

Supplementary Information

eResults

Differences by RSV case definitions

When assessing all infections, regardless of symptom status, we observed similar trends for illness characteristics (Supplementary Table 6) and the risk of any RSV infection (Supplementary Tables 10-11) compared to symptomatic RSV infections.

Binding versus neutralizing antibody measurements

When estimating the variable importance of binding antibody titers in predicting neutralizing antibody titers compared to using demographic characteristics, the additional predictiveness (as measured by R^2) gained by using binding antibody titers compared to using age and sex alone was 0.52 (95% CI: 0.44, 0.60) (Supplementary Table 8). Age and sex alone were poorly predictive of neutralizing antibody titers ($R^2=0.13$; 95% CI: 0.08, 0.23). We observed similar or stronger correlations among participants <5 years of age compared to all pediatric participants.

Impact of swab compliance on proportional hazards regression results

Compliance with weekly swabbing was high; participants missed a median of 2 weekly swab instances (range: 0-46 weeks) during follow-up. As a post-hoc analysis to evaluate whether swab compliance had an impact on the observed association between baseline $\log_{10}$ -transformed binding antibody titers and time to RSV illness, we ran the overall PH model among the subset of participants with higher swab compliance who missed a maximum of 2 weekly swabs (HR=0.66; 95% CI: 0.52, 0.85) and observed similar results to the overall study population including those with who missed >2 weekly swabs (HR=0.66; 95% CI: 0.56, 0.78).

Impact of care-seeking during an RSV illness episode on proportional hazards regression results

Overall, 12.13% of participants sought care during an RSV illness episode (n=37/305). Among participants with RSV, the median $\log_{10}$ -binding antibody titers for participants who sought care was 4.89 (range: 1.48, 5.65) compared to 5.00 (range: 1.48, 6.20) for participants who did not seek care. As a post-hoc analysis to evaluate whether care-seeking had an impact on the observed association between baseline $\log_{10}$ -transformed binding antibody titers and time to RSV illness, we ran the overall PH model using RSV with care-seeking as the outcome of interest. We observed that the HR point estimate increased from 0.66 (95% CI: 0.56, 0.78) for any RSV illness regardless of care-seeking status to 0.79 (95% CI: 0.43, 1.45) for RSV with care-seeking with a wider 95% CI interval including 1, which could be due to care-seeking being relatively rare in our study population.

Co-detection with other pathogens

Of 305 RSV symptomatic infections, 29.84% had another virus detected. Of the RSV illness swabs with another pathogen co-detected (n=91), the following viruses were detected with some swabs testing positive for two or more viruses: rhinovirus (n=64); adenovirus (n=15); influenza (n=11); human coronavirus (n=10); SARS-CoV-2 (n=8); pan-enterovirus (n=4, including n=3 EVD-68); human metapneumovirus (n=1); Parainfluenza virus subtype 1-2 (n=1); Parainfluenza virus subtype 3-4 (n=5). See Supplementary Figure 5 for the distribution of Crt values stratified by co-detection status (Supplementary Figure 5).

Other pathogens detected among RSV-negative swabs

Among the swabs not associated with an RSV illness episode (n=79469), the most frequently detected pathogens were as follows: rhinovirus (n= 2453; 3.09%); human coronavirus (n=872; 1.10%); adenovirus (n=370; 0.47%); pan-enterovirus (n=336, 0.42%; including n=106 EVD-68, 0.13%); human metapneumovirus (n=298; 0.37%); SARS-CoV-2 (n=1878; 2.36%); Parainfluenza virus subtype 1-2 (n=119; 0.15%); Parainfluenza virus subtype 3-4 (n=258; 0.32%); influenza (n=477; 0.60%).

eMethods

CASCADIA cohort study inclusion/exclusion criteria:

Inclusion criteria:

- Age 6 months to 49 years on the date of enrollment;
- Access to the internet and phone;
- Willingness and ability to complete periodic data collection activities online;
- Willingness to collect nasal swabs (either self-collected or collected by the child's parent/guardian) and arrange pick-up time and location at least once per week for swabs to be picked up and sent to the lab;
- Willingness to participate in enrollment blood collection and annual blood draw collection appointments (successful draw is not required);
- Willing and able to provide consent or assent to participate.
- Live within the KPNW catchment area of Oregon and southern Washington, or within the UW catchment area of King, Snohomish, and Pierce Counties in Washington State.

