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Correlates of risk of respiratory syncytial virus disease: a prospective cohort study

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Collrane Frivold[1,2] ✉, Sarah N. Cox[1,2], Lea Starita[3,4], Tara M. Babu[1], Katherine L. Hoffman[5], Marco Carone[5], Christina M. Lockwood[3,6], Jennifer L. Kuntz[7], Richard A. Mularski[7], Alexandra Varga[7], Peter D. Han[5], Jonathan Reed[6], Eli A. Piliper[6], Shah A. K. Mohamed Bakhash[6], Alexander L. Greninger[6], Erica Clark[1], Jeremy Stone[1], Sally Grindstaff[3], Cassandra L. Boisvert[7], Neil Yetz[7], Natalie K. Lo[1], Tara L. Hatchie[1], Grace Marshall[1], Charles J. Wolock[8], Leora R. Feldstein[9], Ana A. Weil[1,10], Janet A. Englund[11,12], Allison L. Naleway[7] & Helen Y. Chu[1,2,3]

Few population-based studies have evaluated the importance of pre-existing respiratory syncytial virus (RSV) antibody on RSV susceptibility among children and adults. We conducted a prospective, community-based cohort study among individuals aged 6 months-50 years in Oregon and Washington State, USA (June 2022-May 2023), with weekly symptom surveys and swab collection regardless of symptoms. Swabs were tested for RSV using RT-qPCR. Enrollment sera were tested for RSV prefusion F IgG binding (all participants) and neutralizing antibodies (pediatric participants). We detected 305 RSV illnesses among 3237 participants from 1188 households. Using proportional hazards regression, higher RSV binding antibody titers were associated with a lower estimated hazard of RSV among pediatric participants (hazard ratio=0.66 per 1-unit difference in $\log_{10}$-RSV antibody titer; 95% CI: 0.56, 0.78). In a post-pandemic period, pre-existing RSV antibody titers were associated with a lower risk of RSV illness in children aged 6 months-17 years, which could inform vaccine development for this age group.

Respiratory syncytial virus (RSV) causes severe respiratory illness in infants, children <5 years, and adults >65 years[1–6]. Multiple prevention products[7], including vaccines for pregnant persons and older adults as well as monoclonal antibodies for infants, are now available to reduce RSV morbidity and mortality[8–11]. At scale, these interventions will likely reduce disease burden among high-risk populations, including young children, and potentially shift the incidence and distribution of RSV in other age groups[7].

RSV circulation was interrupted by COVID-19 mitigation measures[12]. Although infants have historically been disproportionately impacted by RSV, RSV-associated hospitalizations increased in children aged 12–23 months since these measures were lifted, which could

[1]Department of Medicine, University of Washington, Seattle, WA, USA. [2]Department of Epidemiology, University of Washington, Seattle, WA, USA. [3]Brotman Baty Institute for Precision Medicine, Seattle, WA, USA. [4]Department of Genome Science, University of Washington, Seattle, WA, USA. [5]Department of Biostatistics, University of Washington, Seattle, WA, USA. [6]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA. [7]Kaiser Permanente Center for Health Research, Portland, OR, USA. [8]Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY, USA. [9]Centers for Disease Control and Prevention, Atlanta, GA, USA. [10]Department of Global Health, University of Washington, Seattle, WA, USA. [11]Seattle Children's Research Institute, Seattle, WA, USA. [12]Department of Pediatrics, University of Washington, Seattle, WA, USA.
✉e-mail: cfrivold@uw.edu

be due to reduced exposure while mitigations measures were in place leading to lower levels of protective antibody[4,12–14]. To inform the implementation of RSV prevention products, age-specific incidence estimates from the community are needed to better characterize RSV burden since the onset of the COVID-19 pandemic[12] and prior to full-scale implementation of RSV prevention products in these age groups. Updated incidence estimates could also facilitate assessing how RSV prevention products impact disease burden across the age spectrum[15].

Moreover, the impact of pre-existing RSV antibodies on RSV susceptibility is incompletely defined. While previous studies have reported that RSV-specific antibodies protect against symptomatic and lower respiratory tract disease in infants[16–23], there is not a consensus on whether the same level of pre-existing RSV antibody is also protective in older children and adults. Additional research[23] could provide insight into clinical and immunologic factors protective against infection and disease, which could inform the design and implementation of RSV prevention products intended for multiple age groups. For instance, since the approval of RSV prevention products that protect infants and older adults, RSV vaccine research and development efforts are now focused on products intended for other age groups including older children, adolescents, and adults. As such, antibody data from these age groups are needed to inform the development of next-generation prevention products. In particular, vaccine responses in children aged 5–12 years who have likely been exposed to RSV multiple times may differ from RSV-naïve infants entering their first season as well as older adults due to immunosenescence.

Using data from the CASCADIA study[24], we aimed to prospectively evaluate the association between baseline RSV antibody titers and risk of RSV illness among household members in a community setting after COVID-19 mitigation measures were lifted and prior to the approval of RSV prevention products to protect high-risk infants and older adults. We hypothesized that higher RSV antibody titers would be protective against incident RSV illness in children.

Results

Participants

Overall, 3237 individuals in 1188 households (Table 1; Supplementary Fig. 1) were enrolled on a rolling basis beginning in June 2022 through May 2023, with self-collection of weekly swabs. The median follow-up duration from the baseline blood draw to when a participant subsequently tested positive for RSV, withdrew from the study, or the end of the analytic period (May 31, 2023) was 189 days. See Supplementary Fig. 2 for individual participant timelines illustrating when participants enrolled and collected swabs throughout the analytic period among participants with RSV A and B illnesses, respectively. Weekly swabbing compliance was high; participants missed a median of 2 weekly swab instances (range: 0–46 weeks). Participant retention was also high, with 96.42% remaining in the study at the end of the analytic period. A total of 79,779 swabs were collected during the analytic period, of which 0.44% (n = 345 positive; n = 4 inconclusive) and 0.09% (n = 72 positive; n = 1 inconclusive) tested positive/inconclusive for RSV subtypes A and B, respectively (Supplementary Fig. 2). During RSV illness episodes, 29.84% of participants had RSV co-detected with one or more other pathogens (n = 91/305). RSV A/B was most frequently co-detected with rhinovirus (70.33%; n = 64/91); adenovirus (16.48%; n = 15/91); and influenza (12.09%; n = 11/91). Overall, most participants/guardians collected their nasal swabs in a valid manner with sufficient Ribonuclease P (RNase P) detection, which indicates adequate mucosal sampling by measuring nasal epithelial cells, with only 0.72% and 0.93% of the swabs tested for RSV A (n = 549/76284) and B (n = 171/18415), respectively, failing due to insufficient RNase P detection.

