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Serologic responses to COVID-19 vaccination in children with history of multisystem inflammatory syndrome (MIS-C)

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Abstract

Understanding the serological responses to COVID-19 vaccination in children with history of MIS-C could inform vaccination recommendations. We prospectively enrolled seven children hospitalized with MIS-C and measured SARS-CoV-2 binding IgG antibodies to spike protein variants longitudinally pre- and post-Pfizer-BioNTech BNT162b2 primary series COVID-19 vaccination. We found that SARS-CoV-2 variant cross-reactive IgG antibodies variably waned following acute MIS-C, but were significantly boosted with vaccination and maintained for up to 3 months. We then compared post-vaccination binding, pseudovirus neutralizing, and functional antibody-dependent cell-mediated cytotoxicity (ADCC) titers to the reference strain (Wuhan-hu-1) and Omicron variant (B.1.1.529) among previously healthy children (n = 16) and children with history of MIS-C (n = 7) or COVID-19 (n = 8). Despite the breadth of binding antibodies elicited by vaccination in all three groups, pseudovirus neutralizing and ADCC titers were significantly reduced to the Omicron variant.

1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is a severe systemic inflammatory syndrome characterized by multiorgan involvement, myocardial dysfunction, shock, and occasionally death [1]. The pathophysiology of MIS-C is poorly understood, but it is thought to represent a dysregulated immune response following infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2,3]. Early studies found that MIS-C was associated with a robust serologic response to SARS-CoV-2 [4]. Nevertheless, significant declines in antibody titers are observed by 3 months [5], and the risk of reinfection with SARS-CoV-2 or recurrence of MIS-C following the initial diagnosis remains uncertain. Current Centers for Disease Control and Prevention (CDC) guidelines indicate that children with a history of MIS-C may receive COVID-19 vaccination, but should wait until at least 90 days after onset of MIS-C symptoms [6]. In this study, we aimed to characterize the binding and functional serologic responses to COVID-19 vaccination in children with history of MIS-C.

2. Methods

2.1. Patient cohort

Following informed consent and assent, we prospectively enrolled hospitalized children who met the CDC case definition for MIS-C; children with PCR-confirmed symptomatic COVID-19; and healthy pediatric controls into a specimen collection protocol approved by the Institutional Review Board (IRB) at Emory University. Residual plasma and serum specimens were collected, and if the participant agreed, prospective blood was collected and the plasma and serum isolated. Hospitalized participants were invited to follow up longitudinally for repeat blood collection post-hospitalization; and all participants were invited to follow up...
pre- and post-COVID-19 vaccination. Participants were included in this analysis if they had at least one specimen available at 1 month post-dose 2 of a primary BNT162b2 vaccine series.

2.2. Serologic analyses

Binding IgG antibodies to SARS-CoV-2 full-length spike from multiple strains, including wild-type (Wuhan-hu-1), Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Omicron (B.1.1.529; BA.1), were measured using a Mesoscale Discovery (MSD) V-PLEX SARS-CoV-2 panel per the manufacturer's protocol. Titers were expressed as MSD arbitrary units (AU)/mL.

To perform pseudovirus neutralizing antibody assays, we developed lentiviral particles pseudotyped with either the wild-type (Wuhan-hu-1) or Omicron (B.1.1.529; BA.1) spike proteins [7]. We incubated viral particles with serially diluted patient sera and applied the serum-virus mixture to 293T-ACE2 cells for 48 h at 37°C. Following incubation, we added Britelite Plus (PerkinElmer) luciferase substrate and measured relative luminescence units (RLUs) to determine the effective concentration at which 50% of the virus was neutralized (EC50). The lower limit of detection (LLOD) was defined as the starting dilution of 1:30.

To perform antibody-dependent cell-mediated cytotoxicity (ADCC) assays as previously described [7,8], we generated stably transfected dual-reporter SARS-CoV-2 spike protein target cells lines with inducible expression of either wild-type (Wuhan-hu-1) or Omicron (B.1.1.529; BA.1) spike proteins [7]. We then incubated the induced target cells with serially diluted patient sera and applied the serum-virus mixture to 293T-ACE2 cells for 4 h at 37°C. Following incubation, we added Britelite Plus (PerkinElmer) luciferase substrate and measured relative luminescence units (RLUs) to determine the effective concentration at which 50% of the virus was neutralized (EC50). The lower limit of detection (LLOD) was defined as the starting dilution of 1:30.

