Altered COVID-19 immunity in children with asthma by atopic status

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes a spectrum of clinical outcomes that may be complicated by severe asthma. Antiviral immunity is often compromised in patients with asthma; however, whether this is true for SARS-CoV-2 immunity and children is unknown.
Objective: We aimed to evaluate SARS-CoV-2 immunity in children with asthma on the basis of infection or vaccination history and compared to respiratory syncytial viral or allergen (eg, cockroach, dust mite)-specific immunity.
Methods: Fifty-three children from an urban asthma study were evaluated for medical history, lung function, and virus- or allergen-specific immunity using antibody or T-cell assays.
Results: Polyclonal antibody responses to spike were observed in most children from infection and/or vaccination history. Children with atopic asthma or high allergen-specific IgE, particularly to dust mites, exhibited reduced seroconversion, antibody magnitude, and SARS-CoV-2 virus neutralization after SARS-CoV-2 infection or vaccination. T_H1 responses to SARS-CoV-2 and respiratory syncytial virus correlated with antigen-respective IgG. Cockroach-specific T-cell activation as well as IL-17A and IL-21 cytokines negatively correlated with SARS-CoV-2 antibodies and effector functions, distinct from total and dust mite IgE. Allergen-specific IgE and lack of vaccination were associated with recent health care utilization. Reduced lung function (forced expiratory volume in 1 second ≤ 80%) was independently associated with (SARS-CoV-2) peptide-induced cytokines, including IL-31, whereas poor asthma control was associated with cockroach-specific cytokine responses.
Conclusion: Mechanisms underpinning atopic and nonatopic asthma may complicate the development of memory to SARS-CoV-2 infection or vaccination and lead to a higher risk of repeated infection in these children. (J Allergy Clin Immunol Global 2024;3:100236.)

Key words: *Asthma, children, immunity, SARS-CoV-2, RSV, cockroach*

The long-term effects of coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are unknown. How this viral infection or associated postinfection immunity can affect lung function or other lung diseases in children or patients with asthma has been greatly understudied. Asthma is a heterogenous disease marked by chronic airway inflammation with known triggers such as dust mites, cockroach antigens (CRAs), and other inhaled irritants.[1] It can be further defined on the basis of additional patient immune parameters or comorbidities, including atopic allergy for patients with high levels of allergen-specific IgE and nonatopic asthma for patients with high levels of allergen-specific T-cell responses.[2,3] Asthma was not originally identified as a risk factor for hospitalization in children with COVID-19.[4,5] However, SARS-CoV-2 infection in children with asthma was reported to increase hospitalization rates in Spain.[6] In a large Mexican study of COVID-19-related hospitalizations in children and adolescents, asthma was also identified as a comorbidity risk factor.[7] Asthma has also been implicated as a risk factor for post–COVID-19 syndrome in children and adolescents.[8] Currently, the US Centers for Disease Control and Prevention indicates that individuals with moderate to severe asthma are disproportionally affected by SARS-CoV-2 and are more likely to be hospitalized.[9] However, there continues to be great variability in the prevalence of asthma among patients with COVID-19 in different countries.[10]

Human[11-14] and animal[15,16] studies have shown that B cells, antibodies, $CD4^+$ and $CD8^+$ T cells, and human leukocyte antigen alleles play essential roles in protection and memory responses to SARS-CoV-2 infection or vaccination.[13,17-21] Population-based studies have shown a central role for neutralizing antibodies in infection and vaccine-mediated protection against SARS-CoV-2 virus strains,[22-24] yet antibody responses exhibit significant variation among individuals, and the specific antibody levels needed for protection have yet to be defined.[25] Postinfection and vaccine-mediated immunity is critical for preventing symptomatic infection and reinfection, including with SARS-CoV-2 variant strains.[26] However, it is now clear that children and adults can become infected multiple times, and mechanisms impeding the development of long-term protective immunity remain poorly defined.

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Abbreviations used

ACT: Asthma control test
AIM: Activation-induced marker
ARCHS: Allergen Reduction and Child Health Study
COVID-19: Coronavirus disease 2019
CRA: Cockroach antigen
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
I + V: Infected and vaccinated
I: Infected and not vaccinated
Ind: Indeterminate
MIP: Macrophage inflammatory protein
N: Nucleoprotein
NME: Nucleoprotein, matrix, envelope
RSV: Respiratory syncytial virus
S: Spike
SABA: Short-acting β-agonist
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
Tfh: T-follicular helper
Treg: Regulatory T

SARS-CoV-2 immunity in children with asthma remains to be characterized. However, several studies have shown that microbial host defense mechanisms are impaired in these children to viral or bacterial antigens.[27-30] For example, respiratory syncytial virus (RSV) and influenza immunity is compromised in part through IgE mechanisms as part of atopic asthma. Influenza and RSV infection are also linked to development of asthma and reduced lung function.[31,32]

Here, we evaluated a cohort of children with asthma for immunity to SARS-CoV-2 compared to immunity to RSV and atopy (dust mite, cockroach) to better understand postinfection immunity and its relationship to asthma severity and lung function.

METHODS

Study design and subject recruitment

The study population included 53 participants in the Allergen Reduction and Child Health Study (ARCHS), which is a 12-month, 2-group randomized control trial of children with asthma from communities in the greater New Orleans area. Children included in this analysis were recruited between March 2021 and April 2022. Informed consent from the child's caregiver (and assent for children aged >7 years) was obtained before any data collection. The study was approved by the institutional review board of Tulane University (approval FWA 00002055). At the baseline visit, biological, environmental, and questionnaire data were collected in the participants' homes by trained research staff. Sociodemographic data and medication prescriptions were obtained via caregiver self-report.

Lung function testing and questionnaire

Spirometry (EasyOne) was performed using standard techniques with global lung function initiative normative values according to American Thoracic Society criteria.[33] Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio were measured. The proportion of children with predicted FEV_1 and FVC < 80% and FEV_1/FVC < 70% was used to indicate airway obstruction. Indicators of asthma severity were obtained by questionnaire, including asthma control test (ACT) score and asthma health care utilization. Health care utilization in the past 6 months was defined as either an unscheduled clinic or doctor visit, emergency room visit, or hospitalization for asthma. History of SARS-CoV-2 infection was obtained via questionnaire and was confirmed by nucleoprotein-specific IgG testing or plasma viral RNA detection.

