufacturer reported 95.6% (95% CI: 92.2-97.8%) sensitivity and 99.9% (95% CI 99.6-99.9%) specificity for tests performed ≥21 days post positive reverse transcriptase polymerase chain reaction test. An index value ≥1.0 is considered reactive and an index value of 150 is the upper limit of quantification.

We classified responses as absent total RBD Ig antibody, absent semiquantitative IgG antibody (index value <1), attenuated antibody (semiquantitative IgG index value <10) or medium to high antibody (≥10)5. We chose 10 as a cut-point based on data showing that index values ≥10 corresponded with pseudovirus neutralization titers6 > 1:500 in a study of 26 patients tested by Siemens. An additional study (n=74) evaluating correlation with plaque reduction neutralization test reported index values ≥10 had a positive predictive value of 100% for plaque reduction neutralization test50 >1:80 7,8. Finally, in an external study of patients with inflammatory bowel disease on biologic therapy post SARS-CoV-2 vaccination, 22 of 26 patients with inflammatory bowel disease and all 14 healthcare workers who had completed vaccination exhibited semiquantitive titers with index values > 109.

**Correlates:** We extracted electronic health record data on age, sex, self-reported race and ethnicity, years with end-stage kidney disease, diabetes status, and nursing home status as available. We also extracted monthly laboratory results for serum albumin—a valid surrogate of health status10-13. We used the laboratory value closest to the date prior to vaccination.

**Statistical analysis:** We present demographic data and laboratory values using proportions, mean ± standard deviation (SD) or median, 25th-75th percentile, as applicable. We present the range of semiquantitative IgG titers by vaccine period in the seronegative and seropositive prior to vaccination cohorts. Among patients in the ‘fully vaccinated’ window, we present prevalence and 95% confidence intervals, overall and by age group, of absent or attenuated antibody response in the overall, and seronegative and seropositive prior to vaccination cohorts. Finally, we present these parameters by vaccine type. In a sensitivity analysis, we assessed prevalence of absent or attenuated antibody response after at least 28 days post completion of vaccination. Among participants who completed vaccination, we used a Poisson model with robust standard error to assess risk factors for absent or attenuated antibody response. Data missingness was low (5%), and exclusively due to missing self-reported race/ethnicity. We therefore present results of a complete case analysis inclusive of both cohorts, in which we *a priori* selected the following correlates to test: age, sex, race/ethnicity, diabetes status, vintage of ESKD, and serum albumin. We considered statistical significance at α<0.05. We conducted all statistical analyses with SAS (Cary, North Carolina) or Stata/MP 16.1 (College Station, TX 2019).

**Supplemental Table 1** Participant characteristics according to SARS-CoV-2 spike protein receptor binding domain antibody status prior to vaccination

|  |  |  |
| --- | --- | --- |
|  | **RBD Seronegative prior to vaccination****N=1140** | **RBD Seropositive prior to vaccination****N=493** |
| **Age (years)** |  |  |
| 18 to 44  | 67 (5.9) | 41 (8.3) |
| 45 to 64 | 369 (32.3) | 175 (35.5) |
| 65 to 79 | 491 (43.1) | 198 (40.2) |
| ≥ 80 | 213 (18.7) | 79 (16.0) |
| **Gender** |  |  |
| M | 685 (60.1) | 280 (56.8) |
| F | 455 (39.9) | 213 (43.2) |
| **Race and Ethnicity**  |  |  |
| Hispanic | 225 (19.7) | 116 (23.5) |
| Non-Hispanic white | 431 (37.8) | 169 (34.3) |
| Non-Hispanic Black | 245 (21.5) | 111 (22.5) |
| Non-Hispanic Other | 184 (16.2) | 80 (16.2) |
| Missing | 55 (4.8) | 17 (3.5) |
| **Region** |  |  |
| Northeast | 161 (14.1) | 59 (12.0) |
| South | 314 (27.6) | 120 (24.3) |
| Midwest | 194 (17.0) | 85 (17.2) |
| West | 471 (41.3) | 229 (46.5) |
| **ESKD Vintage (years)** |  |  |
| < 2  | 435 (38.2) | 140 (28.4) |
| 2 – 5  | 361 (31.7) | 181 (36.7) |
| ≥ 5  | 341 (29.9) | 172 (34.9) |
| **Diabetes Status** |  |  |
| Y | 661 (58.0) | 297 (60.2) |
| N | 479 (42.0) | 196 (39.8) |
| **Nursing Home Status** |  |  |
| Y | 56 (4.9) | 19 (3.9) |
| N | 1063 (93.3) | 467 (94.7) |
| **Immunosuppression** |  |  |
| Y | 48 (4.2) | 21 (4.3) |
| N | 1092 (95.8) | 472 (95.7) |
| **Albumin (g/dL)** |  |  |
| ≥ 4.0  | 419 (36.8) | 166 (33.7) |
| 3.5 – 4  | 538 (47.2) | 252 (51.1) |
| < 3.5  | 183 (16.1) | 74 (15.0) |
| **Vaccine Type** |  |  |
| Moderna | 716 (62.8) | 341 (69.2) |
| Pfizer-BNT | 390 (34.2) | 131 (26.6) |
| Johnson & Johnson | 34 (3.0) | 21 (4.2) |

