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Antibody responses to the SARS-CoV-2 vaccine in individuals with various inborn errors of immunity

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Background: SARS-CoV-2 vaccination is recommended in patients with inborn errors of immunity (IEIs); however, little is known about immunogenicity and safety in these patients.
Objective: We sought to evaluate the impact of genetic diagnosis, age, and treatment on antibody response to COVID-19 vaccine and related adverse events in a cohort of patients with IEIs.
Methods: Plasma was collected from 22 health care worker controls, 81 patients with IEIs, and 2 patients with thymoma; the plasma was collected before immunization, 1 to 6 days before the second dose of mRNA vaccine, and at a median of 30 days after completion of the immunization schedule with either mRNA vaccine or a single dose of Johnson & Johnson's Janssen vaccine. Anti-spike (anti-S) and anti-nucleocapsid antibody titers were measured by using a luciferase immunoprecipitation systems method. Information on T- and B-cell counts and use of immunosuppressive drugs was extracted from medical records, and information on vaccine-associated adverse events was collected after each dose.
Results: Anti-S antibodies were detected in 27 of 46 patients (58.7%) after 1 dose of mRNA vaccine and in 63 of 74 fully immunized patients (85.1%). A lower rate of seroconversion (7 of 11 [63.6%]) was observed in patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy. Previous use of rituximab and baseline counts of less than 1000 $CD3^+$ T cells/mL and less than 100 $CD19^+$ B cells/mL were associated with lower anti-S IgG levels. No significant adverse events were reported.
Conclusion: Vaccinating patients with IEIs is safe, but immunogenicity is affected by certain therapies and gene defects. These data may guide the counseling of patients with IEIs regarding prevention of SARS-CoV-2 infection and the need for subsequent boosts. (J Allergy Clin Immunol 2021;148:1192-7.)

Key words: *SARS-CoV-2, antibody response, COVID-19, inborn errors of immunity, immunomodulators, immune suppressants, JAK inhibitors, adverse events*

INTRODUCTION

Some groups of immunocompromised patients are at increased risk for severe SARS-CoV-2 infection.[1,2] For patients with inborn errors of immunity (IEIs), some studies have reported an infection fatality rate similar to that in the general population,[3,4] but others have documented increased hospitalization and death rates[5-8] along with younger age at death and prolonged SARS-CoV-2 positivity.[4,5] The nature of the underlying gene defect and associated immunopathology may be important predictors of disease severity and outcome. High morbidity and mortality have been reported in patients with defects of type I interferon production or signaling[9] and in those with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), possibly related to the presence in the latter of neutralizing autoantibodies against type I interferons.[10] Other groups of patients at high risk of severe complications and outcome include those with 22q11del, thymoma, and common variable immune deficiency.[4,5] These data indicate that immunization against SARS-CoV-2 may be particularly important to protect patients with IEIs.

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Abbreviations used
anti-N: Anti-nucleocapsid
Anti-S: Anti-spike
APECED: Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
GM: Geometric mean
HCW: Health care worker
IEI: Inborn error of immunity
LU: Light unit

Lower vaccine efficacy after 2 doses of mRNA vaccines has been reported among certain categories of immunocompromised individuals (solid organ transplant recipients and patients with hematologic malignancies) than among immunocompetent individuals[11,12]; however, limited data are available on the efficacy and safety of COVID-19 vaccines in patients with different genetic forms of IEIs.

Two groups have recently reported vaccine immune responses in patients with IEIs.[13,14] In the study by Hagin et al, 18 of 26 adult patients with predominantly antibody deficiency (70%) developed specific humoral and T-cell responses after 2 doses of SARS-CoV-2 mRNA vaccine.[13] Similarly, in a cohort of 11 patients with predominantly antibody deficiency, only 1 patient with X-linked agammaglobulinemia did not develop anti–SARS-CoV-2 antibodies.[14] However, both studies included relatively few patients, most of whom had antibody deficiencies, making it difficult to draw conclusions on vaccine immunogenicity for a broader range of IEIs. In addition, it is unknown whether the response of patients with IEIs to SARS-CoV-2 immunization may be affected by concomitant or previous therapies, including use of immunosuppressants and hematopoietic cell transplantation.