Overall, 328 participants experienced an RSV infection, regardless of symptom status, during the study period. Of these infections, 92.99% (n = 305/328) were symptomatic, defined as ≥1 respiratory illness symptom (e.g., fever, cough, sore throat, shortness of breath, myalgia, rhinorrhea). RSV illnesses (n = 305) were detected between September 2022 and May 2023, including 247 RSV A (September-May) and 63 RSV B (October-May) illnesses. Five participants had unique RSV A and B illness episodes at different timepoints; only the first illness episode was included in the analysis of incident RSV illness. The proportion of participants with RSV by age group was as follows: 6 months to 1 year (24.00%; n = 24/100); 2–4 years (24.46%; n = 57/233); 5–12 years (11.36%; n = 106/933); 13–17 years (5.41%; n = 19/351); 18–50 years (6.11%; n = 99/1620). Demographic characteristics were generally similar between individuals with and without RSV (Table 1). However, the median age was lower among participants with RSV compared to those without RSV (median age of 9 versus 30 years). Among participants <5 years, a greater proportion with RSV attended daycare compared to those without RSV (71.6% versus 61.9%). Of the adults with RSV (n = 99), 82.83% lived with children <18 years; 42.42% lived with a child <5 years of age attending daycare. Overall, study participants were healthy and few reported comorbidities. See Supplementary Tables 1, 2 for baseline characteristics by study site and RSV prefusion F (pre-F) binding antibody category.

RSV illness incidence

Among participants <5 years, we observed an earlier rise in incidence and higher incidence rates throughout the season compared to other age groups (Supplementary Fig. 3). Similarly, estimated RSV A/B peak monthly incidence rates per 1,000 person-days were higher among children <5 years (7.74 cases [95% confidence interval [CI]: 3.42, 17.52] for 6 months–1 year; 6.34 [95% CI: 3.60, 11.18] for 2–4 years) compared to children 5–17 years of age (2.65 [95% CI: 1.92, 3.68] for 5–12 years; 0.46 [95% CI: 0.15, 1.43] for 13–17 years) and adults (1.04 [95% CI: 0.69, 1.55]). During the months in which each RSV subtype was detected, the average monthly incidence rates were 2.07×10^{-3} (95 CI: 1.54×10^{-3}, 2.77×10^{-3}) and 0.39×10^{-3} (95% CI: 0.29×10^{-3}, 0.53×10^{-3}) per 1000 person-days for RSV A and B, respectively.

RSV illness characteristics

Among all participants, the most frequently reported symptoms were rhinorrhea, cough, and sore throat (Table 2). A higher proportion of participants 6 months–1 year reported shortness of breath (29.17%) compared to participants 2–17 years of age (5.26–6.60%) and adults 18–50 years of age (15.15%). Compared to pediatric participants, adults reported fever (17.17% versus 27.18%), rhinorrhea (86.87% versus 94.17%), and cough (63.64% versus 86.41%) less frequently, but reported sore throat (58.59% versus 35.44%), fatigue (50.51% versus 23.79%), headache (42.42% versus 19.42%), and myalgia (18.18% versus 8.25%) more frequently. See Supplementary Tables 3–6 for illness characteristics by RSV subtype and symptom reporting frequency by illness week.

During RSV illness, absenteeism (n = 24/81; 29.63%) and care-seeking (n = 15/81; 18.52%) were most common among children <5 years (Table 2). Among adults, 15.15% (n = 15/99) reported being absent from work/school. Both adult and pediatric participants sought care at a doctor's office or urgent care facility most frequently (70.27%; n = 26/37) followed by telehealth services (32.43%; n = 12/37) with two participants seeking care at both locations during their illness episodes. One hospitalization was reported among a participant 6 months–1 year with RSV B; no adults were hospitalized. See Supplementary Table 7 for symptom reporting frequency by care-seeking status.

As age increased, relative cycle threshold (C_{rt}) measured on Day 0 of an illness episode increased (Table 2). Although adult participants tended to experience more mild illness, the C_{rt} distribution was similar between children and adults (Supplementary Fig. 4). We also observed a similar C_{rt} distribution stratified by co-detection status (Supplementary Fig. 5). During an illness episode, C_{rt} values typically increased over time corresponding to a decrease in viral load; measurable C_{rt} values on multiple swabs after the first positive swab, suggesting

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Table 1 | Baseline characteristics of CASCADIA study population stratified by RSV A/B illness status (n = 3237 individuals; 1188 households)[a]

	RSV A/B illness		Total (N = 3237)
	No (n = 2932)	Yes (n = 305)	
Overall household characteristics (regardless of enrollment status)			
Enrollment site			
Oregon, USA	1507 (51.40%)	124 (40.66%)	1631 (50.39%)
Washington, USA	1425 (48.60%)	181 (59.34%)	1606 (49.61%)
Household density			
Lives alone	21 (0.72%)	3 (0.99%)	24 (0.74%)
2–4 people	2276 (77.81%)	217 (71.38%)	2493 (77.21%)
5+ people	628 (21.47%)	84 (27.63%)	712 (22.05%)
Number of children in household			
No children	82 (2.80%)	5 (1.64%)	87 (2.69%)
1 child	789 (26.91%)	64 (20.98%)	853 (26.35%)
2–4 children	2018 (68.83%)	234 (76.72%)	2252 (69.57%)
5+ children	36 (1.23%)	1 (0.33%)	37 (1.14%)
Household income			
Below study median (<$100,000)	987 (33.66%)	96 (31.48%)	1083 (33.46%)
Study median ($100,000–$124,999)	719 (24.52%)	78 (25.57%)	797 (24.62%)
Above study median (≥$125,000)	1127 (38.44%)	127 (41.64%)	1254 (38.74%)
Prefer not to say	92 (3.14%)	3 (0.98%)	95 (2.93%)
Enrolled household member characteristics			
Number of fully enrolled participants in household			
Median [Min, Max]	3 [1, 8]	3 [1, 7]	3 [1, 8]
Children in household (yes/no)			
Yes	2746 (93.66%)	288 (94.43%)	3034 (93.73%)
Children < 5 years attend daycare (yes/no)			
Yes	830 (28.31%)	142 (46.56%)	972 (30.03%)
Individual characteristics			
Age group			
6 months–1 year	76 (2.59%)	24 (7.87%)	100 (3.09%)
2–4 years	176 (6.00%)	57 (18.69%)	233 (7.20%)
5–12 years	827 (28.21%)	106 (34.75%)	933 (28.82%)
13–17 years	332 (11.32%)	19 (6.23%)	351 (10.84%)
18–50 years	1521 (51.88%)	99 (32.46%)	1620 (50.05%)
Sex assigned at birth			
Female	1720 (58.66%)	179 (58.69%)	1899 (58.67%)
Gender			
Male	1182 (40.31%)	123 (40.33%)	1305 (40.32%)
Female	1640 (55.93%)	174 (57.05%)	1814 (56.04%)
Transgender	42 (1.43%)	4 (1.31%)	46 (1.42%)
Other	68 (2.32%)	4 (1.31%)	72 (2.22%)
Race			
American Indian or Alaska Native	13 (0.44%)	1 (0.33%)	14 (0.43%)
Asian	217 (7.40%)	21 (6.89%)	238 (7.35%)
Black or African American	72 (2.46%)	4 (1.31%)	76 (2.35%)
Native Hawaiian or other Pacific Islander	4 (0.14%)	1 (0.33%)	5 (0.15%)
White	2226 (75.92%)	220 (72.13%)	2446 (75.56%)
Multiracial	298 (10.16%)	52 (17.05%)	350 (10.81%)
Other	73 (2.49%)	5 (1.64%)	78 (2.41%)
Hispanic			
Yes	253 (8.63%)	26 (8.52%)	279 (8.62%)
Health insurance			
Employer-sponsored health insurance	2440 (83.22%)	285 (93.44%)	2725 (84.18%)
Individual health insurance	114 (3.89%)	3 (0.98%)	117 (3.61%)
Government insurance program	270 (9.21%)	13 (4.26%)	283 (8.74%)