**RBD-receptor binding domain, ESKD-end-stage kidney disease**

**Supplemental Table 2** Prevalence of absent or attenuated response among fully vaccinated individuals overall and by age group, at least 14 days after completion of vaccine\*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Seronegative prior to vaccination cohortN=519 |  | Seropositive prior to vaccination N=91 |
|  | No seroconversion on total RBD Ig | No detectable response on RBD IgG | Attenuated IgG |  | No detectable response on RBD IgG | Attenuated IgG |
| Age (years) |  |  |  |  |  |  |
| 18 to 44  | 9.1% (2.8, 30) | 0% (0, 0) | 4.5% (0.6, 26.2) |  | 0% (0, 0) | 0% (0, 0) |
| 45 to 64 | 6.8% (3.5, 13.1) | 0.9% (0.1, 5.8) | 9.4% (5.3, 16.2) |  | 5.6% (0.8, 31.2) | 5.6% (0.8, 31.2) |
| 65 to 79 | 5.5% (3.2, 9.3) | 3.8% (2.0, 7.2) | 16.5% (12.3, 21.8) |  | 8.3% (3.1, 20.4) | 12.5% (5.7, 25.4) |
| ≥ 80 | 2.8% (1.0, 7.2) | 2.8% (1.0, 7.2) | 18.1% (12.6, 25.2) |  | 8.7% (2.1,29.3) | 13.0% (4.2, 33.9) |
| **Overall** | **5.2% (3.6. 7.5)** | **2.7% (1.6, 4.5)** | **14.8% (12.0, 18.2)** |  | **7.7% (3.7, 15.4)** | **11.9% (6.0, 19.2)** |

\*Data are percentage (95% CI) obtained at least 14 days after two doses of either Moderna or Pfizer-BNT vaccines and 14 days after a single dose of Johnson & Johnson vaccine. Median duration since completion of vaccination was 29 days [25th, 75th percentile: 22, 39 days]. We performed total RBD Ig among all patients in the seronegative prior to vaccination cohort; once a patient seroconverted, we performed the semiquantitative RBD IgG monthly. We performed semiquantitative RBG IgG only among patients known to have a positive total RBD Ig prior to vaccination (seropositive prior to vaccination cohort).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Seronegative prior to vaccination cohortN=355 |  | Seropositive prior to vaccination N=48 |
|  | No seroconversion on total RBD Ig | No detectable response on RBD IgG | Attenuated IgG |  | No detectable response on RBD IgG | Attenuated IgG |
| Age (years) |  |  |  |  |  |  |
| 18 to 44  | 7.1% (1, 37.2) | 0% (0, 0) | 0% (0, 0) |  | 0% (0, 0) | 0% (0, 0) |
| 45 to 64 | 1.4% (0.2, 9) | 0% (0, 0) | 14.9% (8.4, 24.9) |  | 0% (0, 0) | 10% (1.3, 48.1) |
| 65 to 79 | 3.8% (1.7, 8.2) | 3.1% (1.3, 7.4) | 24.5% (18.4, 31.8) |  | 13% (4.1, 34.3) | 17.4% (6.5, 38.9) |
| ≥ 80 | 1.9% (0.5, 7.1) | 4.6% (1.9, 10.7) | 25.0% (17.7, 34.0) |  | 0% (0, 0) | 14.3% (3.5, 43.7) |
| **Overall** | **2.5% (1.3, 4.6)** | **3.2% (1.9, 5.5)** | **20.8% (17.1, 25.1)** |  | **6.3% (2.0, 18.1)** | **14.6% (7.0, 28.0)** |

**Supplemental Table 3** Prevalence of absent or attenuated response among fully vaccinated individuals overall and by age group, at least 28 days after completion of vaccine\*

\*Data are percentage (95% CI) obtained at least 28 days after two full doses of either Moderna or Pfizer-BNT vaccines and 28 days after a single dose of Johnson & Johnson vaccine. We performed total RBD Ig among all patients in the seronegative prior to vaccination cohort; once a patient seroconverted, we performed the semiquantitative RBD IgG monthly. We performed semiquantitative RBG IgG only among patients known to have a positive total RBD Ig prior to vaccination (seropositive prior to vaccination cohort). Among both cohorts the prevalence of no seroconversion on total RBD Ig, no detectable response on RBD IgG and attenuated IgG was 2.8% (1.5, 5.2), 2.8% (1.5, 5.2) and 72.7 (67.8, 77.1) respectively.