To address these questions, we performed a longitudinal analysis of SARS-CoV-2–specific anti-spike (anti-S) and anti-nucleocapsid (anti-N) antibody levels in 83 patients with clinical and/or genetic diagnosis of an IEI (n = 81) or thymoma (n = 2) who received SARS-CoV-2 immunization between December 2020 and May 2021 (see Table E1 in the Online Repository at www.jacionline.org). The underlying gene defect was known for 65 of the 83 patients with IEIs. A total of 22 health care workers (HCWs) with a negative history of SARS-CoV-2 infection who received a SARS-CoV-2 vaccine in the same time period served as controls. SARS-CoV-2 antibody testing was performed via luciferase immunoprecipitation systems assay, as previously described[15] (see the Methods section of the Online Repository at www.jacionline.org).

For patients with IEIs, demographic data and information on history of SARS-CoV-2 infection, type of SARS-CoV-2 vaccine received, interval between completion of the immunization schedule and next blood sample collection (see Fig E1 in this article's Online Repository at www.jacionline.org), immunoglobulin replacement therapy, and use of immunosuppressive or immunomodulatory drugs are reported in Table E1 and in the Methods section in the Online Repository.

RESULTS AND DISCUSSION

Results of serology studies were obtained after completion of the immunization schedule (2 doses of mRNA vaccine or 1 dose of Johnson & Johnson's Janssen vaccine) in all 22 HCW controls and in 74 of the 83 patients with immunodeficiency. For the remaining 9 immunodeficient patients, serology results were available only after the first dose of mRNA vaccine. In addition, levels of anti-S and anti-N antibodies were measured at baseline (before immunization) in all of the HCW controls and in 32 of the 83 immunodeficient patients.

All of the HCW controls developed anti-S IgG after the first dose of vaccine, but with broad distribution of antibody levels, and all but 1 reached high (>10^6 light units [LU]) levels after the second dose of the vaccine; that single HCW had received steroids and rituximab (the last dose was administered 6 months before the SARS-CoV-2 vaccine) for antineutrophil cytoplasmic antibody–associated granulomatous vasculitis. In the immunodeficient group, only 27 of 46 patients (58.7%) had a positive anti-S IgG response after the first dose of an mRNA vaccine, but a higher proportion of subjects (63 of 74 [85.4%]; 95% CI = 74.5%-92%) reached anti-S seropositivity after full immunization (Fig 1, *A*), a proportion that is not significantly different from the seroconversion rate (95% CI = 81.5%-100%) observed in the HCWs included in this study and in immunocompetent individuals enrolled in mRNA vaccine immunogenicity trials.[16,17] The levels of anti-S IgG after the first dose of vaccine were not significantly different in the IEI group (a geometric mean [GM] anti-S IgG level of 126,639 LU [95% CI = 81,038-197,899] and in HCW controls (GM = 212,607 LU [95% CI = 152,732-295,954]) (P = .06). However, levels of anti-S IgG after 2 doses of vaccine were significantly lower in the IEI group (GM = 611,938 LU [95% CI = 400,368-935,310]) than in the HCW controls (GM = 2,403,642 LU [95% CI 1,629,352-3,545,886]) (P = .004) (Fig 1, *A*). This diminished response was particularly pronounced among patients with APECED (Fig 1, *B*), likely reflecting use of immunosuppressants in 9 of 14 patients. In particular, among the 11 patients with APECED who received 2 doses of vaccine, none of the 3 patients who had received rituximab mounted a positive anti-S IgG response compared with 7 of 8 who had not received rituximab (P = .004). Although the majority of patients with *STAT3* dominant negative mutations responded to 2 doses of vaccine, variable levels of anti-S IgG antibodies were observed. *STAT3* dominant negative mutations may impair generation of memory B cells[18]; therefore, it will be important to determine the durability of the SARS-CoV-2–specific antibody responses detected in these patients.

