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OBSTETRICS

Preserved recognition of Omicron spike following COVID-19 messenger RNA vaccination in pregnancy



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BACKGROUND: SARS-CoV-2 infection is associated with enhanced disease severity in pregnant women. Despite the potential of COVID-19 vaccines to reduce severe disease, vaccine uptake remained relatively low among pregnant women. Just as coordinated messaging from the Centers for Disease Control and Prevention and leading obstetrics organizations began to increase vaccine confidence in this vulnerable group, the evolution of SARS-CoV-2 variants of concerns, including the Omicron variant, raised new concerns about vaccine efficacy because of their ability to escape vaccine-induced neutralizing antibodies. Early data point to a milder disease course following infection with the Omicron variant in vaccinated individuals. Thus, these data suggest that alternate vaccine-induced immunity beyond neutralization may continue to attenuate Omicron variant-induced disease, such as Fc-mediated antibody activity.

OBJECTIVE: This study aimed to test whether vaccine-induced antibodies raised during pregnancy continue to bind to and leverage Fc receptors to protect against variants of concern including the Omicron variant.

STUDY DESIGN: The receptor binding domain or whole spike-specific antibody isotype binding titers and Fc gamma receptor binding directed

toward variants of concern, including the Omicron variant, were analyzed in pregnant women after receiving the full dose regimen of either the Pfizer/BioNTech BNT62b2 (n=10) or Moderna mRNA-1273 (n=10) vaccination using a multiplexing Luminex assay.

RESULTS: Reduced isotype recognition of the Omicron receptor binding domain was observed following administration of either vaccine with relatively preserved, albeit reduced, recognition of the whole Omicron spike by immunoglobulin M and G antibodies. Despite the near complete loss of Fc receptor binding to the Omicron receptor binding domain, Fc receptor binding to the Omicron spike was more variable but largely preserved.

CONCLUSION: Reduced binding titers to the Omicron receptor binding domain aligns with the observed loss of neutralizing activity. Despite the loss of neutralization, preserved, albeit reduced, Omicron spike recognition and Fc receptor binding potentially continue to attenuate disease severity in pregnant women.

Key words: antibodies, Fc γ receptor, mRNA vaccine, Omicron variant, pregnancy, SARS-CoV-2, variants of concern

Introduction

Although SARS-CoV-2 infection is more likely to cause severe COVID-19 in pregnant individuals, pregnancy was an exclusion criterion in initial vaccine trials, leading to delayed vaccine roll-outs for this medically complex population.^{1,2} However, following Emergency Use Authorization approval of COVID-19 vaccines, eligible pregnant individuals volunteered for vaccine trials and observational studies, providing highly needed data on the safety and immunogenicity to inform vaccine

policy. Messenger RNA (mRNA) vaccines proved to be both safe and highly immunogenic when administered throughout pregnancy, giving rise to robust antibody titers that provided critical immunity not only to the mother, but also to the infant via transfer of maternal antibodies across the placenta and into breastmilk.

Despite the exciting progress in mRNA vaccine development with the inclusion of pregnant individuals, the emergence of SARS-CoV-2 variants of concern (VOC), including the novel Omicron variant, that can evade neutralizing antibody responses^{3,4} has led to a global surge in infections.⁵ However, the incidence of severe disease and death rates have not increased in parallel, pointing to the persistence of alternate vaccine-induced immune responses that may continue to attenuate disease. Among the proposed mechanisms by which vaccine-induced antibodies may still prevent severe disease include Fc-mediated antibody effector

functions, such as Fc-mediated opsonophagocytosis and cytotoxicity, which have been linked to survival in severe COVID-19⁶ and vaccine-mediated protection in animal models.^{7,8}

Although pregnant individuals exhibit delayed Fc-mediated effector function maturation after the first mRNA vaccine dose, they elicit a fully functional vaccine-induced Fc-mediated response after the second dose.^{9,10} However, whether the COVID-19 mRNA vaccines elicit antibody-mediated protection against emerging VOCs, including Omicron, is not yet known. Thus, in this study, we profiled the binding titers across VOCs and the Fc receptor binding profiles after 2 doses of either the Pfizer/BioNTech BNT162b2 or Moderna mRNA-1273 vaccine at peak immunogenicity in a group of fully vaccinated pregnant individuals.