Table 1 (continued) | Baseline characteristics of CASCADIA study population stratified by RSV A/B illness status (n = 3237 individuals; 1188 households)a

	RSV A/B illness		Total (N = 3237)
	No (n = 2932)	Yes (n = 305)	
None	24 (0.82%)	1 (0.33%)	25 (0.77%)
Other	42 (1.43%)	1 (0.33%)	43 (1.33%)
Any smoking (yes/no)			
Yes	31 (1.06%)	0 (0%)	31 (0.96%)
Missing	*975 (33.25%)*	*180 (59.02%)*	*1155 (35.68%)*
Overall health (self-reported)			
Poor/fair	75 (2.56%)	6 (1.97%)	81 (2.50%)
Good/very good	1711 (58.36%)	128 (41.97%)	1839 (56.81%)
Excellent	1146 (39.09%)	171 (56.07%)	1317 (40.69%)
Comorbidities (self-reported)			
Asthma	436 (14.87%)	32 (10.49%)	468 (14.46%)
Chronicobstructive pulmonary disease (including chronic bronchitis and emphysema)	7 (0.24%)	0 (0%)	7 (0.22%)
Hypertension	140 (4.77%)	8 (2.62%)	148 (4.57%)
Immunocompromised	56 (1.91%)	3 (0.98%)	59 (1.82%)
Other[b]	954 (32.54%)	57 (18.69%)	1011 (31.23%)

[a]Percentages of missing data are shown if variable missingness is ≥5%.
[b]Other comorbidities included sleep apnea, heart disease, congenital heart disease, heart failure, down syndrome, diabetes (high blood sugar), liver condition, weak or failing kidneys, cancer or malignancy, arthritis, stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE), sickle cell disease or thalassemia, depression, anxiety, or thyroid issues. No participants reported any other health issues.

longer time to viral clearance, was more common among children (Supplementary Fig. 6).

Distribution of baseline RSV antibody titers

We assessed RSV binding antibody in all serum samples, and RSV neutralizing antibody in pediatric serum samples (Fig. 1). Overall, median $\log_{10}$-binding antibody titers (Fig. 1A) and $\log_{10}$-neutralizing antibody titers (Fig. 1B) increased with age but titer variability, represented by the standard deviation (SD), decreased. Based on a nonparametric coefficient of determination (R^2), 69.06% of the variability in neutralizing antibody titers could be predicted from binding antibody titers among pediatric participants (95% CI: 0.63, 0.74) (Fig. 2; Supplementary Table 8) suggesting that binding and neutralizing antibody titers were moderately correlated. Antibody titers stratified by age group and RSV illness status are shown in Fig. 2C, D. See Supplementary Fig. 7 for antibody titers stratified by continuous age.

Risk of RSV illness

The overall estimated hazard ratio (HR) of RSV illness was 0.66 (95% CI: 0.56, 0.78) for any two groups differing by 1-unit in $\log_{10}$-binding antibody titers, with the higher titer group having a lower estimated hazard (Table 3). This association was statistically significant among pediatric participants (HR = 0.66; 95% CI: 0.56, 0.78), but not adults (HR = 0.62; 95% CI: 0.32, 1.20). When further stratifying by pediatric age group, the estimated association was strongest among participants aged 5–12 years (HR = 0.41; 95% CI: 0.27, 0.61). Among pediatric participants, higher $\log_{10}$-neutralizing antibody titers were also associated with a lower estimated hazard of subsequent RSV illness (HR = 0.36; 95% CI: 0.25, 0.53).

Standardized antibody titers. We observed similar HRs for binding and neutralizing antibody titers using SD-standardized antibody titers among pediatric participants. For any two groups differing by one SD in $\log_{10}$-antibody titers, the estimated HRs were 0.69 (95% CI: 0.60, 0.80) and 0.59 (95% CI: 0.48, 0.71) for binding and neutralizing antibody titers, respectively, with the higher titer group estimated to have a lower hazard of RSV (Supplementary Table 9).

To explore if there was a threshold effect of antibody titers on the risk of RSV illness, we estimated HRs for this association using antibody titer categories (Fig. 3). Compared to the lowest antibody titer category, we observed a dose-response relationship, with higher antibody titers associated with a lower estimated hazard of RSV for both binding and neutralizing antibody titers. Similarly, the slope of the estimated covariate-adjusted cumulative incidence curve (Fig. 4) was steepest for participants with lower antibody levels for both binding and neutralizing antibodies. At 180 days since baseline blood collection, the cumulative incidence in the low antibody category was estimated to be 21.70% and 19.77% for binding and neutralizing antibodies, respectively. For the very high antibody category, the cumulative incidence was estimated to be 3.50% and 3.95% for binding and neutralizing antibodies, respectively. See Supplementary Tables 10, 11 for additional proportional hazards (PH) sensitivity analyses conducted among all participants regardless of symptom status.

Variable importance analysis. To more directly compare binding and neutralizing antibody titers measured in different units as well as their combination, we also conducted a variable importance analysis to quantify the ability of these antibodies to predict RSV illness at 180 days since enrollment. Using PH regression with baseline covariates alone (age, school/daycare attendance, and immunocompromised status), we estimated the achievable area under the receiver operating curve (AUC) with these models to be 0.70 (Fig. 5). When using antibody titers in addition to baseline covariates, the ability to predict RSV illness beyond random chance (AUC = 0.50) increased by 27.06% (estimated AUC = 0.76) and 29.48% (estimated AUC = 0.76) for binding and neutralizing antibodies, respectively. Using both binding and neutralizing antibody titers combined further increased the ability to predict RSV illness (estimated AUC = 0.77) resulting in a relative increase of 32.72%.

Discussion

We conducted a prospective community-based cohort study among household members in understudied age groups including school-aged children (5–12 years), teenagers (13–17 years), and adults (18–50 years) following a period of suppressed viral circulation due to COVID-

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Table 2 | Illness characteristics among participants with RSV A/B illness episodes[a] stratified by age group (n = 305)