2.3. Statistical analyses

Statistical analyses were performed in GraphPad Prism, v9.1.0. Baseline demographic characteristics were summarized using descriptive statistics. Geometric mean titers (GMTs) and geometric 95% confidence intervals (CIs) were determined. All undetectable titers were assigned a value of ½ LLOD. Statistical comparisons of log-transformed titers were made using Wilcoxon or Kruskal-Wallis tests with Dunn’s multiple comparisons test. P-values <0.05 were considered statistically significant.

3. Results

Seven children with MIS-C (4 females, median age 13 years [IQR 12–16 years], month of symptom onset [MOS] range July 2020 to May 2021); 8 with COVID-19 (4 females, median age 14 years [IQR 12–15], MOS range November 2020 to July 2021); and 15 healthy pediatric controls (13 females, median age 13 years [IQR 13–14 years]) were enrolled and had post-vaccine samples available (Table 1). All children with MIS-C were hospitalized at the time of enrollment, 5 (71%) required intensive care, and the median duration of hospitalization was 5 days (IQR 4–7 days). Two children with COVID-19 (25%) were hospitalized, both required intensive care, and the median duration of hospitalization was 9 days (IQR 6–11 days). The timing of enrollment coincided with predominance of the D614G variant, and largely preceded circulation of the Alpha, Delta, and Omicron variants in the U.S. [9] All children with MIS-C (Fig. 1), 5 children with COVID-19 (Supplementary Figure 1), and 8 healthy control participants (Supplementary Figures 2 and 3) had samples available from 3 or more time points to allow for longitudinal analysis.

Binding IgG antibodies to SARS-CoV-2 full-length spike variants were elevated during the acute hospitalization for MIS-C (Fig. 1) and COVID-19 (Supplementary Figure 1), and variably waned prior to vaccination for some participants [10], although these declines were not statistically significant. At the time of hospitalization for acute MIS-C, the wild-type (Wuhan-hu-1) spike IgG GMT was 26,693 (95%CI 16,535 to 43026). At a median follow-up of 191 days (IQR 118–194 days) from MIS-C symptom onset, pre-vaccine binding IgG GMT was 10,880 AU/mL (95%CI 6011 to 19694; p=0.999) (Fig. 1H). Compared to the pre-vaccine titers, IgG increased significantly following 1 dose (GMT 1302247, 95% CI 407,099 to 4165686; p=0.002) and 2 doses (GMT 4982200, 95%CI 292,200 to 7661363; p=0.004) of BNT162b2 vaccine. These titers were maintained at 1 month (GMT 750335, 95%CI 398,850 to 1411564; p=0.003) and 3 month follow-up (GMT 351,595 to 703939; p=0.058), before gradually waning by 6 months (GMT 83230, 95%CI 10,600 to 653489; p=0.999) post-vaccination. Omicron spike IgG titers followed similar longitudinal trends as wild-type spike (Supplementary Figure 4).

We then compared the post-vaccination binding, pseudovirus neutralizing, and ADCC titers to wild-type vs. Omicron variant in
Fig. 1. Longitudinal SARS-CoV-2 spike IgG antibodies in children with history of MIS-C following BNT162b2 primary series vaccination. Antibody titers are expressed in Mesoscale Discovery (MSD) arbitrary units (AU)/mL. Arrows represent vaccine doses #1 and #2. (F) SARS-CoV-2 spike (Wuhan-hu-1 strain) IgG in children with history of MIS-C during acute presentation with MIS-C, pre-vaccine, post-dose #1, post-dose #2 (<14 days), post-dose #2 (1 month), post-dose #2 (3 months), post-dose #2 (6 months) with antibody titers expressed in arbitrary units (AU)/mL. Statistical comparisons (F) of log-transformed titers compared to pre-vaccine titers were performed using Kruskal-Wallis tests with Dunn’s multiple comparisons test. Each dot represents an individual patient, and geometric means and geometric standard deviations are shown. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001.
children with history of MIS-C, COVID-19, and healthy pediatric controls. Samples were collected approximately 1 month following dose 2 of the BNT162b2 primary series for children with history of MIS-C (median 38 days; IQR 34–41 days); COVID-19 (median 35 days; IQR 30–41 days); and healthy pediatric controls (median 34 days; IQR 34–39 days). Post-vaccination binding IgG titers to wild-type (Wuhan-hu-1) spike were significantly higher for the cohort with prior MIS-C compared to healthy controls (MIS-C GMT 750335, 95%CI 398,850 to 1,411,564 vs. healthy GMT 46591, 95%CI 18,591 to 116758; p=0.047) (Supplementary Figure 2). Binding antibodies to the Omicron spike were reduced 3- to 5-fold compared to wild-type spike for all groups (Fig. 2A).