Despite the decline in immunoglobulin (Ig)M, IgA, and IgG binding to the receptor binding domain (RBD) or whole spike of the Omicron variant

Cite this as: Bartsch YC, Atyeo C, Kang J, et al. Preserved recognition of Omicron spike following COVID-19 messenger RNA vaccination in pregnancy. *Am J Obstet Gynecol* 2022;227:493.e1-7.

0002-9378

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<https://doi.org/10.1016/j.ajog.2022.04.009>

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AJOG at a Glance

Why was this study conducted?

This study aimed to investigate the COVID-19 messenger RNA vaccine-mediated antibody response to variants of concern in pregnant individuals.

Key findings

Antibody binding titers and Fc gamma receptor (FcγR) binding to the whole Omicron spike were preserved despite marked reductions in the titer and FcγR binding to the Omicron receptor binding domain.

What does this add to what is known?

These data are consistent with the apparent loss of Omicron variant neutralizing titers but demonstrate that preserved Omicron spike-specific antibody binding and Fc receptor ligation may provide a second line of defense against Omicron variant infections.

when compared with other VOCs, spike-specific Fc gamma receptor 2a (FcγR2a) and FcγR3a binding was more variable but relatively preserved across both mRNA vaccine platforms for all VOCs, including Omicron. Thus, despite the significant loss of neutralizing antibody responses to Omicron, the preservation of spike-specific Fc receptor binding immunity may permit ongoing capture and clearance of the virus, providing persistent Fc-mediated protection against severe disease and death.

Materials and Methods**Study population**

To compare vaccine-induced antibody responses against SARS-CoV-2 VOCs in pregnant individuals, samples were obtained from 10 pregnant patients who received the full 2-dose BNT162b2 (Pfizer) vaccine regimen and from 10 pregnant patients who received the full 2-dose mRNA-1273 (Moderna) vaccine regimen at 2 to 4 weeks after the second dose (Table). All participants were ≥18 years old and had an uncomplicated singleton pregnancy. All participants gave informed consent before enrollment and this study was approved by the Mass General Brigham Institutional Review Board (protocol #2020P003538).

Antigens

RBD antigens for the wild-type (WT) (Wuhan), Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) VOCs

were obtained from Sino Biological (Beijing, China). Antigens for the Omicron RBD was generously provided by Moderna Inc (Cambridge, MA). The stabilized (HexaPro) spike of D614G (WT variant) or the VOCs was produced in HEK293 cells as described before.¹¹

Immunoglobulin G subclass, isotype, and Fc gamma receptor binding

Antigen-specific antibody subclass and isotypes and FcγR binding were analyzed by Luminex multiplexing. The antigens were coupled to magnetic Luminex beads (Luminex Corp, Austin, TX) by carbodiimide–N-hydroxysuccinimide ester-coupling with an individual region per antigen. Coupled beads were incubated with different plasma dilutions (1:100 for IgG2, IgG3, IgG4, IgM, and IgA1; 1:500 for IgG1; and 1:1000 for FcγR probing) for 2 hours at room temperature in 384-well plates (Greiner Bio-One, Frickhausen, Germany). Unbound antibodies were washed away and subclasses and isotypes were detected with a specific phycoerythrin-conjugated antibody (anti-human IgG1, IgG2, IgG3, IgG4, IgM, or IgA1) (SouthernBiotech, Birmingham, AL) at a dilution of 1:100. For the analysis of FcγR binding, Phycoerythrin-Streptavidin (Agilent Technologies, Santa Clara, CA) was coupled to recombinant and biotinylated human

FcγR2a, FcγR2b, FcγR3a, or FcγR3b protein. Coupled FcγR was used as a secondary probe at a 1:1000 dilution. After a 1-hour incubation, excess secondary reagent was washed away and the relative antibody concentration per antigen determined on an IQE analyzer (IntelliCyt, Albuquerque, NM).

Statistical analysis

If not stated otherwise, we assumed nonnormal distributions, and plots were generated and statistical differences between 2 groups were calculated using GraphPad Prism V8 (San Diego, CA). A Kruskal-Wallis test with a Benjamini-Hochberg posttest correcting for multiple comparisons was used to test for statistical differences between the WT variant and Omicron variant titer. Significance was defined as $P < .05$.