Illness characteristic	6 months–1 year (*n* = 24)	2–4 years (*n* = 57)	5–12 years (*n* = 106)	13–17 years (*n* = 19)	18–50 years (*n* = 99)	Overall (*n* = 305)
RSV relative cycle threshold (C_T) value of first positive swab[b]						
Median [Min, Max]	13.93 [8.79, 24.71]	15.82 [4.91, 27.03]	18.89 [4.62, 27.91]	19.19 [9.84, 26.85]	20.92 [7.68, 27.86]	18.66 [4.62, 27.91]
Missing	2 (8.33%)	7 (12.28%)	8 (7.55%)	1 (5.26%)	9 (9.09%)	27 (8.85%)
Symptom reported (yes/no)[c]						
Rhinorrhea	24 (100%)	55 (96.49%)	96 (90.57%)	19 (100%)	86 (86.87%)	280 (91.80%)
Cough	21 (87.50%)	54 (94.74%)	88 (83.02%)	15 (78.95%)	63 (63.64%)	241 (79.02%)
Sore throat	2 (8.33%)	14 (24.56%)	46 (43.40%)	11 (57.89%)	58 (58.59%)	131 (42.95%)
Fatigue	7 (29.17%)	14 (24.56%)	25 (23.58%)	3 (15.79%)	50 (50.51%)	99 (32.46%)
Headache	1 (4.17%)	6 (10.53%)	28 (26.42%)	5 (26.32%)	42 (42.42%)	82 (26.89%)
Fever	10 (41.67%)	21 (36.84%)	22 (20.75%)	3 (15.79%)	17 (17.17%)	73 (23.93%)
Myalgia	1 (4.17%)	5 (8.77%)	10 (9.43%)	1 (5.26%)	18 (18.18%)	35 (11.48%)
Shortness of breath	7 (29.17%)	3 (5.26%)	7 (6.60%)	1 (5.26%)	15 (15.15%)	33 (10.82%)
Missed work, school, or daycare (yes/no)	7 (29.17%)	17 (29.82%)	20 (18.87%)	4 (21.05%)	15 (15.15%)	63 (20.66%)
Any care seeking (yes/no)[d]	6 (25.00%)	9 (15.79%)	10 (9.43%)	1 (5.26%)	11 (11.11%)	37 (12.13%)

[a]Reporting at least one of the following acute respiratory illness symptoms ± 7 days from the first positive swab date (Day 0) was required based on the symptomatic RSV infection definition: Fever, cough, sore throat, shortness of breath, myalgia, and rhinorrhea. Although fatigue and headache are reported in this table, they were not included as part of the RSV illness definition.

[b]For comparability, relative cycle threshold values are reported for swabs tested on the multipathogen ("open array") assay.

[c]Symptoms were self- and/or caregiver-reported −7 days to +14 days from Day 0; for participants <13 years, surveys were sent to the caregiver instead of the participant; symptoms were not evaluated by a clinician.

[d]Care seeking (yes/no) was defined as seeking care for an illness from a healthcare provider at the following locations: doctor's office, urgent care, pharmacy, hospital, telehealth visit, and other. One hospitalization was reported among a participant 6 months to 1 year with RSV B; no adults were hospitalized.

19 mitigation measures. Using weekly symptom surveillance and home-based swabbing, we detected RSV illnesses at the community level including among individuals who did not seek medical care, a population not typically studied. Young children had the highest incidence of RSV illness, particularly those attending daycare. Adult RSV illness episodes were less severe than pediatric cases, with a lower proportion reporting fever and/or shortness of breath, missing work/school, and seeking care. Among all participants, higher baseline RSV-specific binding antibodies were associated with a decreased hazard of RSV. Among pediatric participants, both baseline binding and neutralizing antibodies were associated with a decreased hazard of RSV. Using antibody titer categories, we observed a potential dose-response relationship with higher antibody titers associated with a lower estimated hazard of RSV for both binding and neutralizing antibody. Furthermore, based on a variable importance analysis among pediatric participants, we found that binding and neutralizing antibody titers had a similar ability to predict RSV illness occurring by 180 days of follow-up after accounting for baseline sociodemographic and clinical risk factors.

We observed similar monthly incidence rates among children aged 6 months–1 year and 2–4 years. Although prior studies have typically documented the highest burden of disease among infants[1,4–6], many of these studies only enrolled young children presenting for medical attention or hospital care. Notably, our study population did not include infants <6 months who are known to be at high risk of RSV morbidity and mortality[1,4–6]. However, our finding of increased RSV incidence rates in participants 2–4 years may be due to suppressed viral circulation and lower population-level immunity as a result of COVID-19 mitigation measures, leading to a greater pool of susceptible children in this post-pandemic period, which has been observed in other studies[4,12–14]. In our study population, we found that RSV illness was more likely to be first detected in the youngest age groups (6 months–1 year; 2–4 years) earlier in the respiratory virus season, followed by detection in older children (5–12 years; 12–17 years) and adults (18–50 years). This seasonality suggests that the predominant site of transmission occurs in settings with young children such as daycares and schools. This finding aligns with previous household-based studies conducted with different study designs, which found that school-aged children frequently introduce RSV into households[25–28].

Fever, shortness of breath, care-seeking, and absenteeism were less frequently reported among symptomatic adult compared to pediatric participants. We also found that while 29.07% of adults in our study lived in households with children <5 years attending daycare (n = 471/1620), 42.24% of adults with RSV lived in those households (n = 42/99). Although RSV burden is not well-characterized among healthy adults, our findings are consistent with prior studies. For instance, a household transmission study among families with young children in Rochester, New York reported that 45.88% of members from positive households became infected with RSV[25]. A key difference in our study population is that we only observed 15.15% absenteeism among adults compared to previous studies reporting up to 38.0% work-absenteeism during RSV illness[29,30]. We may have observed lower absenteeism rates due to changes in telecommuting policies since the COVID-19 pandemic and individuals continuing to work from home during illness.

Higher levels of RSV neutralizing antibody have been shown to protect against disease in both observational studies[20] and clinical trials[8,21,22] of pre-F subunit RSV vaccines administered to maternal and older adult populations and monoclonal antibody prophylaxis administered to infants. Among our pediatric population of children 6 months–17 years, in whom both antibodies were measured, we found that binding and neutralizing antibody were moderately correlated. We also evaluated RSV pre-F binding antibody in serum collected prior to illness and found that (1) antibody titers increased with age and (2)

