Prolonged exposure to antigens, such as allergens or parasitic infections, leads to a class switch toward immunoglobulin (Ig)E, which activates mast cells and basophils. Although uncommon, viral antigens can also trigger IgE responses, as demonstrated after respiratory syncytial virus and varicella-zoster infections, and after hepatitis B and influenza vaccinations. In this study, Brazil's authors investigated IgE levels specific for the receptor binding domain (RBD) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) following SARS-CoV-2 infection or COVID-19 vaccination. The participants received two doses of either vectored (ChAdOx1) or inactivated (CoronaVac) vaccines and one booster dose of the mRNA BNT162b2 vaccine.

The SARS-CoV-2 spike (S) protein, which appears to be a major pathogenic factor that contributes to the unique pathogenesis of SARS-CoV-2, is a glycosylated homotrimer with each monomer composed of subunits S1 and S2. The S1 domain comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains. The RBD in the S1 subunit recognizes angiotensin-converting enzyme 2 (ACE2) and is responsible for attachment to host cells.

About the study

During the first wave of COVID-19 in Brazil, 148 sera samples were collected from 59 health professionals. The study population only included women, which may limit the generalization of findings. The participants who met the following criteria were included: they had a positive test for COVID-19 before vaccination, received two doses of either ChAdOx1 or CoronaVac vaccines and one booster dose of mRNA BNT162b2 (Pfizer) vaccine, did not have a previous history of COVID-19 symptoms or diagnosis between vaccinations, and their blood samples were collected before and after each vaccination. The individuals diagnosed with COVID-19 were asymptomatic or experienced mild clinical symptoms and did not require hospitalization or intensive medical care. None of the subjects in this study reported hypersensitivity after SARS-CoV-2 infection or COVID-19 vaccination.

According to the primary immunization with vectored (ChAdOx1) or inactivated (CoronaVac) vaccines, and history of confirmed COVID-19 (cov or non-cov), participants were categorized into four different groups: ChAd-cov, Corona-cov, ChAd non-CoV, and Corona non-CoV.

Blood samples were collected before the vaccination, after the second, and after the booster dose. The sera samples from confirmed COVID-19 (cov) cases were compared with specimens from individuals without history of acute COVID-19 infection (non-cov). Anti-RBD IgE and IgG4 were identified by ELISA. An avidity assay was used to investigate the binding strength of IgE for the RBD antigen.

Results

Although anti-RBD IgE levels were above the cutoff in 23% of the individuals diagnosed with COVID-19, there was no statistical difference in anti-RBD IgE levels between them and those with no history of acute COVID-19 infection.

Anti-RBD IgE levels were higher after two ChAdOx1 or CoronaVac vaccines than after the SARS-CoV-2 infection. Interestingly, a group analysis according to vaccination schedule and history of acute COVID-19 (ChAd-cov, Corona-cov, ChAd non-CoV, and Corona non-CoV) revealed a more robust response of anti-RBD IgE in individuals vaccinated with two doses of vectored ChAdOx1 vaccine than in those immunized with two doses of inactivated CoronaVac vaccines.

Importantly, after boosting with the mRNA BNT162b2 vaccine, IgE indexes increased across all groups regardless of vaccine type or previous COVID-19 infection. All four groups (ChAd-cov, Corona-cov, ChAd non-CoV, and Corona non-CoV) presented similar levels of anti-RBD IgE.

According to the avidity assay which describes the binding strength of IgE for the RBD antigen, acute SARS-CoV-2 infection induced IgE of intermediary avidity whereas vaccination induced IgE of high avidity with good binding strength for the SARS-CoV-2 RBD.

A Spearman's correlation analysis showed that neutralizing antibodies did not correlate with IgE levels after COVID-19 but strongly correlated with IgE levels after two ChAdOx1 or CoronaVac vaccines.

High levels of IgE were followed by IgG4 isotype

As both IgE and IgG4 are induced in strong Th2 environments, the researchers tested the blood samples for IgG4 levels and found that COVID-19 did not induce detectable levels of this IgG subclass. However, two doses of either ChAdOx1 or CoronaVac vaccines increased IgG4 levels, but only after mRNA BNT162b2 booster immunization. The mRNA BNT162b2 booster immunization increased IgG4 levels in all groups regardless of previous SARS-CoV-2 infection or ChAdOx1 or CoronaVac vaccination. There was a moderate correlation between IgE and IgG4 levels.

The authors noted that B cells require prolonged antigen stimulation to switch to IgG4 antibodies, supported by Th2 cytokines. It is known that aluminum hydroxide triggers a strong Th2 environment that favors this response. However, the ChAdOx1 vaccine without alum induced even higher IgE and IgG4 indexes than CoronaVac, an alum-adjuvanted vaccine, suggesting that another active immunogen plays a role in eliciting IgE and IgG4 responses.

IgG4 is mostly non-inflammatory, and the main concern regarding IgG4 would be the lack of functions, such as antibody-dependent cellular phagocytosis, complement deposition, and cellular cytotoxicity. According to some authors, increased IgG4 levels detected after repeated vaccination with the mRNA vaccines are not a protective but rather a mechanism of immune tolerance to the SARS-CoV-2 S protein. It is suggested that increased IgG4 synthesis due to repeated mRNA vaccination with high antigen concentrations could promote not only SARS-CoV2 infection and replication by suppressing natural antiviral responses but also autoimmune diseases and cancer growth in susceptible individuals. Uversky VN. et al. IgG4 antibodies induced by repeated vaccination may generate immune tolerance to the SARS-CoV-2 spike protein. Vaccines 2023, 11, 991. https://doi.org/10.3390/vaccines11050991

Previous studies reported that repeated mRNA COVID-19 vaccination increased IgG4 antibodies specific for the S protein that appeared late after the second immunization. https://discovermednews.com/repeated-sars-cov-2-mrna-vaccination-results-in-a-class-switch-to-noninflammatory-spike-specific-igg4-antibodies/ Furthermore, a recent study has found an increase in IgG4 levels specific for the S1 and RBD in children aged 5-11 years, one year after BNT162b2 vaccination. https://discovermednews.com/elevated-igg4-children-after-mrna-bnt162b2-vaccinatio Also, some recent studies presented cases of IgG4-related diseases that developed after COVID-19 vaccination. https://discovermednews.com/two-case-reports-of-igg4-related-disease-after-anti-sars-cov-2-vaccination/

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Conclusion

This study revealed increased IgE levels specific for the RBD of the SARS-CoV-2 in

individuals immunized with the ChAdOx1, CoronaVac, and mRNA BNT162b2 vaccines. Vectored vaccines elicited a stronger response compared to inactivated vaccines. However, mRNA boosters further increased IgE to similar levels in all groups, irrespective of the primary vaccine or previous SARS-CoV-2 infection. Anti-RBD IgE showed a high avidity for a key SARS-CoV-2 antigen. Additionally, IgG4 levels detected after booster mRNA BNT162b2 vaccination showed a moderate correlation with IgE levels.

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