Results**Reduced, but still detectable, Omicron-specific isotype immunity following mRNA vaccination**

To begin to determine whether mRNA vaccines provide protection against distinct VOCs, we first profiled the IgM, IgA, and IgG isotype-specific binding capacity of the Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 vaccine-induced antibodies among pregnant individuals across the WT, Alpha, Beta, Delta, and Omicron RBD or whole spike antigen (Figure 1, A and B). At the time of the first dose, BNT162b2-vaccinated individuals had a median age of 33 years (range, 29–41) and were 15.9 weeks pregnant (range, 3–22), whereas mRNA-1273-vaccinated individuals were, on average, 33 years old (range, 30–42) and 14.3 weeks pregnant at the time of vaccination (range, 6.1–32.4) (Table). Despite the largely preserved Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 IgM, IgA, and IgG responses to WT, Alpha, Beta, and Delta VOCs RBDs, a consistent and significant ($P \leq .002$) 16- to 24-fold (for BNT162b2) and 10- to 23-fold (for mRNA-1273) loss of IgM, IgA, and IgG binding was noted for vaccine-induced immune responses to the Omicron RBD (Figure 1, A).

In contrast with the marked loss of binding to the RBD, relatively stable anti-spike IgM and IgG binding antibodies against all VOCs, including Omicron, were induced following Pfizer/BioNTech BNT162b2 vaccination in pregnant individuals, whereas IgA responses to the Omicron variant were significantly ($P=.007$) reduced (Figure 1, B). In contrast with Pfizer/BioNTech BNT162b2 vaccination, Moderna mRNA-1273 vaccination led to more consistent IgM and IgG responses and higher IgA responses among pregnant women across the VOCs (Figure 1, B). However, Moderna mRNA-1273 vaccine responses to the Omicron variant were significantly ($P\leq.03$) lower than the binding levels to the WT spike across all 3 isotypes. However, despite the more substantial loss of Omicron-specific isotype binding among Moderna mRNA-1273—vaccinated pregnant individuals, similar levels of Omicron recognition were observed for both mRNA vaccines owing to the overall more uniform or higher titers achieved by the Moderna mRNA-1273 vaccine. Of note, 2 BNT162b2—vaccinated individuals showed low or no detectable antibody titer. Although no specific characteristics (age, gestational age, body mass index) were identified that differed in these individuals when compared with the rest of the cohort, these individuals may represent an expected natural variation in response to mRNA vaccines.¹²

Preserved spike-specific but not receptor binding domain-specific Fc-mediated responses across variants of concern

The ability of antibodies to recruit the antiviral activity of the innate immune system, including opsonophagocytic or cytotoxic function, depends on the ability of antibodies to interact with Fc receptors found on all immune cells.¹³ Among the Fc receptors, 4 low-affinity Fc receptors, namely FcγR2a, FcγR2b, FcγR3a, and FcγR3b in humans drive IgG-mediated activation.¹⁴ Thus, we next compared the ability of mRNA vaccine-induced antibodies to bind VOCs and leverage Fc receptors.

TABLE

Demographic characteristics of mRNA-1273 or BNT162b2 vaccinated pregnant individuals

Sample ID	Vaccine	Gestational age at vaccine dose 1	Gestational age at vaccine dose 2	Maternal age	Prepregnancy BMI
1	Moderna mRNA-1273	10.4	14.4	38	30.9
2	Moderna mRNA-1273	6.1	10.1	35	21.5
3	Moderna mRNA-1273	12.3	16.3	42	21.8
4	Moderna mRNA-1273	21.6	26	32	21.3
5	Moderna mRNA-1273	12.4	16.6	33	21.8
6	Moderna mRNA-1273	13.5	17.5	33	25.2
7	Moderna mRNA-1273	15.1	19.1	37	31
8	Moderna mRNA-1273	22.0	26	33	22.9
9	Moderna mRNA-1273	19.4	24	30	23.2
10	Moderna mRNA-1273	32.4	36.4	33	19.5
11	Pfizer BNT162b2	6	9	29	22.5
12	Pfizer BNT162b2	4	8	41	20.9
13	Pfizer BNT162b2	3	6	35	23.6
14	Pfizer BNT162b2	3	6.6	35	27.9
15	Pfizer BNT162b2	22	25	32	20.8
16	Pfizer BNT162b2	19.2	23.1	31	20.8
17	Pfizer BNT162b2	15.6	19	34	20.5
18	Pfizer BNT162b2	16.2	19.3	34	20.8
19	Pfizer BNT162b2	16.1	19.1	30	20.9
20	Pfizer BNT162b2	19	22	33	26