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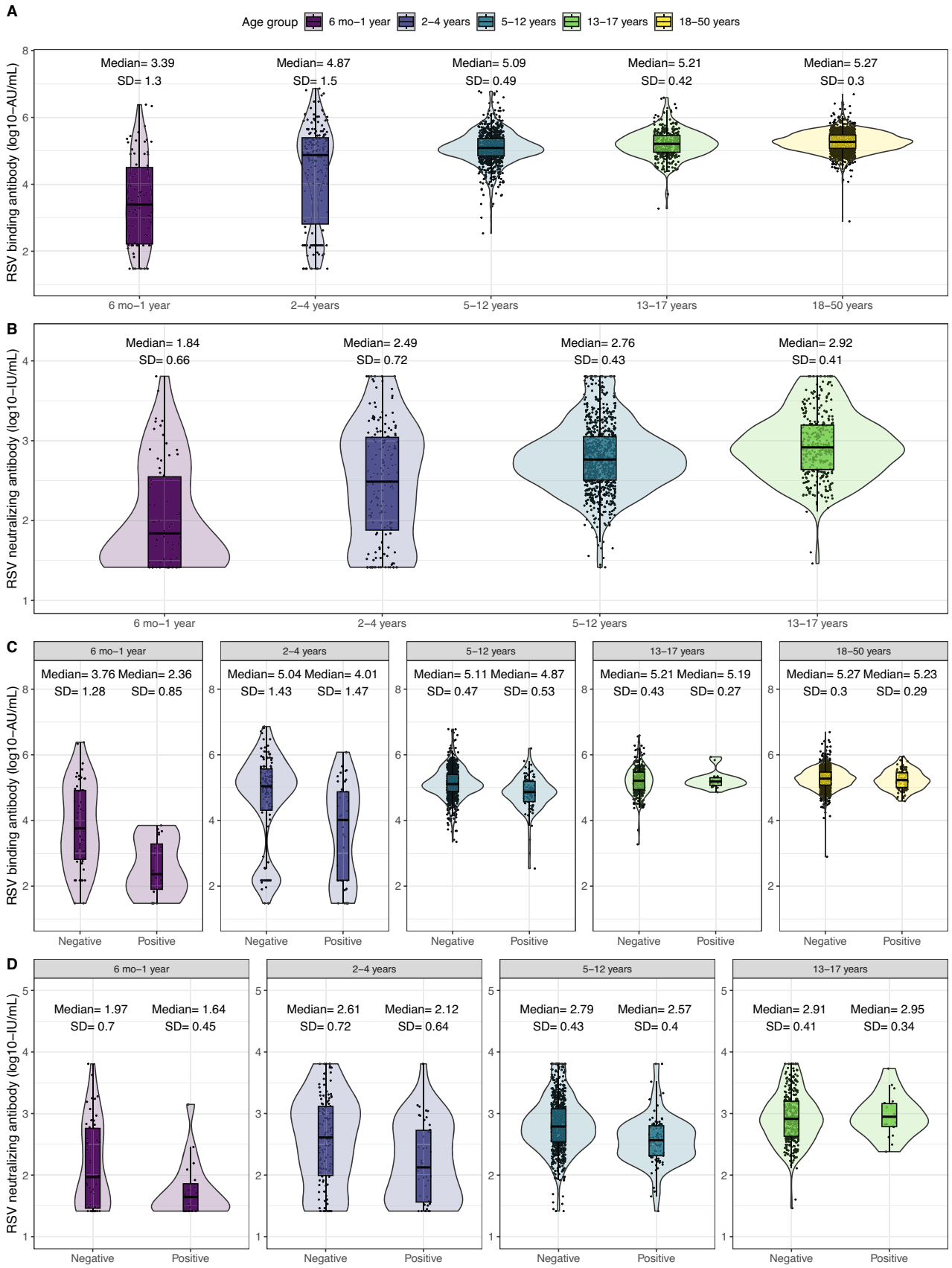

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Fig. 1 | Baseline RSV antibody titers stratified by age group and RSV A/B illness status. Plots show participant-level antibody titers represented by the dots, which are overlaid by box plots and violin plots to illustrate the distribution and density of the antibody data. Box-plot elements are defined as follows: center line, median; box limits, upper and lower quartiles; whiskers, 1.5× interquartile range. Baseline antibody titers are stratified by age group only for (**A**) binding antibody titers (log_{10}-AU/mL) (n = 2996) and (**B**) neutralizing antibody titers (log_{10}-IU/mL) (n = 1373). These plots are further stratified by RSV A/B illness status for (**C**) binding antibody titers (log_{10}-AU/mL) (n = 2996) and (**D**) neutralizing antibody titers (log_{10}-IU/mL) (n = 1373). Abbreviations: log_{10}-AU/mL log_{10}-transformed arbitrary units per milliliter, log_{10}-IU/mL log_{10}-transformed international units per milliliter, RSV respiratory syncytial virus, SD standard deviation.

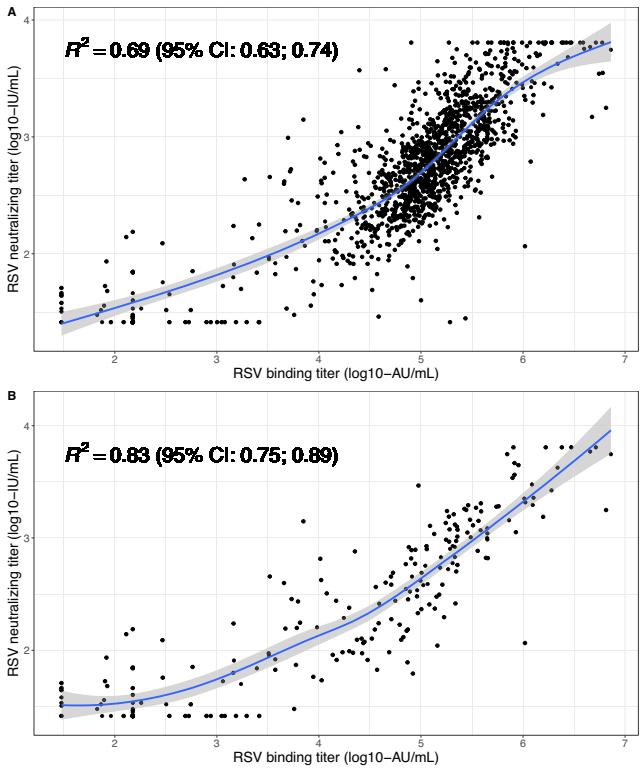

Fig. 2 | Nonparametric coefficient of determination (R^2) between baseline RSV pre-F binding antibody titers and neutralizing antibody titers among pediatric participants. Correlation between binding and neutralizing antibody titers measured at baseline among (**A**) all pediatric participants 6 months–17 years (n = 1355) and (**B**) pediatric participants 6 months–4 years (n = 323). Data are presented as a scatter plot of individual participants' binding and neutralizing antibody titer measurements overlaid with a blue correlation trendline ± the standard error of the smooth as a 95% confidence interval shown in gray. Abbreviations: log_{10}-AU/mL log_{10}-transformed arbitrary units per milliliter, log_{10}-IU/mL log_{10}-transformed international units per milliliter, RSV respiratory syncytial virus, R^2 nonparametric coefficient of determination.

higher antibody titers were associated with a decreased risk of RSV illness in our overall study population and among pediatric participants. Since previous studies have reported that RSV-specific antibodies from both natural infection and vaccination protect against RSV disease in infants, our findings suggest that vaccine-induced RSV antibodies may also provide protection against RSV illness in future clinical trials conducted among children >6 months of age.

Although higher binding antibody titers protected against RSV illness in our overall study population, when further stratifying by adult versus pediatric participants, this association was not statistically significant among adults; this may be because our adult participants had baseline binding antibody titers in a narrow range of high values, consistent with adults being exposed to RSV many times and building up higher antibody titer levels on average compared to young children. Moreover, our adult participants only experienced mild illnesses. As such, we may have observed a stronger protective association of binding antibody titers in a hospital- or outpatient-setting compared to our community-based cohort or if our study had included higher-risk adults.

We observed wider HR CIs using neutralizing compared to binding antibody, which was observed previously[23]. This could be due to a narrower distribution of neutralizing antibody titers, more participants with titers below the lower limit of quantitation for the microneutralization assay, and/or differences in assay measurement error. While these findings should be validated using post-vaccination sera as part of upcoming RSV vaccine clinical trials, our results suggest that binding antibody titers could be a viable RSV correlate of protection and alternative to neutralizing antibody, which is considerably more time- and resource-intensive to measure. The relevance of binding antibody as a potential RSV correlate of protection was further supported by the variable importance analysis, which suggested that binding and neutralizing antibody titers have a similar ability to predict RSV illness beyond baseline covariates when the predictive ability of these antibody titers was directly quantified to account for differences in their measurement scales/units. Moreover, since using binding and neutralizing antibody titers together resulted in the highest estimated AUC, our findings suggest that these biomarkers may partly provide complementary information for predicting RSV illness. Future studies should further explore binding antibodies as a correlate of risk against RSV illness, the role of binding versus neutralizing antibodies in protection against different RSV disease outcomes, as well as a composite biomarker leveraging both binding and neutralizing antibodies[23]. Researchers should also consider incorporating variable importance analyses into future studies to facilitate comparing RSV antibodies reported in different scales/units across studies.