Sample collection, processing, and virus detection

A 5 mL venous blood sample was collected and tested for total and allergen-specific IgE (sIgE as listed in Table I by LabCorp) or processed for antibody and T-cell analyses. Serum IgE > 0.35 kU/L was used as the cut point defining sensitization. The blood sample remaining after T-cell analyses was processed for plasma and peripheral blood mononuclear cells by density gradient centrifugation in Leukosep tubes (Greiner Bio One) and Ficoll-Paque PREMIUM 1.078 g/mL (Cytiva).[34,35] RNA virus load was measured from plasma samples with a sensitive SARS-CoV-2–specific clustered regularly interspaced short palindromic repeat (aka CRISPR) assay, as previously reported.[36,37]

Antibody and T-cell analyses

Blood was processed for plasma, heat inactivated at 56°C for 30 minutes, and then evaluated for viral RNA[36,37] or viral antibodies, including ELISA,[38] neutralization,[39] multiplex assay for antibody isotypes, and fragment crystallization (aka Fc)-mediated effector functions.[40] White blood cells from lysed whole blood were tested by activation-induced markers (AIMs) on 24-hour–restimulated cells. Cells were restimulated with media, SARS-CoV-2 spike (S) proteins/peptides (S_{18}, S_{53}, S_{115}), SARS-CoV-2 non-S peptides (nucleoprotein, membrane, envelope [N, M, E] peptides), RSV nucleoprotein, or cockroach extract (see Table E1 in this article's Online Repository at www.jaci-global.org). Bio-Plex Human Cytokine T_H17 15-Plex and Milliplex MAP Human $CD8^+$ T-Cell Premixed Magnetic Bead Panel (Millipore) kits were used to test culture supernatants for cytokine secretion according to the manufacturers' protocols. Flow cytometry was performed by BD LSRFortessa (AIM assay) or Cytek Aurora Spectral (effector function assays) cytometers.

Data analysis

Data management and statistical analyses were carried out by FlowJo v10 (Becton Dickinson), R v4.1.2 (R Project; www.r-project.org), GraphPad Prism v9.0.0 (GraphPad Software), JMP Pro v16.2.0 (SAS Institute), and SAS v9.4 (SAS Institute). Figures were created using BioRender.com and Adobe Illustrator v.27.2. COVID-19 cases were downloaded from the Louisiana Department of Health (ldh.la.gov) on July 27, 2022.

More detailed information is presented in the Methods section in the Online Repository at www.jaci-global.org.

RESULTS

Antibody responses to SARS-CoV-2 in children with asthma are polyfunctional and driven by infection and vaccination. We evaluated specimens from an ongoing cohort study of children with asthma in New Orleans (Fig 1, *A*). The 53 recruited children provided samples from March 2021 to March 2022. Subject

TABLE I. Characteristics of 53 children at baseline

Demographic characteristic	No. (%) or median (min-max)	No. (%) missing
Median age (years)	10 (5-17)	0
Sex		0
Male	33 (62.2)	
Female	20 (37.8)	
Race/ethnicity		0
Non-Hispanic Black	30 (56.6)	
Non-Hispanic White	5 (9.4)	
Hispanic Black	5 (9.4)	
Hispanic White	8 (15.1)	
Hispanic other	5 (9.4)	
Income		0
Don't know/refused	7 (13.2)	
$0 to $25,000	29 (54.7)	
>$25,000	17 (32.1)	
Allergen sensitization (sIgE > 0.35 kU/L)	**No. (%) or median (min-max)**	**No. (%) missing**
Alternaria alternata (mold)	14 (26.4)	1 (1.9)
Cat dander	13 (24.5)	0
Either dust mite	35 (66.0)	0
Dog dander	18 (34.0)	0
Mouse urine	8 (15.1)	1 (1.9)
American cockroach	8 (15.1)	0
German cockroach	15 (28.3)	0
Either cockroach	18 (34.0)	0
Total IgE	238 (17-4386)	2 (3.8)
Asthma outcome	**No. (%) or median (min-max)**	**No. (%) missing**
Lung function		2 (3.8)
FEV_1 predicted <80%	19 (35.8)	
FEV_1 predicted ≥80%	32 (60.4)	
Asthma control (ACT score)		1 (1.9)
Controlled (>19)	19 (35.8)	
Uncontrolled (≤19)	33 (62.3)	
Asthma health care utilization in previous 6 months		2 (3.8)
ED/unscheduled doctor visit *and* hospitalization	3 (5.7)	
ED/unscheduled doctor visit	28 (52.8)	
Hospitalization	1 (1.9)	
Neither	19 (35.8)	
Asthma symptoms previous 2 weeks (days)	**No. (%) or median (min-max)**	**No. (%) missing**
Symptoms	2 (0-14)	0
Slow down	2 (0-14)	0
Wake up	1 (0-14)	0
Miss school	0 (0-7)	0
Max no. of symptom days	3 (0-14)	0
Asthma attack previous month		2 (3.8)
Yes	18 (34.0)	
No	33 (62.3)	
Corticosteroid use previous month		1 (1.9)
Yes	10 (18.9)	
No	42 (79.2)	
SABA use previous 2 weeks		0
Yes	35 (66.0)	
No	18 (34.0)	
Self-reported COVID-19 history	**No. (%) or median (min-max)**	**No. (%) missing**
Known COVID-19 infection		1 (1.9)
Yes	6 (11.3)	
No	46 (86.8)	
Vaccinated against COVID-19		1 (1.9)
Yes	16 (30.2)	
No	36 (67.9)	

ED, Emergency department.

