SARS-CoV-2 Antibody Longitudinal Profile of Immune Globulin Preparations

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ABSTRACT
Introduction:
Intravenous immunoglobulin (IVIG) preparations, used for the treatment of antibody deficiencies, provide a glimpse of the general population's antibody profile as each preparation is generated from a pool of thousands of donors. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the coronavirus disease 2019 (Covid-19) pandemic, and a vaccine for the prevention of Covid-19 was authorized for emergency use in December 2020. We completed a longitudinal analysis of SARS-CoV-2 antibody levels in commercial IVIG preparations.

Materials and Methods:
We collected IVIG samples from our infusion clinic. IVIG product lot number, product name, and manufacturer information were recorded, with the date of preparation verified from the manufacturer. SARS-CoV-2 antibody titers as well as total immunoglobulin levels were measured using commercially available assays. The study received Institutional Review Board approval.

Results:
We found no SARS-CoV-2 antibodies in preparations generated on or before January 2020. Overall, SARS-CoV-2 antibody levels in IVIG preparations tended to increase with progressing preparation date. We observed a dramatic and continual rise of SARS-CoV-2 antibody levels in IVIG preparations made in the beginning after January 2021, coinciding with the peak in incidence of confirmed cases and availability of Covid-19 vaccines in the United States.

Conclusion:
SARS-CoV-2 antibody levels in IVIG mirror case prevalence, and vaccination resulted in a far more rapid rate of rise in antibody levels. IVIG preparations or serum repositories can provide an accessible way to model a population's evolving novel pathogen exposure, immunity, and vaccine response.

INTRODUCTION

Intravenous immunoglobulin (IVIG) is a cornerstone treatment modality for not only patients with primary humoral immunodeficiency but also for a steadily increasing number of indications.[1] IVIG products provide a glimpse of the general population's antibody profile as each preparation is generated from a pool of thousands of donors.[1–3] The Food and Drug Administration requires each IVIG lot to represent a pooling of no less than 1,000 donors.[4] The Food and Drug Administration (Center for Biologics Evaluation and Research) and Plasma Protein Therapeutics Association have recommended IVIG to be generated from pools of 15,000-60,000 donors.[5,6] Also, the efficacy of most vaccinations is measured by quantifying the amount of specific antibody produced in response to the vaccine, and failure to mount a humoral response to immunizations is generally one criterion required to diagnose a humoral or combined immunodeficiency.[6] Thus, IVIG preparations can display a historical picture of the population's exposure history via natural disease as well as population vaccination rates.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the coronavirus disease 2019 (Covid-19) pandemic with cases in the United States tallied from January 2020.[7] Efficacious vaccines for the prevention of Covid-19 were authorized for emergency use in December 2020.[8,9] Manufacturers have reported the increasing presence of anti-SARS-CoV-2 antibodies in IVIG preparations with the rise in infection rates.[2,10] We report the results after examining the increase of SARS-CoV-2 antibody levels using widely available testing in IVIG preparations manufactured at different stages of the Covid-19 pandemic to demonstrate natural and vaccine-induced seroprevalence.

METHODS

We collected IVIG samples from February 2021 to January 2022 at the Walter Reed National Military Medical Center's Allergy & Immunology clinic. The clinic has a large cohort of patients with a primary or secondary humoral immunodeficiency who require regular IVIG infusions. Following completion of an IVIG infusion, samples were collected from IVIG remaining in the infusion tubing that would have otherwise been discarded. IVIG lot number, product name, and manufacturer were recorded. The IVIG products collected were Gammunex-C (Grifols Therapeutics, Inc., North Carolina, USA) and Gammagard Liquid (Baxter Healthcare/Takeda Pharmaceutical Company Limited, California, USA). Preparation date was obtained from manufacturer based on the product's lot number. The IVIG products collected were prepared between August 2019 (before the first confirmed Covid-19 case in the United States) and September 2021.