Since our study population was relatively homogeneous with most individuals reporting few comorbidities and from households with higher socioeconomic status, our results may not be generalizable to the overall United States population or specific high-risk groups such as infants <6 months, older adults, or individuals with comorbidities. Moreover, we did not evaluate serology from the timepoint immediately prior to illness, which may have provided more precise estimates of the association of interest compared to baseline serology. In addition to pre-F antibody, there may be other RSV antibodies that protect against illness not captured in this analysis. Neutralizing antibody testing was not performed on adult sera, and it is possible that we may have observed different trends among adults using neutralizing compared to binding antibody. Moreover, our ability to capture asymptomatic disease was partially limited by our protocol, whereby all swabs were tested for RSV A, but only a subset were tested for RSV B, particularly for symptomatic participants. There is also a potential risk for misclassification of RSV illness status if a false-negative RT-qPCR result was reported and/or due to missing swabs. Furthermore, although RSV is often the driver of the illness when co-detected with other pathogens, co-detections may have impacted our observed association between RSV antibodies and RSV illness. However, we expect the impact of co-detections to be minimal since RSV was most frequently co-detected with rhinovirus (70.33%; n = 64/91) and C_{rt} values were similar by co-detection status. Although severe morbidity and mortality were not observed in this study, preventing mild to moderate RSV illness in the community is of public health importance to prevent community transmission, protect vulnerable populations, and alleviate the burden on strained health systems.

This study represents a unique approach to the evaluation of RSV in children >6 months of age and adults, and provides an evaluation of RSV antibodies within a large, community-based cohort. In a period after COVID-19 mitigation measures were removed, we estimated RSV incidence across a broad age range finding that higher antibody levels were associated with a lower risk of mild to moderate RSV illness overall (6 months–50 years) and in children 6 months–17 years of age. Both our approach to tracking disease in the community and the correlation of clinical and laboratory findings are innovative approaches that will facilitate evaluation of RSV prevention products across the age spectrum. These data provide important baseline evidence for immunization policy decision-making and implementation of RSV prevention products, particularly next-generation RSV vaccines targeting young children 2–4 years of age as well as school-aged children 5–12 years of age.

Table 3 | Hazard ratios of the association between baseline antibody titers and RSV A/B illness[a,b]

Age Group	Hazard Ratio	95% CI	*P* value
Binding antibody titers (log_{10}-AU/mL)			
Overall	0.66	0.56, 0.78	6.20×10^{-7}
Pediatric participants (6 months–17 years)[c]	0.66	0.56, 0.78	6.77×10^{-7}
6 months–1 year	0.63	0.46, 0.88	6.33×10^{-3}
2–4 years	0.72	0.60, 0.86	3.88×10^{-4}
5–12 years	0.41	0.27, 0.61	1.56×10^{-5}
13–17 years	1.56	0.77, 3.16	0.22
Adult participants (18–50 years)	0.62	0.32, 1.20	0.15
Neutralizing antibody titers (log_{10}-IU/mL)			
Pediatric participants (6 months–17 years)	0.36	0.25, 0.53	1.22×10^{-7}
6 months–1 year	0.57	0.24, 1.36	0.20
2–4 years	0.42	0.25, 0.69	5.87×10^{-4}
5–12 years	0.20	0.11, 0.38	7.09×10^{-7}
13–17 years	1.28	0.45, 3.65	0.64

[a]Hazard ratios (HR) represent the estimated difference in the hazard of symptomatic RSV infection for any two groups differing by 1-unit in log_{10} antibody titers, with the higher log antibody titer group having a lower hazard of symptomatic RSV infection when the HR is less than 1. Since binding and neutralizing antibody titers have different units and scales, the strength of the association between these two antibodies and RSV illness are not directly comparable.
[b]Cox proportional hazard models were adjusted for age group, school/daycare attendance, and immunocompromised status; clustered by household ID to account for correlated data between household members; and stratified by 2-week enrollment intervals to account for seasonality. All models were two-sided, and no adjustments were made for multiple comparisons. Effect sizes are reported as HRs with Wald-type 95% CIs constructed using robust standard errors. Degrees of freedom are equal to 1 for each covariate. All p-values are exact and two-sided based on the Wald z statistic. In the Cox proportional hazards models, we tested the null hypothesis that the HR is equal to 1. See Supplementary Table 13 for details.
[c]When evaluating whether the association of interest is modified by pediatric versus adult age group, we fail to reject the null hypothesis that the estimated difference in the hazard of symptomatic RSV infection for two groups differing by 1-unit in log_{10} antibody titers is equal for adults and children (p = 0.80).

Methods

Data source

We used data from the first year of the CASCADIA study (June 2022-May 2023), a community-based prospective cohort study of households in the states of Washington and Oregon in the United States[24,31]. The study protocol was reviewed and approved by the Kaiser Permanente Inter-regional Institutional Review Board, with reliance from University of Washington (UW) and Seattle Children's Research Institute (See 45 C.F.R. part 46.114; 21 C.F.R. part 56.114). Informed consent was obtained from all adult participants. For pediatric participants, informed consent was obtained from the minor's parent or legal guardian. We also obtained assent from children 7–17 years of age. If a participant turned 18 years old while participating in the study, we then consented these individuals as adults.

Data collection

Upon enrollment, participants (or their parent/guardian) completed an enrollment survey on demographic characteristics and health status, and attended a baseline blood draw appointment. Nasal swab kits were mailed to participants' homes with instructions for self- and parent/guardian-collection. Participants completed weekly online symptom surveys and home nasal swabs regardless of symptoms. Participants could also report new or worsening symptoms at any time; if this occurred >72 h after their last swab, they were prompted to collect another swab. Participants with a reported illness or a positive test for SARS-CoV-2, influenza A, or RSV A completed additional surveys about symptoms, care-seeking, and absenteeism. For participants <13 years of age, symptoms were reported by the participant's parent/