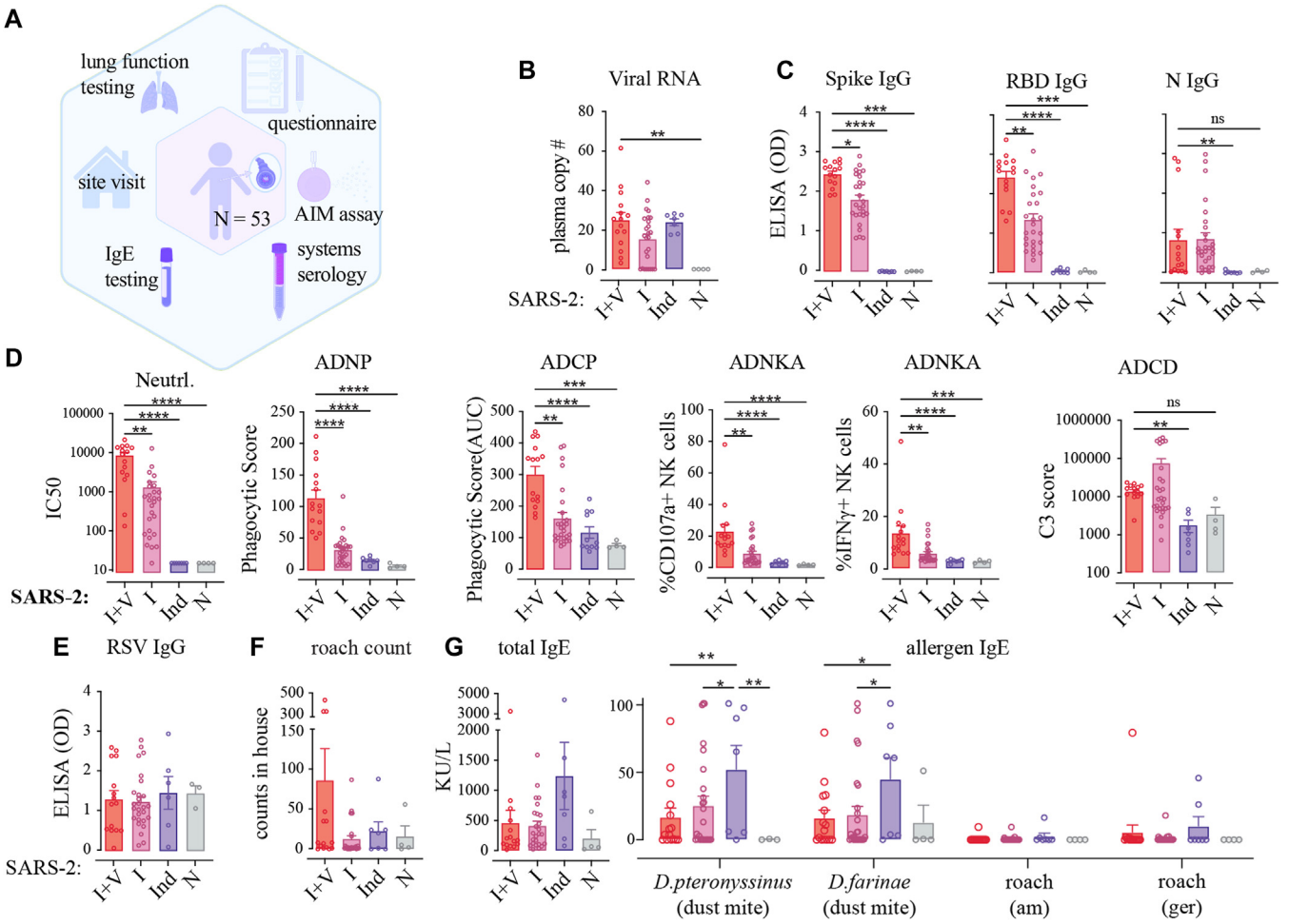

FIG 1. Polyfunctional antibody responses to SARS-CoV-2 and allergen IgE detected in ARCHS children. ARCHS participants were grouped by infection status using patient history, serology, or viral RNA detection (*N* indicates negative). From left to right, graphs are coded by colored bars/symbols as I + V *(red),* I *(pink),* Ind *(purple),* and N *(gray).* **(A)** Schematic of study design overview. **(B)** SARS-CoV-2 virus RNA reported as copy number. **(C)** Level of SARS-CoV-2 S, RBD, or N protein IgG detected in plasma by ELISA reported as OD. **(D)** SARS-CoV-2–neutralizing plasma antibodies and levels of SARS-CoV-2 antibody effector functions including ADNP, ADCP, ADNKA (CD107a, IFN-γ), and ADCD. **(E)** Level of RSV F protein IgG detected in plasma by ELISA reported as OD. **(F)** Cockroach counts in house of each subject. **(G)** Clinical test results for total or allergen-specific IgE (kU/L). Significance by ANOVA with Dunn posttest indicated by $*P < .05$, $**P < .01$, $***P < .001$, $****P < .0001$. *ADCD,* Antibody-dependent complement deposition; *ADCP,* antibody-dependent cellular phagocytosis; *ADNKA,* antibody-dependent natural killer cell activation; *ADNP,* antibody-dependent neutrophil phagocytosis; *OD,* optical density; *RBD,* receptor binding domain.

demographics and asthma measures were similar to other urban asthma studies.[41,42] The median age of participants was 10 years (range, 5-17 years), 33 were classified as male (62%), 30 (57%) self-reported race/ethnicity as non-Hispanic Black, and 29 (55%) were from a household reporting income of $25,000 or less per year (Table I). Of these subjects, 19 (36%) had reduced lung function (FEV_1 < 80%) and 33 (62%) had uncontrolled asthma (ACT score < 19). Caregivers were also asked about the prevalence of asthma symptoms and asthma medications, including short-acting β-agonist (SABA) or steroid use frequency, reported in Table I.

SARS-CoV-2 infection was confirmed in 42 children (79.2%) using either patient history (6, 11.3%) or serologic testing for anti-N antibodies (36, 68%) (Table I, Fig 1, *B,* and see Table E2 in the Online Repository at www.jaci-global.org). Vaccination was determined by patient history (Table E2). Viral polymerase RNA was detected in the plasma of 41 children (77.4%).[36,37] Seven children (13.2%) had detectable viral RNA but without detectable SARS-CoV-2 antibodies and were labeled indeterminate for categorical analyses (this included one subject with COVID-19 vaccination history). Four subjects were negative for all infection parameters. Thus, our cohort was stratified as 15 infected and vaccinated (I + V), 27 infected and not vaccinated (I), 7 indeterminate (Ind), and 4 negative subjects.

Levels of anti-S or anti-S receptor binding domain were elevated with infection compared to uninfected children (Fig 1, *C*). Vaccination further boosted the S-specific antibodies (eg, I + V vs I groups), similar to previous reports.[43] Anti-S antibody functions and activation of innate effector functions exhibited similar trends, including for SARS-CoV-2 neutralization,

neutrophil and monocyte phagocytosis (antibody-dependent neutrophil phagocytosis, antibody-dependent cellular phagocytosis), natural killer cell activation (antibody-dependent natural killer cell activation using IFN-γ and CD107a expression), and complement deposition (Fig 1, *D*). These effector functions have been inversely correlated with disease severity after infection.[22,23,44,45] Only antibody-dependent complement deposition had a unique pattern, with no difference observed with vaccination from infected-only children.

We next evaluated our cohort for any evidence that other virus- or allergen-specific immunity was altered within these COVID-19 stratifications. Anti-RSV IgG levels were detectable but not different by SARS-CoV-2 study groups (Fig 1, *E*). Total household cockroach counts and total IgE were also not different among groups (Fig 1, *F* and *G,* Table I). However, the Ind group exhibited higher levels of total and allergen-specific IgE antibodies to dust mite antigens from *Dermatophagoides pteronyssinus* and *D farinae* (Fig 1, *G*).

Allergen-specific IgE is negatively correlated with SARS-CoV-2 humoral immunity after infection or vaccination

We next looked at all serologic, visit, and demographic factors that might affect detection of SARS-CoV-2 antibodies in these children. Cases occurred during COVID-19 waves due to the Delta and Omicron virus variants in New Orleans (Fig 2, *A*). Childhood vaccinations were approved for widespread delivery to children >5 years of age on November 2021 in the United States; accordingly, vaccinated children were included in our study. Higher antibody responses were observed with infection and vaccination, and because these vaccinations started midstudy, sample collection date was correlated with antibody levels and function (Fig 2, *A* and *B*). Measured SARS-CoV-2 antibody levels in ARCHS children (but not IgE levels) were also similar to those found in children without asthma from samples taken during a similar time frame (see Fig E1 and Table E3 in the Online Repository at www.jaci-global.org).