Of note, among patients included in the "other IEI" group, 2 of the 4 patients with warts-hypogammaglobulinemia-infections-myelokathexis syndrome failed to produce anti-S antibodies after the first dose of mRNA vaccine and 1 rituximab-treated patient remained negative also after the second dose (Fig 1, *B*). Previous studies have shown that specific antibody titers tend to decline rapidly in patients with warts-hypogammaglobulinemia-infections-myelokathexis syndrome, presumably owing to impaired germinal center trafficking.[19,20] One patient with SASH3 deficiency failed to make anti-S IgG after 2 doses of an mRNA vaccine, which is consistent with the disease phenotype.[21]

In the immunodeficient cohort, a $CD3^+$ cell count of less than 1000 cells/mL at baseline (before vaccination) was associated with lower anti-S IgG levels at the second time point after immunization (Fig 2, *A*). Furthermore, patients with $CD19^+$ cell counts of less than 100 cells/μL at baseline had a significantly lower GM of anti-S IgG levels than did patients with a $CD19^+$ cell count of 100 cells/μL or higher both after the first dose (60,621 LU

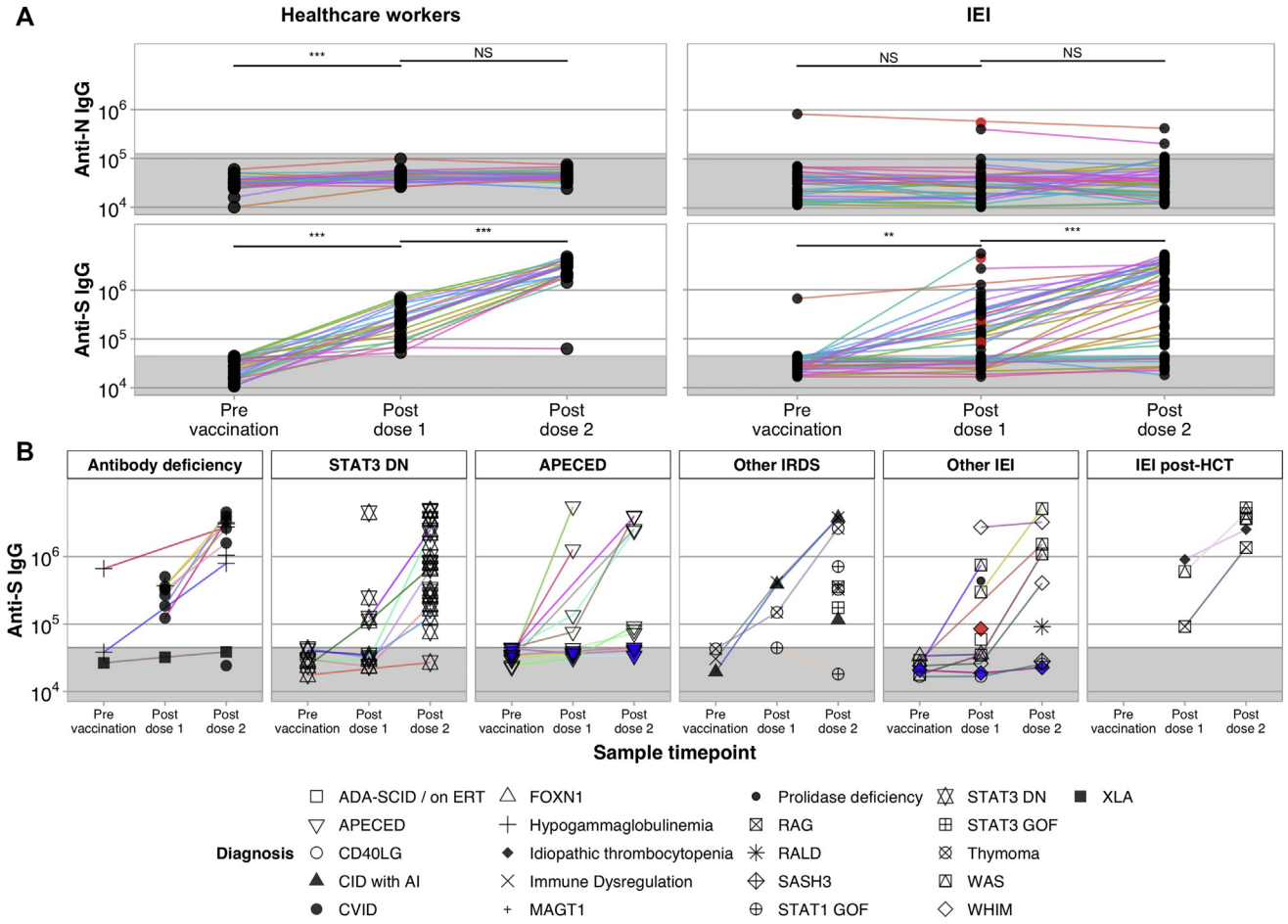

FIG 1. SARS-CoV-2 serology before and after vaccination. **A,** Anti-N and anti-S IgG levels (in LU) in HCWs and in patients with IEIs. **B,** Prevaccination and postvaccination anti-S IgG levels by IEI group. Red symbols indicate patients (2 *STAT3* with dominant negative [DN] mutations and 1 with warts-hypogammaglobulinemia-infections-myelokathexis [WHIM] syndrome) who received Johnson & Johnson's Janssen vaccine; blue symbols indicate individuals (3 with APECED and 1 with WHIM) who had received rituximab. $^{**}P \leq .01$; $^{***}P \leq .001$. *AI,* Autoimmunity; *CID,* combined immunodeficiency; *CVID,* common variable immunodeficiency; *ERT,* enzyme replacement therapy; *GOF,* gain of function; *HCT,* hematopoietic cell transplantation; *IRDS,* immune regulatory disorders; *NS,* not significant; *RALD,* RAS-associated leukoproliferative disease; *WAS,* Wiskott-Aldrich syndrome; *XLA,* X-linked agammaglobulinemia.