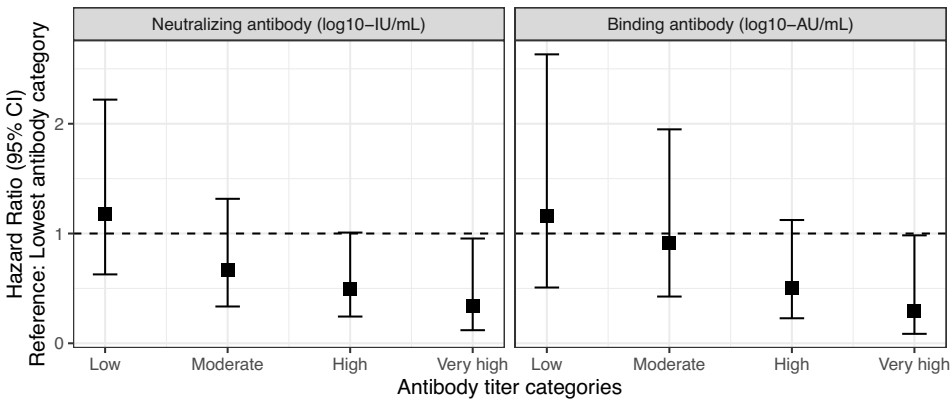

Fig. 3 | Hazard ratios of the association between categorical baseline antibody titers and RSV A/B illness by antibody type. The x-axis shows the low, moderate, high, and very high antibody titer categories for neutralizing and binding antibody. The y-axis shows the hazard ratio of the association between categorical baseline antibody titers and RSV A/B illness for the low, moderate, high, and very high antibody titer categories using the very low antibody category as the reference group. Data are presented as the hazard ratio (measure of center) ± the upper and lower bound of the 95% Wald-type confidence interval for the hazard ratio estimate using robust standard errors. The proportional hazards analysis was conducted among pediatric participants in whom both antibodies were measured (n = 1355). Abbreviations: CI confidence interval, log_{10}-AU/mL log_{10}-transformed arbitrary units per milliliter, log_{10}-IU/mL log_{10}-transformed international units per milliliter, RSV respiratory syncytial virus.

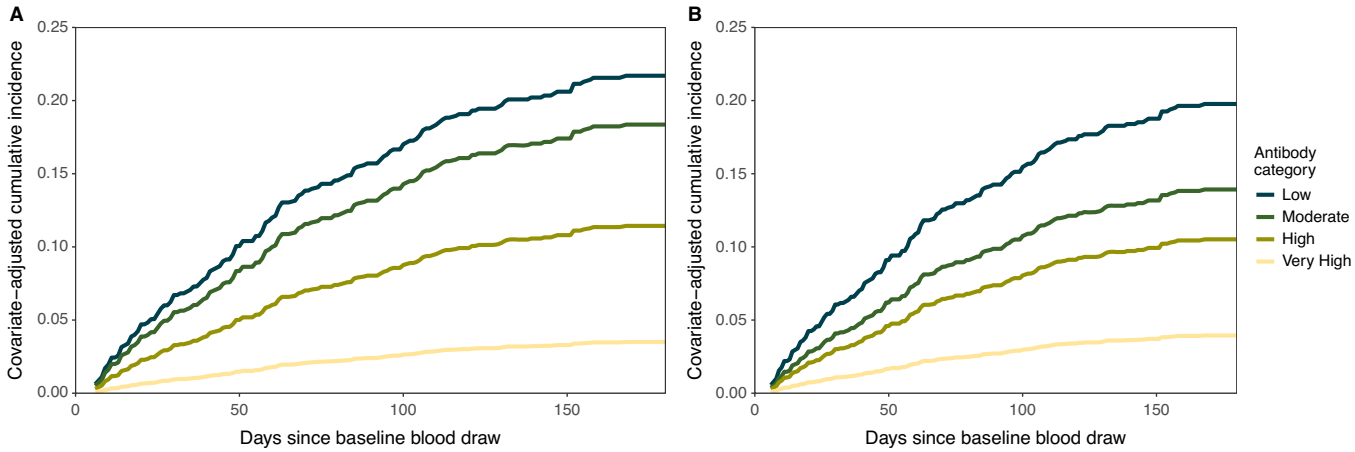

Fig. 4 | Covariate-adjusted RSV illness cumulative incidence. Cumulative incidence curves by 180 days since the baseline blood draw for **A** binding and **B** neutralizing antibody among pediatric participants in whom both antibodies were measured. The x-axis shows days since a participant's baseline blood draw and the y-axis shows the cumulative incidence. Cumulative incidence curves are averaged over covariates and stratified by low, moderate, high, and very high antibody titer categories. The curves for the lowest antibody titer category where titers were below the lower limit of quantitative are not shown. The cumulative incidence estimates were obtained from the proportional hazards regression analysis. Abbreviation: RSV respiratory syncytial virus.

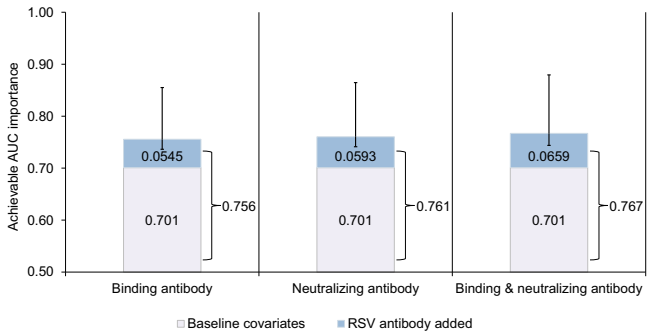

Fig. 5 | Area under the receiver operating curve variable importance for baseline antibody titers relative to covariates. Among pediatric participants, in whom both antibodies were measured (n = 1355), estimated gain in achievable AUC is shown on the y-axis for time to RSV illness by 180 days from enrollment based on adding each RSV antibody to a prediction model containing only baseline covariates (age; school/daycare attendance; immunocompromised status). The AUC is measured on a scale of 0-1 with the y-axis starting at 0.50 to represent the ability to predict RSV illness beyond random chance (AUC = 0.50). The measure of center of the error bars represents the estimated difference in AUC comparing the model with the baseline covariates only to the model with the baseline covariates and the RSV antibody. The error bars represent the 2.5 and 97.5 percentile of the bootstrap replicate estimates for this AUC difference. The AUC estimates are the average of all the bootstrap replicate estimates, which are themselves averages within bootstrap datasets of sample splitting over 10 different seeds. Confidence intervals for the variable importance estimates were constructed using 500 bootstrap replicates with sampling accounting for within-household correlation. Abbreviations: AUC area under the receiver operating curve, RSV respiratory syncytial virus.

guardian; symptoms were not evaluated by a clinician. All data were collected using REDCap[32,33].

Nasal swab PCR testing. Mid-turbinate nasal swabs (RHINOstic™) were collected and shipped dry without preservative or media to UW. RSV A, influenza A, and SARS-CoV-2 testing was performed on all samples via RT-qPCR[34–36]. Additionally, multipathogen testing was performed using a multiplex RT-qPCR assay including RSV A/B on swabs from participants who reported symptoms within 72 h of swab collection, and swabs with a positive/inconclusive result for any virus during the first phase of testing. We defined an RSV-positive swab as a cycle threshold (C_t) value ≤ 37 for RSV RT-qPCR testing and a C_{rt} < 28 for multipathogen testing. We considered all inconclusive results as positive for the analysis. C_{rt} values were used as a proxy for semiquantitative viral load.

RSV antibody assays. RSV pre-F IgG levels were measured in serum samples using a commercial electrochemiluminescence immunoassay (ECLIA) with plates pre-coated with RSV pre-F antigen (Mesoscale Diagnostics). Pediatric serum samples were also tested using an RSV subtype A microneutralization assay and reported in standardized units based on the World Health Organization's first international standard for antiserum to RSV (16/284)[37]. Additional laboratory methods are detailed in the Supplementary Information.