Allergen-specific IgE to dust mite (*D pteronyssinus* and *D farinae*) negatively correlated with levels of SARS-CoV-2 antibodies, including postinfection antibodies (anti-N IgG, Fig 2, *B*). Virus-neutralizing antibodies were also negatively correlated with dust mite IgE for all or just vaccinated subjects (Fig 2, *C* and *D*). Network analysis further confirmed this negative correlation (Fig 2, *E*).

$CD4^+$ and $CD8^+$ T-cell activation and cytokine secretion observed with viral peptides or cockroach allergen stimulation

T cells play an important role in viral immunity and asthma. Allergen-specific CD4 T cells have traditionally been associated with asthma development and persistence, and CD8 T cells in both blood and lung have also been reported to play a role in severe asthma.[46] Activated or AIM^+ T cells and antiviral cytokines have also been reported after COVID-19 infection.[13,47,48] We analyzed AIM^+ T cells ($CD69^+CD137^+CD8$ T cells or $CD134^+CD137^+CD4$ T cells) and cytokine secretion after 24 hours' stimulation with antigens using lysed whole blood of 35 children (Fig 3, *A*). Viral and allergen antigens included SARS-CoV-2 nucleoprotein (N pep and nucleoprotein, matrix, envelope [NME]), spike (S_{18}, S_{53}, S_{115}), RSV peptide pools, and CRA. AIM^+ CD4 or CD8 T cells were significantly detected compared to mock-treated cells for virtually all viral and allergen stimulation conditions, although with significant variability by subject (Fig 3, *B,* and see Fig E2, *A,* in the Online Repository at www.jaci-global.org). Antiviral T_H1 cytokines and chemokines were significantly upregulated to viral S (IFN-γ, IL-2, macrophage inflammatory protein [MIP]-1β, MIP-1α, granzyme B) or nucleoprotein (MIP-1α), granzyme B, and TNF-α peptide stimulation (Fig 3, *C,* and see Fig E3 in the Online Repository). Restimulation with RSV or CRA generated distinct profiles composed of these and other cytokines associated with T-follicular helper (Tfh, IL-21), T_H17 (IL-17A, IL-22), T_H2 (IL-31), and regulatory T-cell (Treg, IL-10) responses. No stimulation resulted in T_H2-assoiated cytokines linked to atopic asthma (eg, IL-4, IL-5, IL-13). The number of children tested for cellular immunity precluded a robust analysis by SARS-CoV-2 infection group (Fig E2, *B*). Regardless, we observed that SARS-CoV-2–specific T-cell response, in addition to RSV and roach, was readily detectable in these children with asthma.

Cytokine response, but not CD4 or CD8 AIM^+ T cells, is significantly associated with correlating viral or allergen antibodies

To ascertain the relationship of T cells to humoral immunity, we correlated antigen-specific AIM^+ CD4 and CD8 T-cell and cytokine secretion to antibody responses in these children (Fig 4, *A,* Fig E2, *C*). Antigen-specific associations were significantly observed between viral or allergen T-cell measures and corresponding antibodies. This included S-specific cytotoxic and T_H1 responses (eg, S_{115}-specific AIM^+ CD8 T cells, IL-2, IFN-γ, MIP-1α, perforin) correlated with S IgG, receptor binding domain IgG, SARS-CoV-2 neutralization, and S antibody effector functions (Fig 4, *A-C*). In addition, nucleoprotein/non-S (NME)-specific IFN-γ cytokine correlated with N IgG; RSV-specific MIP-1α cytokine correlated with RSV IgG; and CRA-induced MIP-1α, IL-17A, IL-21, and IL-10 correlated with American cockroach IgE (Fig 4).

Unusual relationships were also observed between viral and allergen-specific responses. CRA-specific IL-17A, IL-21, and IL-10 cytokine secretion negatively correlated with SARS-CoV-2 IgG, neutralization, and S antibody effector functions (Fig 4, *A-C*). Nucleoprotein/non-S (NME)-specific IL-2 and MIP-1α cytokines also correlated with dust mite IgE (Fig 4, *A* and *D*). Network analyses confirmed several of these relationships (Fig E2, *C*), including that CRA-stimulated cytokine secretion was negatively correlated with SARS-CoV-2 antibody responses in infected ARCHS children. Thus, immune responses to allergens in children with asthma were associated with impaired or altered immunity to SARS-CoV-2 humoral responses distinct from the allergen-specific IgE negative correlation discussed above (Fig 2).

Recent health care utilization for asthma in SARS-CoV-2 infected children was predicted by allergen IgE and vaccination history, but asthma control and lung function exhibited a more complicated relationship to immunity.

Our study population included a number of children reporting recent health care utilization (eg, emergency room visit, unscheduled doctor visit, hospitalization for asthma), poor asthma control (ACT score ≤ 19), reduced lung function (FEV_1 ≤ 80%), and