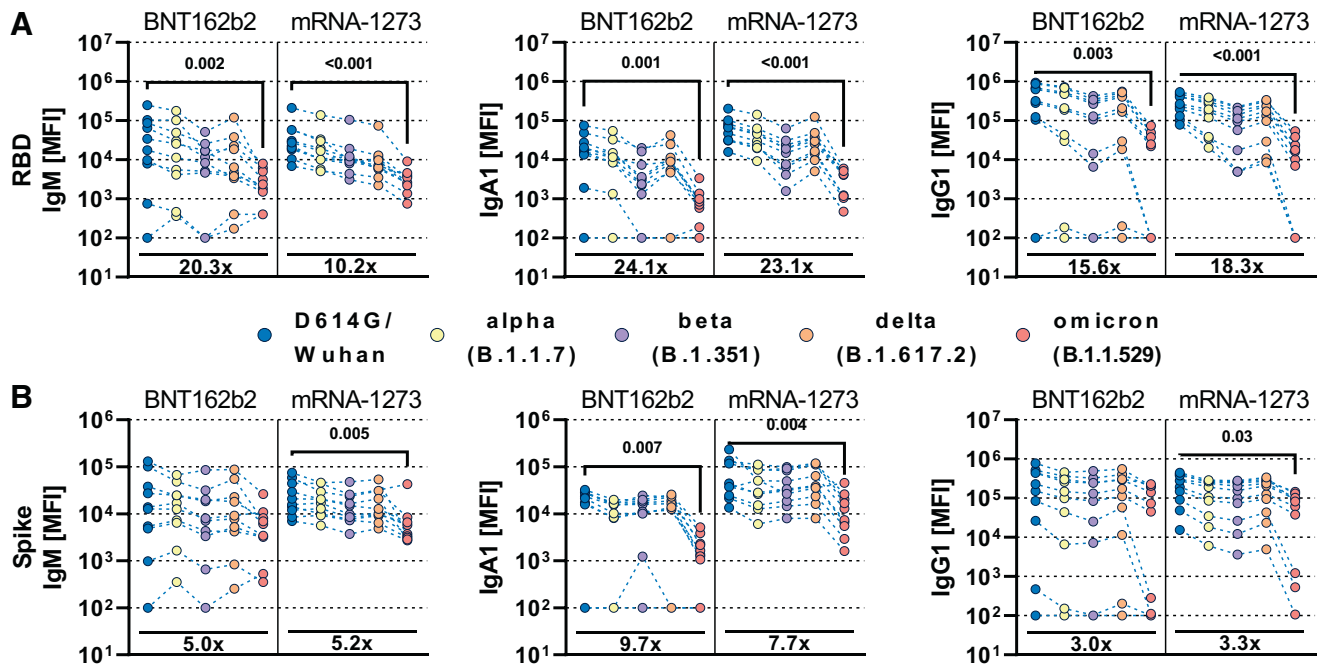
BMI, body mass index; mRNA, messenger RNA.

Bartsch et al. SARS-CoV-2 vaccine variants of concern antibodies. Am J Obstet Gynecol 2022.