We tested the collected IVIG samples with commercially available SARS-CoV-2 and associated assays by Labcorp (North Carolina, USA). At the time of this study, Labcorp utilized Elecsys Anti-SARS-CoV-2 immunoassays from Roche (Basel, Switzerland).[11−13] Tests performed included the SARS-CoV-2 Semi-Quantitative Spike Total Antibody (Test #164090), SARS-CoV-2 Nucleocapsid Antibodies (Test #164068), and Quantitative Immunoglobulin G (Test #001776). We also tested for SARS-CoV-2 Antibody Spike IgM (Test #164034) and Quantitative Immunoglobulin M (Test #001792) for sample control. The sensitivity of the SARS-CoV-2 immunoassay is published in the manufacturer's data sheet at the time of this study.[14,15] The sensitivity of these SARS-CoV-2 immunoassays has also been examined by other authors accordingly.[16−18] The SARS-CoV-2 Semi-Quantitative Spike Total Antibody test results were reported in units U/mL at the time of this study as defined by the immunoassay manufacturer (1 nM of Roche standard monoclonal antibodies that binds SARS-CoV-2 spike receptor-binding domain corresponds to 20 U/mL of the assay target).[14]

To examine the potential increase in antibody levels, we log-transformed the SARS-CoV-2 antibody seroprevalence levels in IVIG and fitted a linear regression model. SARS-CoV-2 antibody seroprevalence levels in IVIG are reported alongside the number of Covid-19 cases and Covid-19 vaccine doses administered by date reported per the Centers for Disease Control and Prevention.[7]
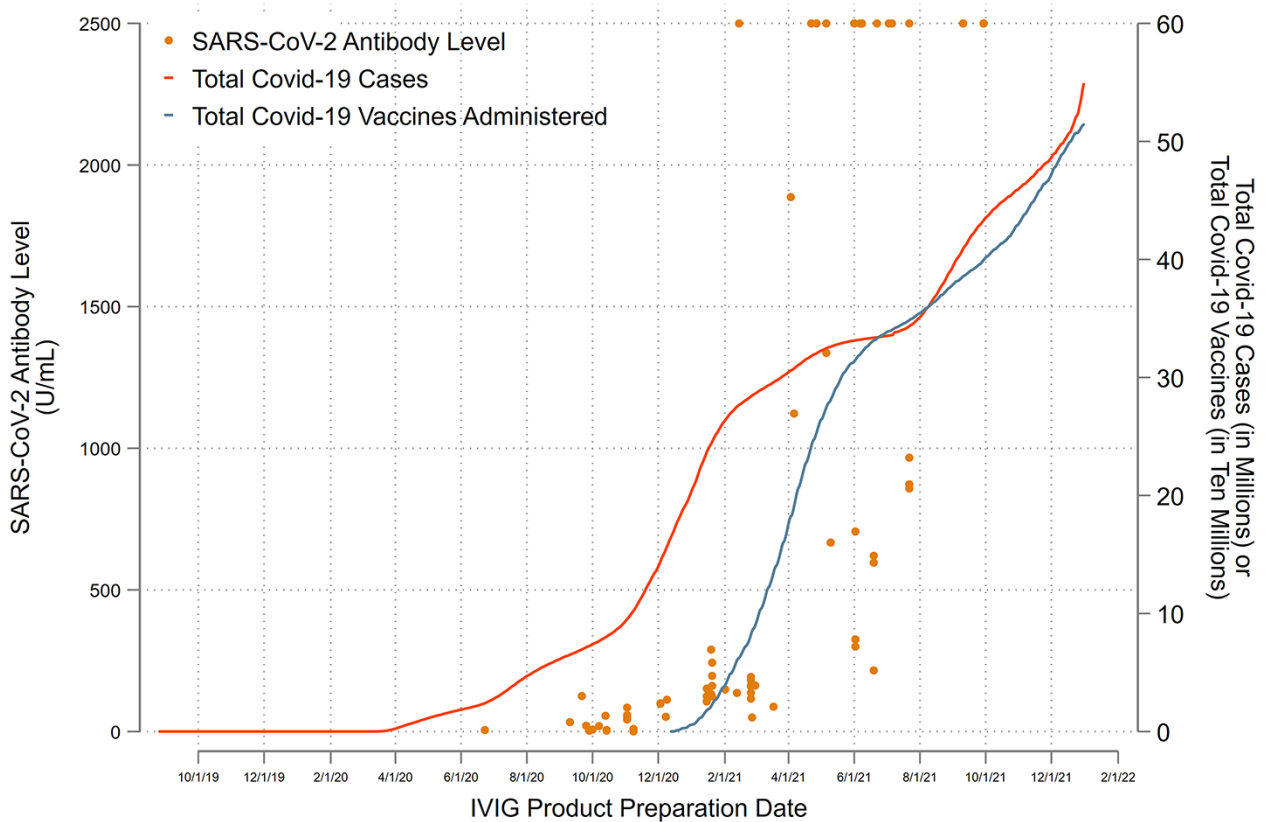
FIGURE 1. Distribution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antibody levels in intravenous immunoglobulin (IVIG) with coronavirus disease 2019 (Covid-19) cases and Covid-19 vaccines administered over time of study. SARS-CoV-2 spike antibody levels of IVIG products prepared between August 2019 and September 2021 (n = 87) (circle). Centers for Disease Control and Prevention's (CDC) cumulative Covid-19 cases (left line) and vaccines administered (right line). Note: SARS-CoV-2 spike antibody levels ≥2,500 U/mL plotted at 2,500 U/mL due to report limit.