Exclusion criteria:

- Participation in a clinical trial of investigational prevention therapies for SARS-CoV-2 infections, such as prophylactic antiviral medications or other immune system modifying interventions in the 3 months prior to enrollment;
- Unwilling or unable to provide consent or assent to participate;
- Registered in KPNW exclusion database;
- Unable to comply with study procedures, as determined by the investigators.

RSV analysis inclusion/exclusion criteria:

Inclusion criteria:

- All CASCADIA participants fully enrolled and with at least one resulted/successful swab by May 31, 2023.
 - To be fully enrolled, participants needed to complete an enrollment survey, attend a baseline blood draw appointment, and self-collect at least one swab.
 - While the upper age cutoff was 49 years on the date of consent, some individuals turned 50 by the time they completed all enrollment activities. Therefore, the age range used in the analysis is 6 months to 50 years.
- Include withdrawn/lost to follow-up as long as they contributed some follow up time

Exclusion criteria:

- Exclude individuals who screened eligible, but never fully enrolled

Covariates

Absenteeism (yes/no) was defined as whether a participant missed work, attending school (remote or in-person), or daycare due to their symptoms or positive test result. 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.

Laboratory methods

Serum Specimen collection and processing

Serum was collected through venipuncture, and allowed to clot at room temperature for 30 minutes before centrifuging at 1,200xG for 10 minutes. Serum separator tubes (SST) were kept at 4°C for a maximum of 96 hours before processing. Tubes were then transported on ice packs to the processing lab, aliquoted, and frozen at -80°C. Throughout the entire CASCADIA study period, 61% (n=5,822/9,567) of the samples were processed and frozen

down on the same day as collection and 39% (n=3,745/9,567) of the samples were collected, centrifuged, and stored at 4°C for 24-96 hours before processing and freezing.

The Tasso+ blood collection device was used as an alternative method for blood collection in clinic. This device contains a SST without additives (Tasso, Seattle, WA). The Tasso+ device was placed on the upper arm or lower back, and when deployed collected liquid whole blood over 3-5 minutes into a microcollection tube. Tasso+ is FDA-approved for use in adults, and is approved for investigational use in individuals aged 17 and under.

Electrochemiluminescence immunoassay (ECLIA)

ECLIAs were performed for RSV antibody using pre-coated RSV MSD plates (Mesoscale Diagnostics, Rockville, MD) according to the manufacturer's instructions. Samples collected during June 2022-August 2023 were tested using V-PLEX Respiratory Panel 1 with the following antigens: P.1, Flu A/Hong Kong H3, Flu A/Michigan H1, Flu A/Shanghai H7, Flu B/Brisbane HA, Flu B/Phuket HA, and RSV Pre-Fusion F. Plates and reagents were included in the MSD kit for each plate type.¹