Although both the BNT162b2 and mRNA-1273 vaccines induced RBD-binding antibodies against the WT, Alpha, Beta, and Delta VOCs that were able to bind across all Fc receptors, Omicron RBD-specific antibodies lost

FIGURE 1

Compromised RBD, but not spike-specific Omicron recognition in pregnant individuals



Pregnant individuals received either the full dose regimen of the BNT162b2 ($n=10$) or the mRNA-1273 ($n=10$) vaccination. Samples were taken at peak immunogenicity 2 to 4 weeks after the last dose. IgM, IgA1, and IgG1 binding titers to D614G (wild-type [WT]; blue), Alpha (B.1.117; yellow), Beta (B.1.351; purple), Delta (B.1.617.2; orange), and Omicron (B.1.529; red) variants of concern RBD (A) or whole spike (B) were measured by Luminex. Background corrected data are shown, and negative values were set to 100 for graphing purposes. A Kruskal-Wallis test with a Benjamini-Hochberg posttest correcting for multiple comparisons was used to test for statistical differences between WT variant and Omicron variant titers. P values for significantly different features are shown above and the fold-change reduction in Omicron titer compared with WT titer is given below each data set.

Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

Bartsch et al. SARS-CoV-2 vaccine variants of concern antibodies. Am J Obstet Gynecol 2022.

all Fc receptor binding capabilities (Figure 2, A). This striking loss of Fc receptor binding was observed despite the presence of detectable levels of Omicron RBD-specific IgG levels (Figure 1, A), highlighting the disconnect between antibody titers and Fc receptor activation. However, despite this dramatic loss of Omicron RBD-specific Fc receptor binding, mRNA vaccine-induced, spike-specific antibodies leveraged all Fc receptors against the WT, Alpha, Beta, and Delta variants for all individuals with detectable antibody titers. Compared with antibody titers and Fc receptor binding for other VOCs, the ability of Omicron spike-specific antibodies to bind to Fc receptors was more variable, pointing to a disconnect between binding and Fc receptor interactions, potentially attributable to substantial

mutation-induced geometric changes in spike antibody targets that may render the Fc domain of antibodies less accessible to Fc receptors on the Omicron spike.¹⁵ Despite losing some Fc-receptor binding capabilities to the Omicron-Spike, both the BNT162b2 and mRNA-1273 vaccine-induced immune responses continued to show detectable binding across all Fc receptors, with slightly more preserved binding to the activating phagocytic FcγR2a and cytotoxic FcγR3a and a greater loss of binding to the sole inhibitory FcγR2b and neutrophil-activating FcγR3b (Figure 2, B).

Comment

Principal findings

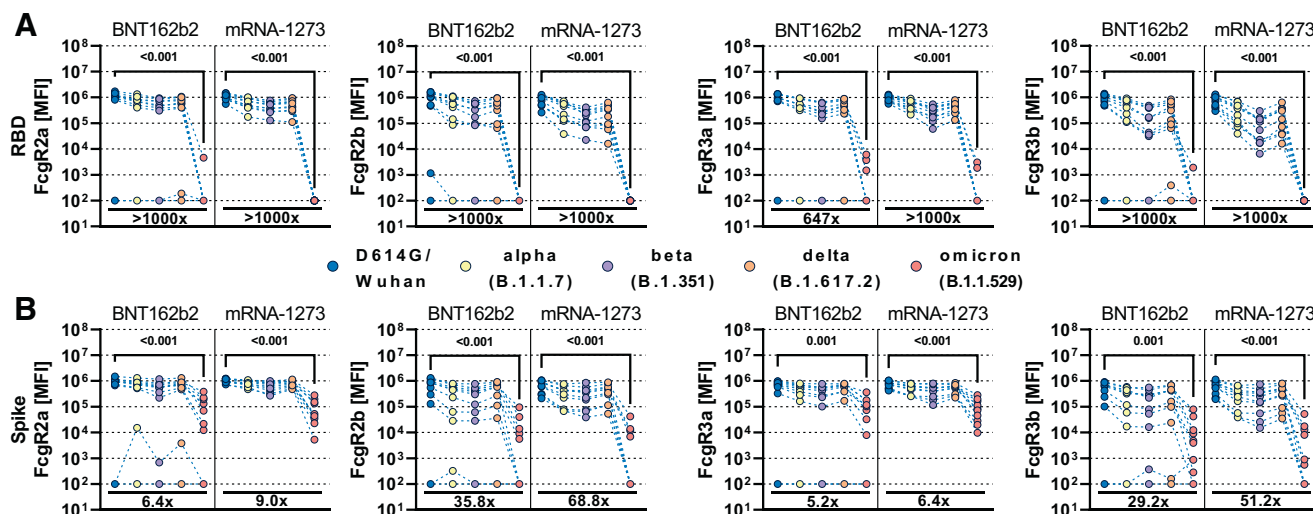
Our data show a significant loss of Omicron RBD-specific antibody titers

and Fc receptor binding, but preservation of Omicron spike-specific antibody binding that may continue to recognize, clear, and control infection, contributing to persistent protection against neutralization-resistant VOCs.