RESULTS

No IVIG products we tested that were manufactured on or before January 2020 had any detectable SARS-CoV-2 antibodies. However, we observed an increase in SARS-CoV-2 antibody levels in IVIG products with progressing IVIG product manufacture date, number of total Covid-19 cases, and Covid-19 vaccine doses administered (Fig. 1). This increase in SARS-CoV-2 antibody levels in IVIG products was statistically significant (log of U/ml, $\beta = 0.015$; $P < .001$) (Fig. 2). Prior to vaccine availability in December 2020, we observed SARS-CoV-2 antibodies at increasing levels corresponding with the increasing number of Covid-19 cases. However, we observed a dramatic rise of SARS-CoV-2 antibody levels in IVIG products that coincided with manufacture dates after the availability of Covid-19 vaccines (Fig. 2). Post hoc analysis using a multiple linear regression model showed an increase in SARS-CoV-2 antibody levels after December 2021 ($P = .008$). As the total number of Covid-19 vaccine doses given increased, overall higher SARS-CoV-2 antibody levels were also observed.

In our study, we tested IVIG products that were infused into our clinic's patients between February 2021 and January 2022. The difference between the time of infusion and the manufacture date ranged from 70 to 547 days with an average of 150 days and a median of 116 days. The dates of donor plasma collection are earlier than the date of manufacture or pooling. Our figure presumes dates based on the latest possible date of collection, which is the date of manufacture (Figs 1, 2, and S1).

Labcorp's SARS-CoV-2 Semi-Quantitative Spike Total Antibody test's reported upper limit threshold is 2,500 U/mL. For IVIG products manufactured after January 2021, we noted an increase in products with SARS-CoV-2 antibody levels above 2,500 U/mL. Our report is limited at levels ≥2,500 U/mL in this study, due to the limitations of the available test.