Plates and reagents Diluent 100 and Blocker A were brought to room temperature before adding 150µL of Blocker A to plates and incubated on plate shaker at ~700rpm for 30 minutes. Frozen serum samples, MSD calibrators and controls were removed from -80°C and allowed to thaw at room temperature or on ice. CASCADIA serum samples were scanned into an internal QC tracker to ensure correct samples run. Dilution blocks were made into 2mL deep well 96 well plates for every MSD plate containing 19 serum samples. Diluent 100 was added to the dilution blocks to create a 1:50 dilution, 1:5,000 dilution and 1:25,000 dilution. MSD calibrators and controls were removed from ice to come to room temperature. CASCADIA serum samples were vortexed for 3s and 10µL are added to the 1:50 dilution column of the dilution block. The 1:50 dilution was used to then make the 1:5,000 and 1:25,000 dilutions. The Reference Standard 1 calibrator was used to make a 4-fold dilution to use as a standard calibration curve. MSD plates were washed three times using plate washer and MSD Wash Buffer. 50µL of the 1:5,000 and 1:25,000 dilutions were added to each MSD plate following the plate layout, along with 50µL of Control 1.2, Control 1.3, and the diluted Reference Standard 1 calibrator. Plates were sealed and incubated on plate shaker for 2 hours. MSD plates were washed three times using plate washer and MSD Wash Buffer. Using a 200X stock of SULFO-TAG Anti-human Ig Antibody, make a 1X solution with Diluent 100. Add 50µL to every well, seal the plates and incubate on the plate shaker for one hour. MSD plates were washed three times using plate washer and MSD Wash Buffer. 150µL of MSD Gold Read Buffer B was then added to each well and read plate on MSD instrument. In addition to the 1:5,000/1:25,000 dilutions, a subset of serum samples were tested in duplicate at one of the following dilution sets: 1:1,000/1:10,000; 1:4,500/1:22,500.

All plates were read on the MSD instrument and the raw data were processed in MSD Discovery Workbench software (v4.0, Mesoscale Diagnostics, Rockville, MO, USA). IgG antibody levels for each antigen were calculated in Workbench based on the calibrator standard curve fit and reported in Arbitrary Units per mL (AU/mL). IgG concentrations outside of the manufacturer's detection range were excluded. After processing the raw data, we set antibody levels below the manufacturer's lower limit of quantitation (LLOQ) to LLOQ/2. For the final analysis, we used the antibody levels reported at the lower (e.g., 1:5000) dilution unless the sample was above the upper limit of quantitation. In those instances, we used the antibody levels reported at the upper dilution (e.g., 1:25000) sample if the upper dilution sample was within the manufacturer's detection range. RStudio v1.3.1073 (Boston, MA) was utilized for data cleaning.¹

RSV A microneutralization assay

Pediatric serum samples were tested using an RSV subtype A microneutralization assay. Testing was only performed for pediatric samples and not adult samples due to limited funding.

Heat-inactivated sera were incubated in final dilutions of 1:20 to 1:4860 in a total volume of 140µL in presence of 165-350 ffu of RSV A2 (BEI NR-12149) at 37° C 5% CO₂ for 1h. 96-well plates seeded with 10,000 VeroE6 cells/well (ATCC #CCL-1587) and infected with 50µL/well of serum-virus mixture in duplicate and incubated at 37° C 5% CO₂ for 26 – 30 hours before fixation with 25µL 4% formaldehyde in DPBS with 100mg/L calcium and 100mg/L magnesium for 60 min at room temperature. Plates were washed with 3 times with 150µL room-

temperature PBS and incubated for 2h at room temperature with 50µL/well of mouse mAb 131-2G against RSV-A2 F-protein (Sigma-Aldrich MAB8582) diluted 1:4000 in FFA staining buffer (1x PBS, 1 mg/mL saponin, 0.1% IgG-free BSA). Plates were washed 3 times with 150µL room-temperature FFA wash buffer (1x PBS, 0.05% Triton-X100) after primary and secondary staining. Plates were incubated for 1h at room temperature with 50µL/well of peroxidase-conjugated secondary antibody (Bethyl Laboratories A90216P) diluted 1:4000 in FFA staining buffer. Plates were developed with 50µL TrueBlue peroxidase substrate (KPL 5510-0054) for 15 minutes at room temperature. Development was stopped by washing 3 times with 150µL room-temperature DI water, and the plates were dried for 10-15 minutes to minimize visual artifacts from liquid. Plates were scanned and counted on the S6 Universal M2 ImmunoSpot analyzer (Cellular Technology Ltd, Cleveland, OH). Initial sensitivity/detection settings were calibrated via the Smart Well™ feature trained on no-serum, virus-only control wells. Counts were used to determine percent foci reduction at each dilution. For each specimen, the response between percent foci reduction and serum dilution was modeled via 4-parameter logistic regression, which was used to obtain neutralizing dose 50 (ND50) and neutralizing dose 80 (ND80) values. High (10-fold dilution) and low (100-fold dilution) levels of FDA CBER human reference immune globulin to RSV (NR-21973) were run as standard specimens as above along with Ig-depleted sera (NR-49447) for each batch of 21 specimens for assay quality control and followed by Levy-Jennings plots and Westgard rules. Neutralization titers were reported in IU/mL based on conversion factors calculated from running WHO reference sera NIBSC 16/284 on 12 separate occasions.