[95% CI = 36,185-101,557] vs 200,593 LU [95% CI = 100,634-399,841]; $P = .02$) and after the second dose (268,271 LU [95% CI = 121,944-490,181] vs 905,757 LU [95% CI = 561,442-1,461,230]; $P = .01$) (Fig 2, *B*).

Most patients receiving immunoglobulin replacement therapy developed protective anti-S antibody titers, and the only 2 patients (patients 10 and 75 [see Table E1]) who tested positive for anti-N antibodies after immunization had a history of SARS-CoV-2 infection, which is consistent with the fact that most currently available immunoglobulin preparations are not derived from SARS-CoV-2–exposed donors (Fig 3, *A*). As expected, patients who had received rituximab failed to mount an anti-S IgG response after either dose of the vaccine. In contrast, patients taking Janus kinase inhibitors had preserved humoral immune responses to SARS-CoV-2 vaccine (Fig 3, *B* and *C*). However, more patients with IEIs who are undergoing active treatment with Janus kinase inhibitors need to be studied before it can be concluded that these medications need not be discontinued during immunization. Finally, all 6 subjects with IEIs after hematopoietic cell transplantation developed protective anti-S IgG levels consistent with correction of their primary hematopoietic intrinsic defect (Fig 1, *B*).

The adverse events associated with vaccination included local injection site pain, redness, swelling, and systemic symptoms, and they were observed more frequently in patients with IEIs than in HCWs (see Table E2 in the Online Repository at www.jacionline.org). However, none of the patients experienced severe adverse reactions, the intensity and duration of their symptoms were similar to those reported by immunocompetent individuals, and systemic symptoms tended to occur more commonly after the second dose.[17,22-24] Interestingly, 2 weeks following the second immunization, 1 of the patients with thymoma developed urticaria that was persistent at more than 4 weeks after vaccination.