Post-vaccination pseudovirus neutralizing antibody titers to the wild-type strain were similar between the cohorts (Supplementary Figure 2B). However, pseudovirus neutralizing titers to the Omicron variant were significantly reduced compared to wild-type (Wuhan-hu-1) in all three groups, including the healthy control group (20-fold; Wuhan-hu-1 GMT 5684, 95%CI 3532 to 9147 vs. Omicron GMT 284, 95% CI 77 to 1052; p<0.001), children with history of MIS-C (5-fold; Wuhan-hu-1 GMT 10099, 95%CI 3614 to 28,220 vs. Omicron GMT 2032, 95% CI 880 to 4690; p=0.031) and COVID-19 (12-fold; Wuhan-hu-1 GMT 10387, 95%CI 3405 to 31683; vs. Omicron GMT 897, 95%CI 119 to 6748; p=0.031) (Fig. 2B).

Post-vaccination functional ADCC titers to the Wuhan-hu-1 strain were also similar among the cohorts. However, ADCC titers to the Omicron variant were significantly reduced in all three groups, including the healthy pediatric controls (11-fold; Wuhan-hu-1 GMT 1401, 95%CI 868 to 2264 vs. Omicron GMT 131, 95%CI 67 to 257; p<0.001); children with history of MIS-C (5-fold; Wuhan-hu-1 GMT 6151, 95%CI 2654 to 14,258 vs. Omicron GMT 1220, 95%CI 682 to 2181; p=0.016); and children with history of COVID-19 (12-fold; Wuhan-hu-1 GMT 7154, 95%CI 3884 to 13,175 vs. Omicron GMT 585, 95%CI 142 to 2400, p=0.016).

4. Discussion

We analyzed the serologic responses to SARS-CoV-2 wild-type and variant strains among children with a history of MIS-C, COVID-19, and healthy pediatric controls who received a BNT162b2 primary vaccine series. Children with MIS-C and COVID-19 had elevated SARS-CoV-2 spike IgG antibodies against Wuhan-hu-1 during acute hospitalization that variably waned prior to vaccination. Administration of a BNT162b2 primary series boosted broadly cross-reactive binding antibodies in these children which were maintained for up to 3 months. Despite improvements in the breadth of binding antibodies elicited by vaccination in all three groups, the binding, pseudovirus neutralizing, and ADCC titers were significantly reduced against the Omicron variant.

Currently, the CDC advises that children with a history of MIS-C may receive COVID-19 vaccination, but that they should wait at least 90 days following resolution of MIS-C symptoms [6]. The rationale for this delayed interval has been that children with MIS-C are likely to have increasing risk of re-infection as more time elapses from their MIS-C hospitalization. This risk has been balanced with the uncertain risks of adverse effects from vaccination in this unique population. Accumulating evidence has provided reassurance about the safety of COVID-19 vaccination among children with prior history of MIS-C. Among a cohort of 51 children with history of MIS-C who received COVID-19 vaccination, the vaccine was found to be safe and well tolerated during short-term follow-up [11]. A subsequent cross-sectional study of 185 children with history of MIS-C also found that the vaccine was associated with no serious adverse events [12]. Further, a recent multicenter U.S. study demonstrated that a 2-dose primary BNT162b2 vaccine series was 91% effective (95% CI 78% to 97%) in preventing MIS-C [13]. Importantly, no children with history of MIS-C in our study developed recurrent MIS-C or any adverse events requiring medical attention following COVID-19 vaccination.

Recent studies have illuminated immune correlates of protection from COVID-19 illness and hospitalization. For example, an analysis of the ChAdOx1 nCoV-19 (AZD1222) vaccine found that a spike IgG titer of 264 binding antibody units (BAU)/mL (95% CI 108–806) correlated with a vaccine efficacy of 80% against symptomatic infection with majority Alpha (B.1.1.7) variant [10]. Other correlates of protection identified in that study included RBD binding antibodies, pseudovirus neutralizing, and live-virus neutralizing antibodies. An analysis of the mRNA-1273 phase 3 efficacy trial found similar correlates of protection and estimated that neutralizing antibodies mediate approximately two-thirds of mRNA-1273 vaccine efficacy [14]. Nevertheless, a correlate of protection against the Omicron variant has not been established, and the contributions of other humoral responses, such as functional ADCC antibodies, memory B cells, and T cell responses to protective immunity are incompletely understood.