**Supplemental Table 4** Risk factors for absent or attenuated response to SARS-CoV-2 vaccination in fully vaccinated patients receiving dialysis

|  |  |
| --- | --- |
|  | Risk Ratio^ |
| **Age (years)** |  |
| <65  | Ref |
| ≥65 | 1.22 (0.81-1.85) |
| **Race and ethnicity** |  |
| Non-Hispanic white | Ref |
| Hispanic | 0.37 (0.21-0.65) |
| Non-Hispanic Black | 0.88 (0.60-1.31) |
| Non-Hispanic Other | 0.61 (0.38-0.98) |
| **ESKD Vintage (years)** |  |
| < 2 | Ref |
| 2 to <5  | 1.39 (0.96-1.99) |
| ≥ 5 | 1.62 (1.11-2.36) |
| **Diabetes**  |  |
| No | Ref |
| Yes | 0.90 (0.66-1.23) |
| **Serum albumin (0.5 g/dL) change** | 0.77 (0.63-0.93) |

^Includes seronegative and seropositive cohorts; adjusted for all presented correlates

**Supplemental Table 5** Prevalence of absent or attenuated response among fully vaccinated individuals by vaccine type, at least 14 days after completion of vaccine\*

|  |  |  |
| --- | --- | --- |
|  |  | Fully vaccinatedN=610 |
|  |  | No detectable response on total RBD or RBD IgG | Attenuated IgG |
| Moderna  | 353 | 2.8% (1.5, 5.2) | 9.1% (6.5, 12.5) |
| Pfizer-BNT | 239 | 9.6% (6.5, 14.1) | 22.6% (17.7, 28.3) |
| Johnson & Johnson | 18 | 83.3% (59.1, 94.5) | 5.6% (0.8, 30.7) |

\*Data are percentage (95% CI) obtained at least 14 days after two full doses of either Moderna or Pfizer-BNT vaccines and 14 days after a single dose of Johnson & Johnson vaccine. We performed total RBD Ig among all patients in the seronegative prior to vaccination cohort; once a patient seroconverted, we performed the semiquantitative RBD IgG monthly. We performed semiquantitative RBG IgG only among patients known to have a positive total RBD Ig prior to vaccination (seropositive prior to vaccination cohort).

**Supplemental Figure 1 Study flowchart of participants** 

\*Seroconversion between August to January

^Semiquantitative IgG titer 14 days post second dose

**Supplemental Figure 2a&b: Semiquantitative IgG values in patients receiving Moderna (a) or Pfizer-BNT (b)**



**References**

1. Bruguera M, Rodicio JL, Alcazar JM, Oliver A, Del Rio G, Esteban-Mur R. Effects of different dose levels and vaccination schedules on immune response to a recombinant DNA hepatitis B vaccine in haemodialysis patients. *Vaccine.* 1990;8 Suppl:S47-49; discussion S60-42.

2. U.S. Food & Drug Administration. EUA Authorized Serology Test Performance. [*https://wwwfdagov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance*](https://wwwfdagov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance)*.* 2020;Date Last Accessed: March 18 2021.

3. Schnurra C, Reiners N, Biemann R, Kaiser T, Trawinski H, Jassoy C. Comparison of the diagnostic sensitivity of SARS-CoV-2 nucleoprotein and glycoprotein-based antibody tests. *J Clin Virol.* 2020;129:104544.

4. Public Health England. Evaluation of sensitivity and specificity of 4 commercially available SARS-CoV-2 antibody immunoassays. [*https://wwwgovuk/government/publications/covid-19-head-to-head-laboratory-evaluation-of-4-commercial-serological-assays*](https://wwwgovuk/government/publications/covid-19-head-to-head-laboratory-evaluation-of-4-commercial-serological-assays)*.* 2020;Date Last Accessed: July 8 2020.

5. Anand S, Montez-Rath, M., Han, J., Garcia, P. Serial SARS-CoV-2 Receptor Binding Domain Antibody Responses in Patients on Dialysis. *Annals of Internal Medicine.* 2021;In press.

6. Legros V, Denolly S, Vogrig M, et al. A longitudinal study of SARS-CoV-2 infected patients shows high correlation between neutralizing antibodies and COVID-19 severity. *medRxiv.* 2020:2020.2008.2027.20182493.

7. Lee WT, Girardin RC, Dupuis AP, et al. Neutralizing Antibody Responses in COVID-19 Convalescent Sera. *J Infect Dis.* 2021;223(1):47-55.

8. Addetia A, Crawford KH, Dingens A, et al. Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate. *medRxiv.* 2020.

9. Wong SY, Dixon R, Pazos VM, et al. Serological response to mRNA COVID-19 vaccines in IBD patients receiving biological therapies. *Gastroenterology.* 2021.

10. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis.* 1990;15(5):458-482.

11. Rocco MV, Soucie JM, Reboussin DM, McClellan WM. Risk factors for hospital utilization in chronic dialysis patients. Southeastern Kidney Council (Network 6). *J Am Soc Nephrol.* 1996;7(6):889-896.

12. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney Int.* 1993;44(1):115-119.

13. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol.* 1999;10(6):1309-1316.