RSV A/influenza A/SARS-CoV-2 PCR testing

Midnasal swabs were self-collected or collected by the child's parent/guardian and shipped to the UW Brotman Baty Laboratory for testing. A comparison of unsupervised, home-collection of midnasal swabs compared to clinician-collected nasopharyngeal swabs was previously published for SARS-CoV-2, which found that sensitivity and specificity of home tests were 80.0% (95% CI, 63%-91%) and 97.9% (95% CI, 94%-99.5%), respectively.²

RSV A, influenza A virus, and SARS-CoV-2 testing was performed on all samples via RT-qPCR using a clinically validated assay.³ Validation of RSV B and influenza B targets were added to this clinically validated assay during our study, and thus, a subset of swabs were also tested for influenza B and RSV B via RT-qPCR. We included all available RSV A/B swab results from both RT-qPCR and multipathogen testing in our analysis that met the RSV outcome definitions. However, our ability to capture asymptomatic RSV B infections is limited by our swab testing protocol where all swabs were tested for RSV A, but RSV B testing was only performed on (1) symptomatic swabs via multipathogen testing and (2) a subset of swabs via RT-qPCR during assay validation.

Swabs were stored dry, with no preservative or media,³ and nucleic acids were eluted with 300 µL Tris-EDTA from RHINOstic™ nasal swabs. Specimen stability was confirmed by IATA-recommended shipping studies that mimic winter conditions for 75 hours. High (cycle threshold [C_t] <30) and low (C_t >30) concentration specimens were tested for the RSV A pathogen. C_t values shifted by -0.22 for high-concentration specimens and -0.2 for low-concentration specimens, indicating negligible differences in C_t when cycling dry-swabs through varied winter shipping temperatures.

Nucleic acids were eluted from swabs with 300 µL Tris-EDTA. Fifty µL of eluent was treated with proteinase K and heated at 37C for 15 min then 95C for 15 min 37C for 15 min then 95C for 15 min for direct RT-qPCR (Swab-Express RT-qPCR) as previously described referred to as the CRI PCR-based test modality (SARS CoV 2, RSV, and Influenza PCR using extraction free methods)³ or 200 µL of eluent underwent total nucleic acid purification (Magna Pure 96 System, Roche Diagnostics, MagNA Pure 96 DNA and Viral NA Small Volume Kit; #06543588001) prior to RT-qPCR referred to as the CRIMP PCR-based test modality (CRI on the MagnaPure).

The RT-qPCR assay was arranged in two multiplexed reactions run in duplicate for each specimen. Both multiplexed reactions incorporate human RNase P as human tissue control. The pathogen targets were arranged as RSV A, Influenza B, and SARS-CoV-2 S-Gene in the first mix, and RSV B, Influenza A, and SARS-CoV-2 Orf1b in the second. The assay employs custom probe sets for the pathogens; RSV targets were identified by Gunson et al., Influenza by the CDC (<https://www.cdc.gov/coronavirus/2019-ncov/downloads/lab/multiplex-primers-probes-printer.pdf>), and SARS-CoV-2 Orf1b and S-gene designed against the ancestral strain (GenBank: MN908947.3) and are proprietary to Thermo Fisher. For SARS-CoV-2, positive samples had targets detected in three or four reactions.