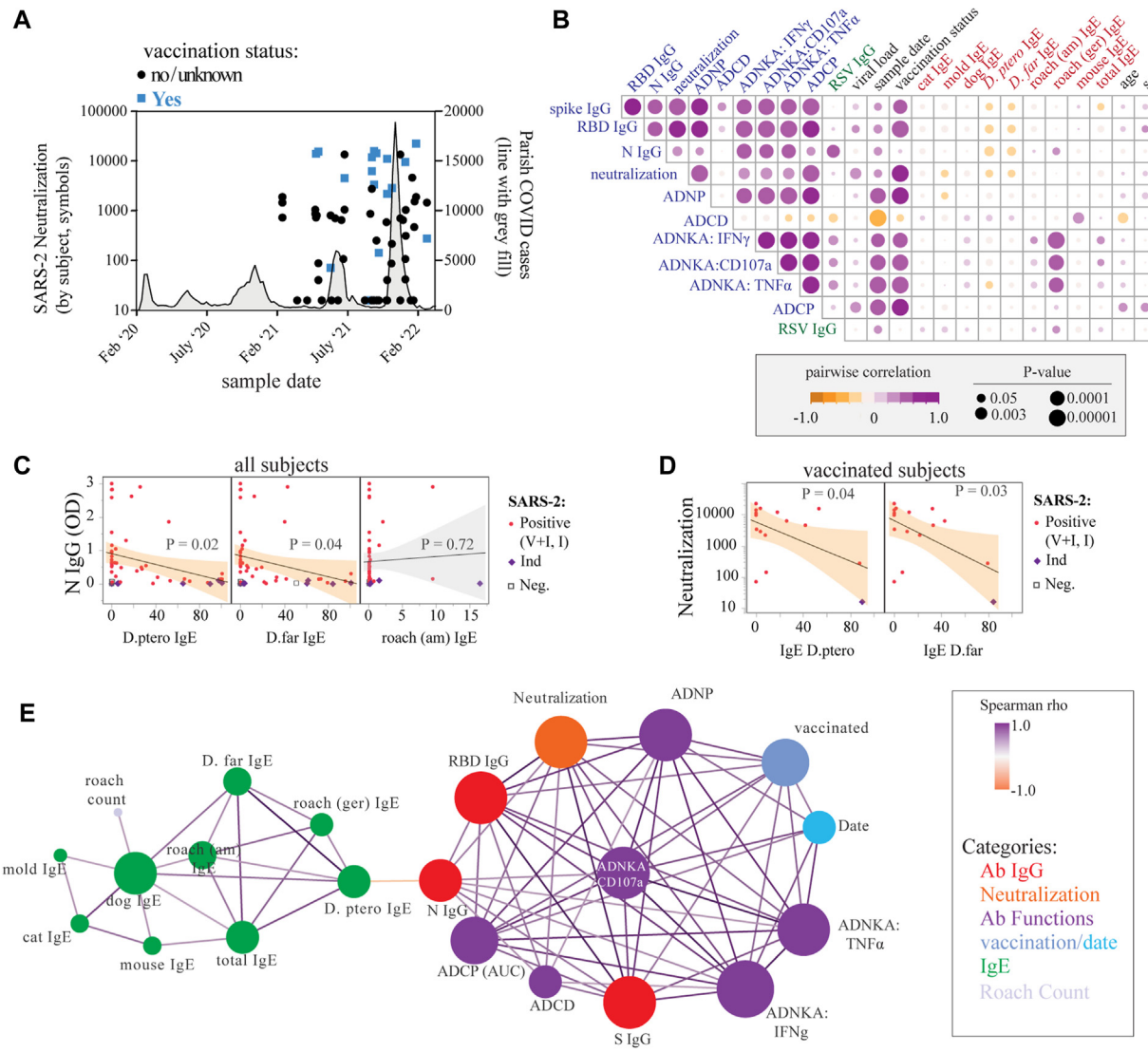

FIG 2. High levels of allergen IgE negatively correlate with SARS-CoV-2 antibodies after infection or vaccination in children with asthma. **(A)** Orleans and Jefferson Parish SARS-CoV-2 cases *(gray peaks)* by subject blood collections *(symbols)* indicated level SARS-CoV-2 neutralization (y-axis) or vaccination status (*blue* for vaccinated subjects and *black* for unvaccinated/unknown vaccination status). **(B)** Correlation analysis of viral or allergen antibodies, subject, or sample variables. Circle size indicates *P* value colored according to pairwise correlation based on Spearman ρ (*orange* indicates negative; *purple,* positive) **(C)** N IgG versus allergen-specific IgE responses. Subjects separated by SARS-CoV-2 infection status. **(D)** Neutralization versus allergen-specific IgE. Subjects separated by vaccination status and SARS-CoV-2 infection status. **(E)** Network analysis of antibody, vaccination, and date of sample collection variables.

asthma medication usage (Table I, Fig 5, *A*). COVID-19 stratifications (eg, infection, vaccination) or levels of SARS-CoV-2 antibody neutralization were not significantly altered by these asthma-related measures, except for medication history. Specifically, virus neutralization was lower in infected children reporting SABA use in the last 14 days versus those not reporting SABA use (see Fig E4, *A,* in the Online Repository at www.jaci-global.org). Steroid use in the month before sample collection was not associated with reduced virus neutralization (Fig E4, *A*). When children with recent steroid use were removed from analyses (n = 10), we still observed that SARS-CoV-2 antibody responses were driven by infection status, with the trend that allergen-specific IgE negatively correlated with postinfection antibodies, and that T-cell cytokine profiles correlated with antibodies (Fig E4, *B-D*).

To more comprehensively examine the relationship between immunity and asthma in these children, we focused on the 49 COVID-19–infected subjects (I, I + V, and Ind). These children were distributed across a range of ACT scores, lung function scores, and health care utilization history (Fig 5, *A*). A variable reduction strategy was performed by predictive modeling for each of these 3 asthma variables using regression analyses (see Fig E5, *A* and *B,* and Fig E6, *A* and *B,* in the Online Repository at www.jaci-global.org). Date of sample collection and demographic factors (race, ethnicity, income, sex, age) were included but were not identified as significant predictors of asthma