Results in the context of what is known

With the emergence of SARS-CoV-2 VOCs, like Omicron, that are able to evade vaccine-induced neutralizing antibody responses, more vaccine breakthrough infections have been noted.^{3,4} However, severe infection has not increased concomitantly, suggesting that other vaccine-induced mechanisms are likely critical for protection against COVID-19. Given our recent appreciation of the differences in the overall magnitude and kinetics of the evolution

FIGURE 2

Inability of RBD-specific but not spike-specific IgG to recruit Fc γ receptors

Pregnant individuals received either the full dose regimen of the BNT162b2 ($n=10$) or mRNA-1273 ($n=10$) vaccination (compare Figure 1). Binding to Fc γ R2a, Fc γ R2b, Fc γ R3a, and Fc γ R3b of D614G (wild-type [WT]; blue), Alpha (B.1.17; yellow), Beta (B.1.351; purple), Delta (B.1.617.2; orange), and Omicron (B.1.529; red) variants of concern RBD (A) or whole spike-specific (B) antibodies were determined by Luminex. Background corrected data are shown and negative values were set to 100 for graphing purposes. A Kruskal-Wallis test with a Benjamini-Hochberg posttest correcting for multiple comparisons was used to test for statistical differences between the WT variant and the Omicron variant titer. *P* values for significantly different features are shown above and the fold-change reduction in Omicron titer compared with WT titer is shown below each data set.

Ig, immunoglobulin; mRNA, messenger RNA; RBD, receptor binding domain.

Bartsch et al. SARS-CoV-2 vaccine variants of concern antibodies. Am J Obstet Gynecol 2022.

of the vaccine-induced immune response following COVID-19 mRNA vaccination during pregnancy,⁹ we sought to determine whether Omicron-specific Fc-mediated antibody effector functions, previously associated with the resolution of severe disease,⁶ were preserved in vaccinated pregnant women in this study. Recently, we reported a near complete loss of RBD-specific antibodies in mRNA vaccinated nonpregnant individuals, whereas spike-specific antibodies and Fc receptor binding was only slightly reduced.¹⁶ Similarly, here we observed a slight loss, but overall robust preservation of Omicron spike binding by mRNA vaccine-induced antibodies. Although Omicron-induced breakthrough infections in vaccinated individuals are more frequent than for previous VOCs, vaccination continues to confer protection against severe disease and hospitalization, potentially via the induction of nonneutralizing antibody functions. Although most studies on breakthrough infections and severity

have been conducted in nonpregnant populations, no significant differences were noted in the antibody profiles of nonpregnant and pregnant individuals, pointing to potentially comparable persistent protection against severe disease and death by these preserved antibody functions in pregnant individuals.¹⁶ Because of its importance in binding to the host angiotensin converting enzyme 2 receptor, the SARS-CoV-2 RBD is the main target for neutralizing antibodies.¹⁷ Although mutations in the RBD may easily disrupt neutralizing antibody recognition (because they target the same site that is involved in receptor binding), non-neutralizing antibodies likely target the entire surface of the spike antigen and thus are likely to be minimally affected by variation in the RBD. Thus, persistent binding and recruitment of Fc-mediated effector functions by nonneutralizing antibodies could continue to contribute to antiviral immunity in the setting of viral evolution.