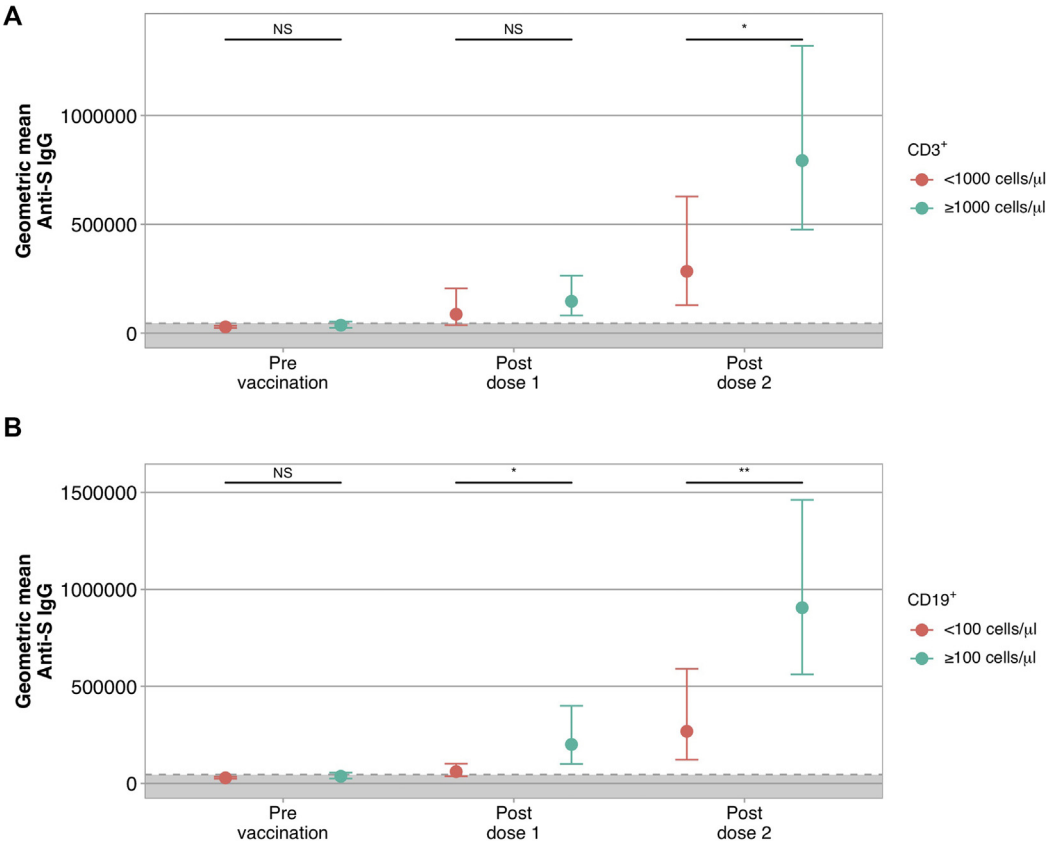

FIG 2. Prevaccination and postvaccination anti-S IgG GM levels in patients with IEIs by level of prevaccination CD3 (**A**) and level of prevaccination CD19 (**B**). Counts of $CD3^+$ and $CD19^+$ cells are expressed as cells/mL. $*P \leq .05$; $**P \leq .01$. *NS*, Not significant.

The limitations of our study include lack of serology data at each of the 3 time points in all patients and the broad time frame within which antibodies were measured after completion of the immunization schedule. Antibody responses were measured for a limited period of time after immunization; however, we plan to monitor levels of anti-S IgG responses during longer-term follow-up to gain insight into the strength and durability of the specific antibody responses in immunocompromised individuals. Although our data have shown that low B-cell counts (owing to underlying IEIs and/or use of rituximab) may affect production of anti-S IgG, measurement of SARS-CoV-2–specific T-cell responses may help assess whether SARS-CoV-2 vaccines induce protective cellular immunity in this group of patients. It is also important to recognize that demonstration of a positive anti-S IgG response cannot be used to indicate protection from infection; on the other hand, inability to produce specific antibodies (as observed in patients with X-linked agammaglobulinemia) may not necessarily lead to an increased risk of severe infection.[25] Finally, some categories of IEIs were not represented or were underrepresented in our study. Patients with phagocytic cell disorders should tolerate vaccination and mount a robust and durable antibody response. On the other hand, whether patients with interferonopathies are at higher risk of serious inflammatory complications following immunization remains to be seen, although incorporation of pseudouridine into mRNA vaccines should decrease such a risk. It will also be important to assess the safety profile of SARS-CoV-2 vaccines in patients with immunodysregulation polyendocrinopathy enteropathy, X-linked because administration of vaccines is known to trigger autoimmune disease exacerbation in these patients. Notably, no autoimmune exacerbation has been noted following SARS-CoV-2 vaccination in the patients with APECED who have been examined thus far.

Notwithstanding these limitations, this study provides useful information on vaccine immunogenicity in patients with IEIs, and it supports the recent recommendation from the Advisory Committee on Immunization Practices that consideration be given to administering an additional dose of COVID-19 mRNA vaccine to individuals with moderate or severe forms of primary immunodeficiencies and those undergoing active treatment with high-dose corticosteroids and biologic immunosuppressive or immunomodulatory drugs who have completed the 2-dose immunization schedule. If validated in independent cohorts, these data may offer the opportunity to counsel patients with IEIs according to their specific genetic diagnosis, immunologic status, and immunomodulatory treatment, including determination of optimal intervals between doses and/or need for additional doses to maximize vaccine efficacy.