ADCC is one of several functional, non-neutralizing antibody responses elicited by SARS-CoV-2 infection [8,15,16]. While functional antibodies have been found to correlate with COVID-19 severity [15] and mortality [16] in adults, less is known about their role in protection against disease in children. We have previously demonstrated that vaccination elicits broader ADCC and pseudovirus neutralizing antibodies than COVID-19 or MIS-C alone [17]. Future studies are needed to elucidate the role of ADCC,
including variant-specific functional antibodies, in protection against disease.

Our study has some limitations. This was a single-center analysis with a small sample size, and longitudinal samples were lacking for several participants. The infecting strain was not known for children with previous COVID-19 or MIS-C. T cell and memory B cell responses, non-spike antibody responses, and the effects of booster vaccination and bivalent variant-specific vaccination were not ascertained. In conclusion, following hospitalization for MIS-C, binding IgG antibodies variably waned prior to administration of COVID-19 vaccine. A primary BNT162b2 series elicited broadly cross-reactive antibodies that persisted for up to 3 months. Nevertheless, binding and functional antibodies to the Omicron variant were significantly reduced compared to wild-type SARS-CoV-2. Future studies are needed to define the durability of immunity in this unique patient population and the correlates of protection.

Data availability
Data will be made available on request.

Declaration of Competing Interest
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Evan J. Anderson reports a relationship with AbbVie Inc that includes: consulting or advisory. Evan J. Anderson reports a relationship with Medscape LLC that includes: consulting or advisory. Evan J. Anderson reports a relationship with Pfizer Inc that includes: consulting or advisory and funding grants. Evan J. Anderson reports a relationship with Sanofi Pasteur Inc that includes: board membership, consulting or advisory, and funding grants. Evan J. Anderson reports a relationship with AstraZeneca MedImmune that includes: funding grants. Evan J. Anderson reports a relationship with Regeneron Pharmaceuticals Inc that includes: funding grants. Evan J. Anderson reports a relationship with GlaxoSmithKline USA that includes: consulting or advisory and funding grants. Evan J. Anderson reports a relationship with Merck & Co Inc that includes: funding grants. Evan J. Anderson reports a relationship with Novavax Inc that includes: funding grants. Evan J. Anderson reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Evan J. Anderson reports a relationship with Micron Biomedical that includes: funding grants. Evan J. Anderson reports a relationship with Kentucky BioProcessing Inc that includes: board membership. Christina A. Rostad reports a relationship with Biofire Diagnostics Inc that includes: funding grants. Christina A. Rostad reports a relationship with GlaxoSmithKline USA that includes: funding grants. Christina A. Rostad reports a relationship with AstraZeneca MedImmune that includes: funding grants. Christina A. Rostad reports a relationship with Micron Biomedical that includes: funding grants. Christina A. Rostad reports a relationship with Novavax Inc that includes: funding grants. Christina A. Rostad reports a relationship with Merck & Co Inc that includes: funding grants. Christina A. Rostad reports a relationship with Regeneron Pharmaceuticals Inc that includes: funding grants. Christina A. Rostad reports a relationship with Sanofi Pasteur Inc that includes: funding grants. Evan J. Anderson reports a relationship with WIRB-Copernicus Group Inc that includes: board membership. Evan J. Anderson reports a relationship with ACI Clinical that includes: board membership. Christina A. Rostad has patent

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Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest
E.J.A. has consulted for Pfizer, Sanofi Pasteur, Janssen, GSK, and Medscape, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Sanofi-Pasteur, Janssen, and Micron. He also serves on data and safety monitoring boards for Kentucky BioProcessing, Inc., and Sanofi-Pasteur. He serves on a data adjudication board for WCG and ACI Clinical. His institution has also received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines.

C.A.R.’s institution has received funding to conduct clinical research unrelated to this manuscript from BioFire Inc., GSK, MedImmune, Micron, Merck, Novavax, PaxVax, Regeneron, Pfizer, and Sanofi-Pasteur. She is co-inventor of patented RSV vaccine technology, which has been licensed to Meissa Vaccines, Inc. Her institution has received funding from NIH to conduct clinical trials of Moderna and Janssen COVID-19 vaccines.

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Prior Presentations
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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.03.021.
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