Clinical implications

Pregnancy represents an unusual immunologic state during which the maternal immune system must balance tolerance to the fetal graft with protecting the maternal-fetal dyad against foreign pathogens. This delicate balance has been associated with dampened vaccine-induced immune responses.¹⁸ The data presented here suggest that mRNA vaccines induce robust binding antibodies across VOCs that are able to induce antiviral clearance mechanisms via Fc receptors in pregnant women. Moreover, vaccine-induced antibodies exhibit preserved recognition of the neutralization-resistant SARS-CoV-2 Omicron variant, potentially continuing to confer protection against severe disease via the rapid deployment of the immune system to control and clear the virus in the lower respiratory tract. Thus, despite the loss of protection against transmission, mRNA vaccines likely play a key role in attenuating disease in pregnant women who remain at increased risk for severe COVID-19.^{1,2}

Research implications

Beyond blocking infection, antibodies confer protection against disease via the rapid elimination of antibody-opsonized viruses via the recruitment of the innate immune system. Specifically, all immune cells express Fc receptors that are rapidly recruited by antibody-coated targets, leading to the rapid recognition, destruction, and clearance of pathogens if they escape transmission blockade. The data presented here argue that the persistent recognition of the Omicron spike antigen by mRNA vaccine-induced antibodies, able to continue to interact with Fc receptors, may represent a key persistent mechanism by which vaccines provide protection against severe disease in pregnant women. Thus, defining the ability of antibodies to continue to recognize and leverage the antiviral activity of the immune system may provide critical clues on the mechanism(s) of vaccine efficacy and the need for additional boosters in pregnant individuals.

Strengths and limitations

To date, we are not aware of any studies that have examined the efficacy of the mRNA vaccines against new VOCs, including Omicron, in the pregnant population. Such data are critical to framing and potentially combating new concerns about vaccine efficacy against the Omicron variant and other VOCs and to address the continued importance of vaccination in the pregnant population. Although we were unable to comprehensively profile the humoral immune response induced by additional vaccine platforms or across various trimesters of pregnancy, the data presented here provide promising insights into the persistent additional neutralizing properties of mRNA vaccine-induced antibodies that may continue to provide protection against the Omicron variant. Whether boosters can further augment these Fc receptor recruiting qualities, whether these Fc-mediated functions persist over time, and whether Fc receptor recruitment alone, in the absence of neutralization, can confer robust protection against the Omicron variant and beyond remains unclear.

Conclusion

Although Omicron RBD-specific antibody recognition and Fc receptor binding were significantly lower than the responses to other SARS-CoV-2 variants, spike-specific binding antibodies were able to bind robustly across VOCs, including Omicron, and continued to leverage Fc receptor binding. Similar to the reported loss of neutralization in the nonpregnant population, here we observed a significant loss of RBD-specific titers and RBD-specific Fc receptor binding. Conversely, the persistence of Omicron spike-specific responses following administration of both the BNT162b2 and mRNA-1273 vaccines retained the capacity to recruit Fc receptors, demonstrating the potential for vaccine-induced antibodies to rapidly control and eliminate Omicron infections even in the face of a loss of neutralization. Moreover, the selective preservation of FcγR2a and FcγR3a can rapidly leverage phagocytic and cytotoxic immune mechanisms, positioned to rapidly capture and clear opsonized virus particles on infection.

These initial data may provide critical clues related to the mechanistic correlates of immunity that can guide future vaccine design and boosting in pregnant individuals. ■

Acknowledgments

We thank Nancy Zimmerman, Mark and Lisa Schwartz, an anonymous donor (financial support), Terry and Susan Ragon, and the Samana Kay MGH Research Scholars award for their support. We acknowledge support from the Ragon Institute of MGH, MIT and Harvard, the Massachusetts Consortium on Pathogen Readiness (MassCPR), and the Musk foundation.

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Received Jan. 14, 2022; revised April 6, 2022; accepted April 7, 2022.

G.A. is a founder and equity holder of Seromyx Systems, a company developing a platform technology to profile antibody immunity. G.A. is an employee and equity holder of Leyden Labs, a company developing pandemic prevention therapeutics. G.A.'s interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. All other authors report no conflict of interest.

This study was funded by the National Institutes of Health (NIH) under grants 3R37AI080289-11S1,

R01AI146785, U19AI42790-01, U19AI135995-02, 1U01CA260476-01, and CIVIC75N93019C00052, and by the Bill and Melinda Gates Foundation: Global Health Vaccine Accelerator Platform under grants OPP1146996 and INV-001650. A.G.E. received funding from the NIH under grant R01HD100022-S2 and from the March of Dimes Foundation under grant 6-FY-20-223 to support sample collection.

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