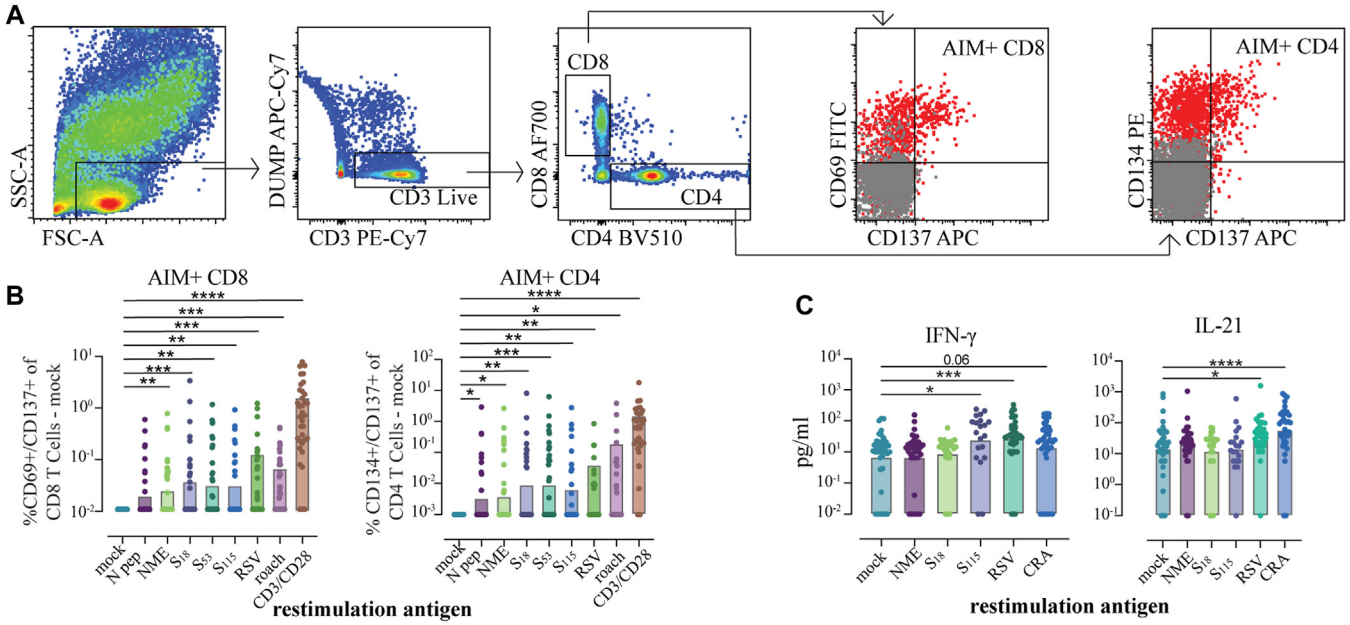

FIG 3. Children with asthma have evidence of $CD4^+$ and $CD8^+$ T cells or secreted cytokine responses to SARS-CoV-2, RSV, and roach antigens. **(A)** Flow cytometry gating strategy used in AIM^+ CD4 or CD8 T-cell analysis of 24-hour restimulated lysed whole blood. **(B)** Bar graphs of AIM^+ CD8 and CD4 T-cell data values minus mock treatment by indicated restimulation condition for each subject. **(C)** Bar graph of IFN-γ and IL-21 secretion by indicated restimulation condition for each subject. Significance by ANOVA with Dunn posttest indicated by $*P < .05$, $**P < .01$, $***P < .001$, $****P < .0001$.

outcomes in these models. We found 5 variables including COVID-19 vaccination status (yes/no) and allergen-specific IgE (eg, *D pteronyssinus* IgE, dog dander IgE, cat dander IgE, mold IgE) completely predicted recent health care utilization for asthma (model-specific principal component analysis; Fig 5, *B,* Fig E5, *B*). Higher levels of dust mite IgE but lower levels of N IgG and S-specific IFN-γ secretion were also independently associated with recent health care utilization (Fig 5, *C*). Cat, dog, and mold allergen-specific IgE levels were not independently associated with recent health care utilization (Fig E5, *C*), suggesting that each child may have unique allergen-specific associations related to health care utilization.

Both asthma control and lung function were predicted by regression analyses with select immunologic or subject-specific variables, but required >25 variables to do so (Fig E6). However, several of these variables were verified independently by correlation analyses (Fig 6). This included the finding that higher levels of cockroach-specific IgE, T-cell activation, and cytokine secretion (eg, CRA-stimulated AIM^+ CD8 T cells, IL-23, TNF-α) correlated with lower asthma control scores (Fig 6, and see Fig E7, *A,* in the Online Repository at www.jaci-global.org). In contrast, the levels of RSV IgG and IL-5 cytokine secretion correlated with higher lung function scores, whereas infection (NME)-induced IL-31 cytokine secretion correlated with worse lung function (Fig 6, Fig E7, *B*). Thus, children with asthma and poor lung function exhibited evidence of uniquely altered viral and allergen immunity.

DISCUSSION

Asthma has been associated with poor immune responses to viral and bacterial infections,[27-30] but this has not been described for COVID-19. Here, we report a high level of SARS-CoV-2 infection in a cohort of 53 children with asthma participating in an allergen reduction study (ARCHS) during the Delta and Omicron waves in New Orleans. Infection was confirmed primarily by serologic responses against the nucleoprotein of SARS-CoV-2 (36 children), as only a few reported a history of infection during their household visit (6 children). Although our cohort lacked a large number of uninfected children, we observed polyfunctional antibody levels and effector functions that differed by vaccination status similar to studies in adults.[43]

Pediatric asthma is caused by many factors, including genetic susceptibility and environmental exposures. Our study is similar to the results of other urban asthma studies in terms of subject demographics (race, ethnicity, sex, household income).[34,45] Overall, the cohort studied here is approximately representative of the New Orleans population in terms of race, with 57% self-reporting non-Hispanic Black in our study and 58% in the New Orleans population, according to 2022 census data.[49] There was a larger proportion of people reporting as Hispanic/Latino in our study (15%) compared to the general population (5.6%). To contextualize our analysis of SARS-CoV-2 immune responses, we also evaluated antibody and T-cell responses to RSV and common household allergens like dust mite and cockroach. Participants had high levels of atopy, with predominantly dust mite IgE (Table I).[41,42,50] Strikingly, we observed the atopic status, specifically dust mite–specific IgE, negatively related to levels of SARS-CoV-2–specific antibodies to infection (N IgG) or infection/vaccination (neutralization)—and even correlated with altered T-cell measures to infection (eg, NME-specific IL-2, MIP-1α cytokine). This indicates mechanisms underpinning atopic asthma may complicate the development of memory to SARS-CoV-2 infection or vaccination.