Study population

In the 2022–2023 respiratory season prior to the introduction of novel RSV vaccines and monoclonal antibodies, we included participants who completed an enrollment survey, attended a baseline blood draw appointment (regardless of blood draw success), and provided at least one nasal swab by May 31, 2023. To complement other studies focused on the highest-risk groups and align with the target populations of other RSV vaccines in the pipeline, we recruited individuals 6 months–50 years who are underrepresented in studies of RSV burden.

Variables

Exposures. We evaluated $\log_{10}$-transformed baseline RSV pre-F IgG binding (arbitrary units per milliliter [AU/mL]) and neutralizing antibody (international units per milliliter [IU/mL]) titers measured at enrollment as primary and secondary exposures, respectively. To increase comparability of binding and neutralizing antibody titers among pediatric participants, in whom both antibodies were measured, titers were divided by their sample SD and discretized empirically into five categories of equal range to generate standardized and discretized[38,39] antibody variables, respectively. See Supplementary Table 12 for antibody category ranges.

Outcome. The primary outcome was an incident RSV illness defined as ≥1 respiratory symptom (e.g., fever, cough, sore throat, shortness of breath, myalgia, rhinorrhea) ±7 days from a participant's first RSV-positive swab via RT-qPCR.

Covariates. Potential confounders included age at enrollment (6 months–1 year; 2–4 years; 5–12 years; 13–17 years; 18–50 years);

school/daycare attendance (yes/no); and self-reported immunocompromised status (yes/no). To describe RSV illness characteristics, we assessed symptoms reported on Days −7 to +14; work, school, or daycare absenteeism; and medical care-seeking reported within the 30 days of any reported symptom or positive test result. Sex assigned at birth and gender were self-reported or reported by a parent/guardian as part of the enrollment survey. These variables were included as part of the descriptive statistics, but no analyses were adjusted for sex or gender. Sex and gender were not considered in the study design.

Statistical methods

We estimated overall and age-specific RSV illness incidence rates by month using an intercept-only Poisson regression model with log-number of days at risk of RSV as offset. Participants contributed person-time at risk during the weeks they self-collected a nasal swab beginning on the date of their first nasal swab collection. We used generalized estimating equations with an independence working correlation structure to account for within-household correlation. Wald-type CIs were constructed using distribution- and correlation structure-robust standard errors.

We assessed the association between baseline RSV $\log_{10}$-antibody levels (binding for all participants and neutralizing for pediatric participants) and time to RSV illness using PH regression. Time at risk was calculated as the time elapsed between baseline blood draw and when a participant subsequently tested positive for RSV, withdrew from the study, or the end of the analytic period (May 31, 2023). We fit stratified PH models to estimate overall and age-specific HRs adjusting for potential confounders identified a priori (Supplementary Table 13; Supplementary Fig. 8). Model fits accounted for possible within-household correlation and included a baseline hazard stratified by 2-week enrollment intervals to account for seasonality. Wald-type CIs were constructed using robust standard errors. Additionally, all models were run using SD-standardized and discretized[38] (very low; low; moderate; high; very high) antibody exposure variables. Based on the PH analysis using the discretized antibody variables, we also estimated covariate-adjusted cumulative incidence curves, which were plotted across time since baseline blood draw, to characterize absolute incidence. We conducted a complete-case PH analysis under the assumption that participants with missing RSV serologic measurements, due to unsuccessful blood draws and contaminated samples, were similar in outcome, exposure, and potential confounders as observed participants (Supplementary Table 14).

To complement the PH analysis, we conducted a variable importance analysis to assess the extent to which baseline binding and neutralizing antibody titers improve illness prediction within a time horizon of 180-days since enrollment compared to prediction based on adjustment variables alone (age; school/daycare attendance; immunocompromised status). This approach enables a direct comparison of antibodies that are quantified differently. AUC was used as a unit-independent measure of predictive ability and presented on a scale of 0–1[40,41]. We restricted the variable importance analysis to our pediatric study population in whom both antibodies were measured. Confidence intervals for the variable importance estimates were constructed using 500 bootstrap replicates with sampling accounting for within-household correlation. Repeated sample splitting across 10 different seeds was used to ensure valid testing of null importance while limiting variance inflation[40,42].

All hypothesis tests were two-sided and conducted at significance level 0.05. CIs were constructed to achieve a nominal coverage of 95%. All statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing) in RStudio 2023.12.1 + 402 (RStudio, Inc; Boston, MA)[43]. The variable importance analysis was implemented using the R package survML with Cox PH regressions[40]. Additional statistical methods are detailed in the Supplementary Information.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The raw data underlying the figures in the main text are available in the Supplementary Datasets. Due to ethical restrictions and to protect participant confidentiality, the complete datasets are available under restricted access. Deidentified individual participant data (including data dictionaries), study protocols, the statistical analysis plan, and the informed consent form can be obtained by submitting a request to the corresponding author (cfrivold@uw.edu), subject to approval by the Institutional Review Board of the University of Washington and the CASCADIA Steering Committee. Access will be granted for a period of 1 year, with the option to renew, to researchers with a methodologically sound proposal for use in achieving the goals outlined in the approved proposal. Requests will be reviewed within 30 days. Source data are provided with this paper.

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Author contributions

Collrane Frivold conceptualized and designed the study, performed data analysis, contributed to the Electrochemiluminescence immunoassay testing, drafted the initial manuscript, and critically reviewed and revised the manuscript. Helen Y. Chu conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. Ana A. Weil conceptualized and designed the study, contributed to the RT-qPCR testing, and critically reviewed and revised the manuscript for important intellectual content. Tara M. Babu conceptualized and designed the study, contributed to the Electrochemiluminescence immunoassay testing, and critically reviewed and revised the manuscript for important intellectual content. Janet A. Englund, Allison L. Naleway, and Jennifer L. Kuntz conceptualized and designed the study, and critically reviewed and revised the manuscript for important intellectual content. Marco Carone conceptualized and designed the study, supervised data analysis, and critically reviewed and revised the manuscript for important intellectual content. Sarah N. Cox, Katherine L. Hoffman, Alexandra Varga, and Charles J. Wolock performed data analysis, and critically reviewed and revised the manuscript for important intellectual content. Lea Starita, Christina M. Lockwood, Peter Han, Jeremy Stone, Sally Grindstaff, contributed to the RT-qPCR testing, and critically reviewed and revised the manuscript for important intellectual content. Erica Clark and Grace Marshall contributed to the Electrochemiluminescence immunoassay testing and critically reviewed and revised the manuscript for important intellectual content. Jonathan Reed, Eli A. Piliper, Shah A K Mohamed Bakhash, and Alexander L. Greninger contributed to the RSV A microneutralization assay testing, and critically reviewed and revised the manuscript for important intellectual content. Richard A. Mularski, Cassandra L. Boisvert, Neil Yetz, Natalie K. Lo, Tara L. Hatchie, and Leora R. Feldstein critically reviewed and revised the manuscript for important intellectual content. All authors contributed to the acquisition, analysis, and/or interpretation of data; and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Competing interests

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Additional information

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Correspondence and requests for materials should be addressed to Collrane Frivold.

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