DISCUSSION

Our results found that although SARS-CoV-2 antibody levels in IVIG preparations increase with case prevalence, vaccination resulted in a far more rapid rate of rise in antibody levels. Our results do support the results released from studies from the manufacturers.[2,10,19,20] These data also support the effectiveness of the current vaccines at generating SARS-CoV-2
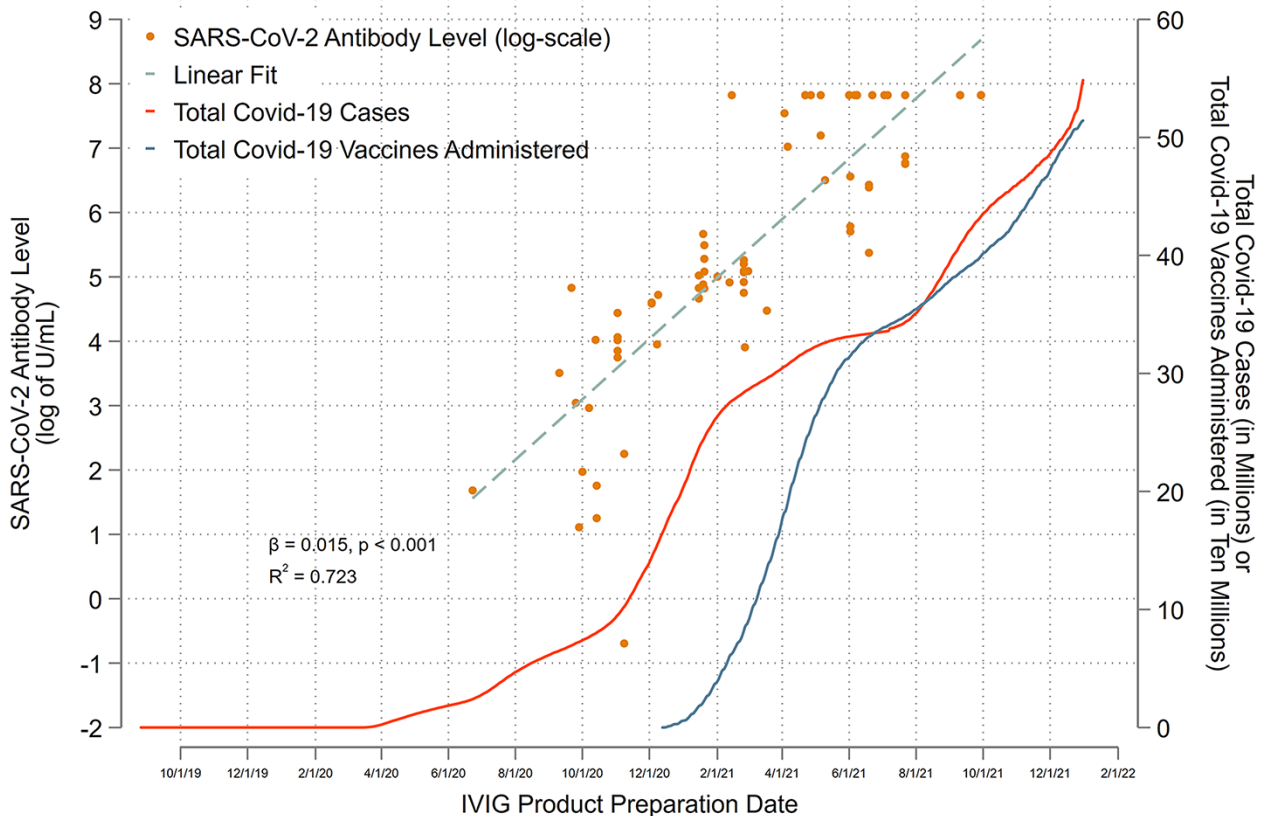
FIGURE 2. Logarithmic trend of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antibody levels in intravenous immunoglobulin (IVIG) with coronavirus disease 2019 (Covid-19) cases and Covid-19 vaccines administered over time of study. SARS-CoV-2 spike antibody levels (log-transformed) of IVIG products manufactured between August 2019 and September 2021 (n = 87) (circle) and their linear fit (dashed line). Centers for Disease Control and Prevention's (CDC) cumulative Covid-19 cases (left line) and vaccines administered (right line). Note: SARS-CoV-2 spike antibody levels ≥2,500 U/mL plotted at 2,500 U/mL due to report limit.

spike-specific antibodies. These results help to understand the natural history of antibody levels in commercial IVIG and indirectly the general population's seroprevalence profile during a pandemic before and after the deployment of a vaccine. In the future, these IVIG collections may also serve to model antibody levels of significant variants of SARS-CoV-2 and new vaccines.

Overall, these IVIG preparations can serve as a historical model of the SARS-CoV-2 antibody profile due to their correlation to case and immunization prevalence. Of course, this model has its limitations as IVIG preparations are generated by a subpopulation of donors whose information is not public. Separately, how much Covid-19 protection these IVIG products provide their recipients is unclear. To date, many Covid-19-specific convalescent plasma studies have not demonstrated protection or treatment benefit in clinical trials.[21-24] But convalescent plasma trials demonstrating clinical benefit have also emerged.[25-27] These inconsistent results reflect that the subpopulation that benefits from Covid-19-specific convalescent plasma is still unknown. In conclusion, the availability of serum repositories and IVIG products provide an accessible and feasible way to trend and monitor a general population's evolving novel pathogen exposure, immunity, and vaccine response. An understanding of our general population's serology may help in elucidating the subpopulations that may benefit from pathogen-specific antibody infusions. Significantly, this study's data also support the efficacy of the Covid-19 vaccines available in the United States.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

CONFLICT OF INTEREST STATEMENT

All authors acknowledge no financial or organizational association that might pose conflict of interest.

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