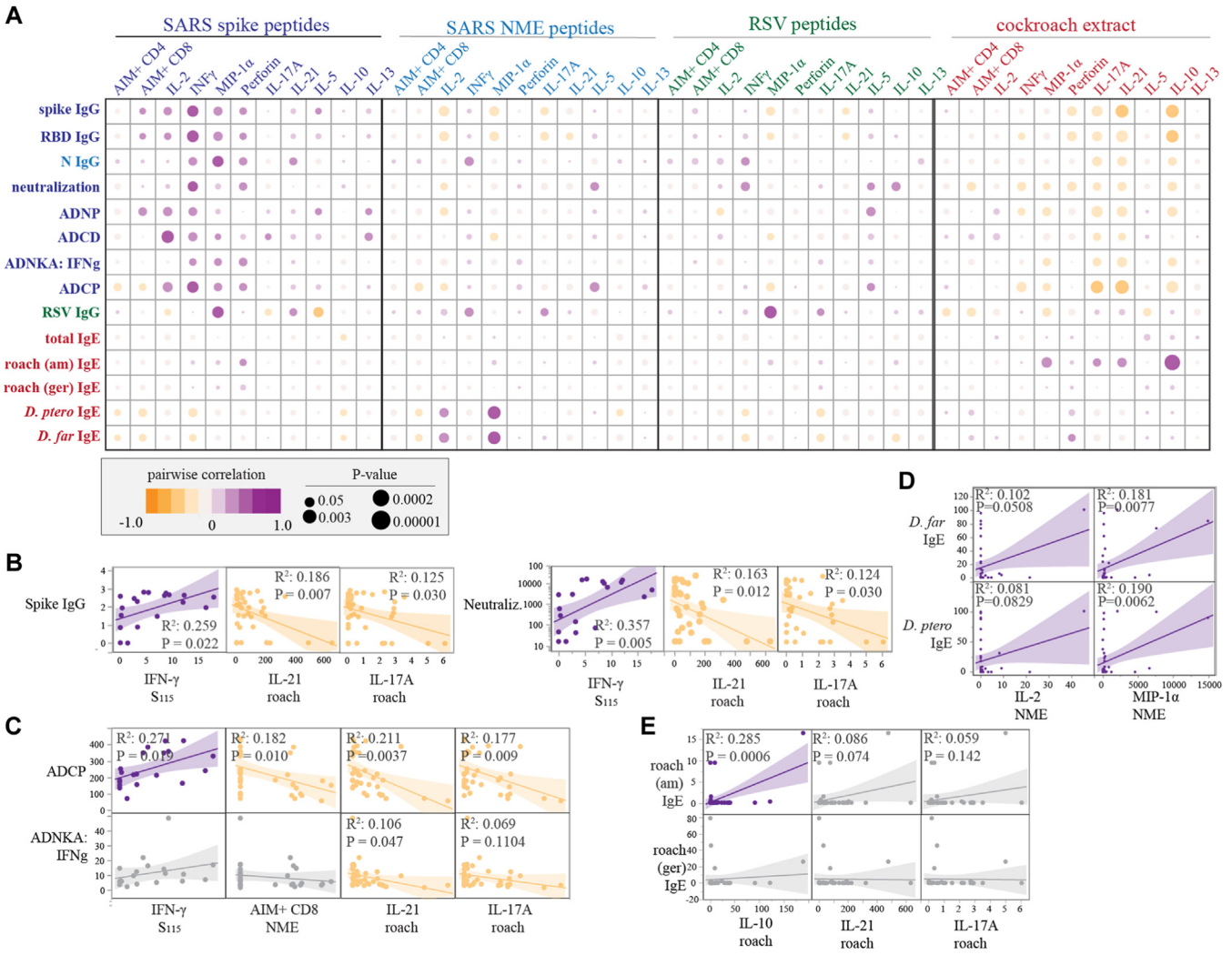

FIG 4. T-cell–mediated cytokine responses to cockroach extract and SARS-CoV-2 S peptides correlate with level of SARS-CoV-2 antibodies and allergen IgE. **(A)** Correlation analyses depicting relationships between cytokine response levels to SARS-CoV-2 spike (S_{115}), NME, RSV peptides, or cockroach extract and antibody response levels to SARS-CoV-2 and various allergens. Circle size indicates *P* value colored according to pairwise correlation based on Spearman ρ (*orange* indicates negative; *purple,* positive). **(B)** Graphs of plasma spike IgG or SARS-CoV-2 neutralization by antigen-specific IFN-γ, IL-21, or IL-17A cytokine secretion. **(C)** Graphs depicting antibody effector functions against IFN-γ, AIM^+ CD8 T cells, IL-21, and IL-17A responses to indicated SARS-CoV-2 peptides (S_{115}, NME) and cockroach extract. **(D)** Graphs depicting dust mite IgE levels against IL-2 and MIP-1α responses to NME peptides. **(E)** Graphs depicting allergen IgE levels against IL-10, IL-21, and IL-17A as response to cockroach extract. Trend lines shown for individual graphs with symbols representing individual children and associated *P* value and R^2 statistics indicated.

Even though we were limited by collected blood volumes, we were able to test 35 children for T-cell immunity using restimulation of fresh, lysed blood samples. Using this technique, we observed clear evidence for cellular immunity, with S or non-S peptide induced T_H1 cytokine secretion (eg, IFN-γ), strongly correlating to levels of anti–SARS-CoV-2 antibodies and functions. We also observed clear evidence of cockroach-specific T-cell activation and cytokine secretion, with a profile strongly distinct from that induced to SARS-CoV-2 peptide antigens. Unexpectedly, several of these cytokines negatively correlated with SARS-CoV-2 antibody responses, including those indicative of T_H17 (IL-17A), Tfh (IL-21), and Treg (IL-10) subsets, although only cockroach-induced IL-10 and IL-5 cytokine secretion was significantly associated with cockroach sIgE (Fig 4 and Fig 2, *C*). Together, these results suggest the existence of a heterotypic immune profiles to roach antigens in our cohort that warrants further investigation. However, these allergen-specific T-cell responses are consistent with published reports on T_H17/Treg dysfunction in children with asthma,[51,52] although cockroach-specific T-cell subsets have not been clearly reported. Older epidemiologic studies in this population identified similar ratios of dust mite sIgE to cockroach sIgE (one-third lower levels for cockroach), even though household pesticides targeting cockroach reduction were able to improve asthma measures (Table I).[41,42,50] Thus, we provide evidence for a second mechanism whereby cellular immune dysfunction specific to cockroach

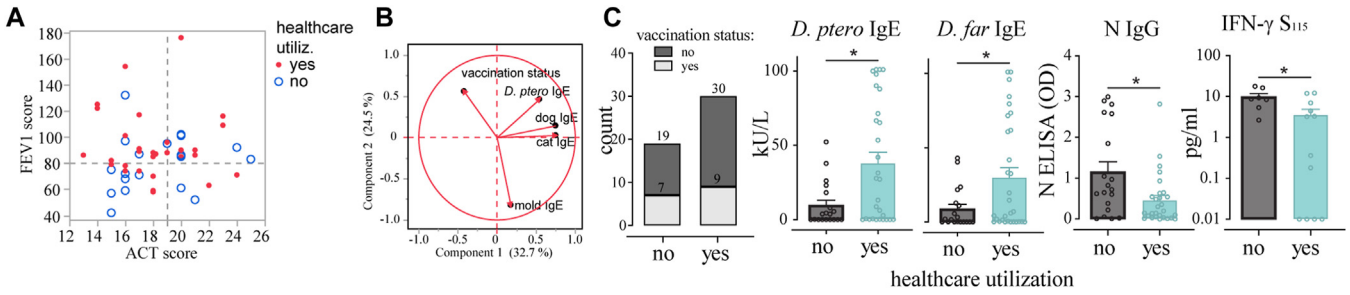

FIG 5. Vaccination history and allergen-specific IgE are key indicators of recent health care utilization for childhood asthma. **(A)** ACT versus FEV_1 score for individual subjects colored according to self-reported health care utilization in last 6 months. **(B)** PCA of 5 variables contributing to fit model for health care utilization in last 6 months from all subjects, antibody, and T-cell variables compiled from 49 infected children with missing data imputed. **(C)** Bar graphs of individual immunologic variables significantly altered by status of health care utilization in last 6 months by Mann-Whitney analysis indicated by $*P < .05$. *PCA,* Principal component analysis.