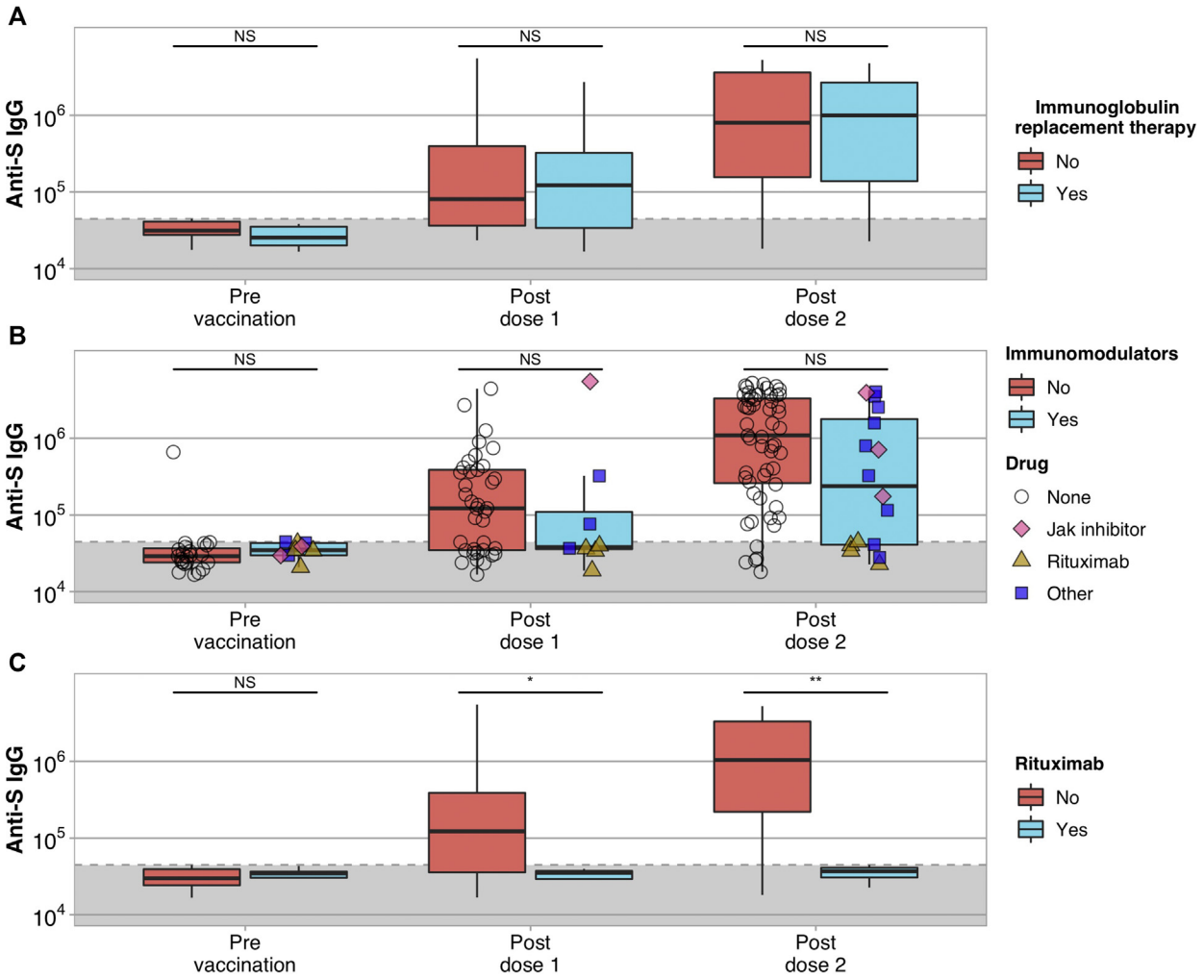

FIG 3. Prevaccination and postvaccination anti-S IgG levels in patients with IEIs by receipt of immunoglobulin replacement therapy (IgRT) (**A**), immunomodulators (**B**), and rituximab (**C**). *Diamonds* indicate Janus kinase (JAK) inhibitors, *triangles* indicate rituximab, *squares* indicate another drug, and *open circles* indicate no drug therapy. $*P \leq .05$; $**P \leq .01$, $***P \leq .001$. *NS*, Not significant.

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Clinical implications: Immunodeficient patients require full immunization against SARS-CoV-2 to produce adequate antibody responses. For patients who fail to respond, infection prevention measures and vaccination of close contacts are important.

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