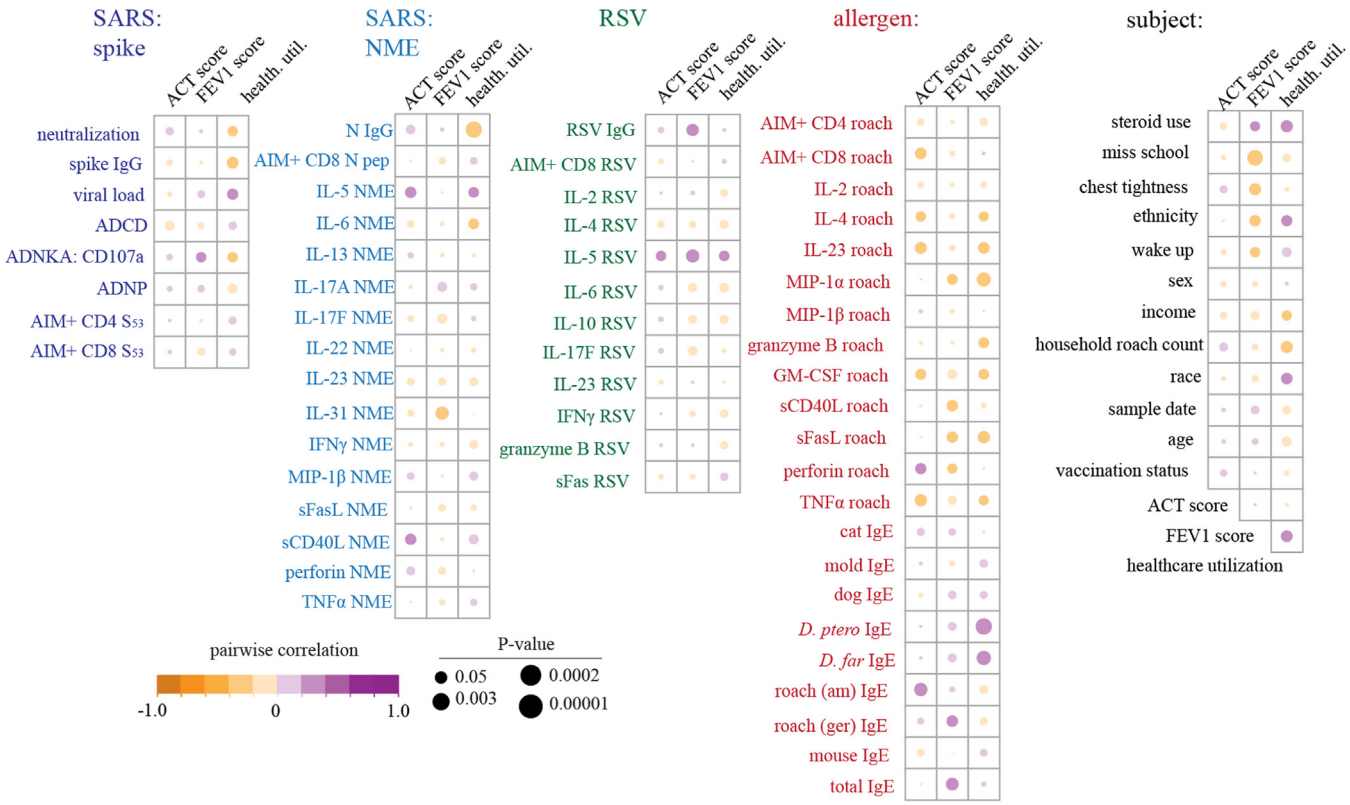

FIG 6. Feature-selected variables' correlation to health measures in children with asthma indicates that allergen and viral responses uniquely relate to asthma. Correlation analysis of ACT score, FEV_1 score, and health care utilization with various variables contributing to such variables. Circle size indicates *P* value colored according to pairwise correlation based on Spearman ρ (*orange* indicates negative, *purple,* positive).

allergens affected generation and memory responses to COVID-19 in nonatopic asthma.

As in previous studies, we observed that risk of hospitalization, emergency department visit, or unscheduled doctor visit (ie, health care utilization) in the 6 months leading up to the study visit was reduced with a history of COVID-19 vaccination or anti-N IgG,[6,7] although in our study COVID-19 vaccination may not have been available to all participants. Thus, health care utilization was observed to increase with allergen-specific atopy. We observed that cockroach-specific T-cell activation and cytokine secretion were negatively associated with our measures of asthma severity, which include ACT and FEV_1 scores. We also observed unexpected findings with SABA medication (although not steroids) as well as IL-31 responses to SARS-CoV-2 infection (eg,

induced by non-S peptides) that may indicate dysfunctional immunity in a subset of children. IL-31 is particularly interesting given the past association with abnormal T_H2 responses and asthma[53] and that in our study it correlated with poor lung function. It is tempting to speculate that an aberrant virus-induced IL-31/T_H2 responses may contribute to asthma severity and poor lung tissue function, in part through pleotropic cytokine effects on lung tissue remodeling.

Our study suggests several mechanisms whereby children with asthma have impaired host defense to SARS-CoV-2 infection or vaccination. This would complement the previous reports including atopy-related defective plasmacytoid dendritic cell responses in response to viral infection[28,29] and macrophage dysfunction with severe eosinophilic asthma, which leads to recurring infection.[33] Whether these or other mechanisms are responsible for the correlations we identified remains unknown and bears further examination.

It has also been reported that high levels of blood eosinophils in patients with or without asthma play a protective role against death due to COVID-19.[54,55] However, a limitation of our study is that we did not test for eosinophils in these children and cannot comment on how eosinophilia may have altered SARS-CoV-2 immunity. Another limitation of our study was the lack of consistent comparisons to healthy children or adults with asthma; therefore, our main conclusions are focused on comparisons between children with asthma. However, we did not find a significant difference in SARS-CoV-2 antibody response between infection children with asthma (n = 27) and infected control children (n = 9, Fig E1), although individual children exhibited considerable variations in their antibody responses. This contrasts with at least one report that found 11 adults with asthma exhibited higher levels of SARS-CoV-2–neutralizing antibodies compared to adult controls.[56] The difference in our findings could reflect intrinsic differences in study design, including asthma severity or alterations in host immunity from age-related factors, such as preexisting antibodies to coronaviruses. We also did not follow these children over time to understand their risk for repeated SARS-CoV-2 infections or more closely examine frequency of steroid or SABA use over time before sampling. Additionally, we were limited by a lack of available allergen peptide pools, so only cockroach-specific T-cell responses were evaluated. Future studies into cockroach and other allergen-specific T-cell responses in this population seem warranted given the unexpected finding that cockroach-induced T-cell activation or associated cytokines were negatively correlated with SARS-CoV-2 antibody response.

In conclusion, we report the first in-depth profiling of SARS-CoV-2 specific immunity in children with asthma compared to other virus- or allergen-specific responses. We identified evidence that allergen-specific IgE or T cells compromise the development of COVID-19 immunity. This indicates that multiple mechanisms underpinning asthma may complicate the development of memory to SARS-CoV-2 infection or vaccination and lead to a higher risk of repeated infection.

DISCLOSURE STATEMENT

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Key messages

- **Immunity to SARS-CoV-2 in populations with asthma is understudied, particularly in children.**
- **Atopic and nonatopic asthma are associated with impaired immunity to SARS-CoV-2 infection and vaccination in children and adolescents.**
- **Multiple mechanisms underpinning asthma may complicate the development of memory to SARS-CoV-2 infection or vaccination, leading to a higher risk of repeated infection.**

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