The 157-158 deletion in the Delta variants resulted in S-gene target failure or delay in our assay; thus, positive samples were identified by two Orf1b amplifications for this variant. Other pathogens required detection from both replicate reactions to be identified as positive. The internal RNase P control was detected in at least three of four reactions for the assay result to be considered valid.

Five µl of specimen was added to each well of a 384-well plate (Applied Biosystems, 4309849 city country) and each reaction was performed at a final volume of 10 µl. Plates were sealed with optically clear microseal B (Biorad) tape. RT-qPCR was performed on the Applied Biosystems QuantStudio 6 Pro (25°C for 2 minutes, 50°C for 15 minutes, 95°C for 2 minutes, followed by 40 cycles of 95°C for 3 seconds and 60°C for 30 seconds). Cycle threshold (C_t) values were obtained from the QuantStudio Design and Analysis software using predetermined ΔR_n thresholds. The **delta** R_n value is the R_n value of an experimental reaction minus the R_n value of the baseline signal generated by the instrument. Positive controls contain nucleic acid sequences amplified by the Orf1b, S, Flu-A, Flu-B, RSV-A, and RSV-B assays and human RNA. A no-template control (low-TE blank) was included on each plate in a random position.

- **RSV A Positive Criteria:** Both replicates detected below the cycle threshold cutoff (C_t) of ≤ 37 along with suitable RNase P detection.
- **RSV A Inconclusive Criteria:** One replicate detected below the cycle threshold cutoff (C_t) of ≤ 37 along with suitable RNase P detection.
- **RSV B Positive Criteria:** Both replicates detected below the cycle threshold cutoff (C_t) of ≤ 37 along with suitable RNase P detection.
- **RSV B Inconclusive Criteria:** One replicate detected below the cycle threshold cutoff (C_t) of ≤ 37 along with suitable RNase P detection.

Multipathogen testing

Samples were selected for multipathogen (“open array”) testing if the swab was positive for SARS-CoV-2, influenza A, or RSV A on the multiplex assay, if the participant reported any new symptom within the following 72 hours, or if the participant reported any new symptom at the time the swab was taken. Multipathogen testing provides research-only results for detection of a broader array of pathogens including influenza A/H3N2, influenza A/H1N1, influenza B, parainfluenza, enterovirus, rhinovirus, adenovirus, human coronaviruses, SARS-CoV-2, RSV A/B, human metapneumovirus, and *Streptococcus pneumoniae*. Specimens selected for open array were processed as in prior studies.⁴ Briefly, samples underwent nucleic acid purification and extracted nucleic acids underwent a pre-amplification RT-PCR prior to a re-array and qPCR by TaqMan real-time PCR (RT-PCR) on the OpenArray platform (Thermo).⁵ Assays were run in duplicate.

We report C_{rt} values from our arrayed RT-qPCR assay (Open Array). The Open Array performs 14 cycles of pre-amplification and dilution before the detection qPCR. Thus, Open Array C_{rt} values are ~10 cycles lower than conventional RT-qPCR C_t values (C_{rt} of 5 would be equivalent to a C_t ~15).

Our ability to capture asymptomatic RSV B infections is partially limited by our swab testing protocol where all swabs were tested for RSV A, but multipathogen testing (RSV A/B) was only performed on symptomatic swabs.

For multipathogen testing, specimens were classified as positive or inconclusive for RSV if they had a suitable RNase P detection and a relative cycle threshold (C_{rt}) <28.

Assay validation

To evaluate the RT-qPCR assays developed by UW Brotman Baty Laboratory, we performed a minimum of 24 replicate reactions for each RT-qPCR target and determined limit of detection (LoD). LoD is defined by the minimum number of molecules that can be detected in greater than 95% of replicate RT-qPCR reactions. For RSV A, the LoD for the CRI, extraction-free assay was 625 molecules in a 5 µl reaction. The LoD for the extracted assay was 75 molecules in a 5 µl reaction for RSV A. For RSV B, the LoD for extraction-free was 83.3 molecules in a 5 µl reaction; for assay with extraction it was 30 molecules/5 µl reaction. Analytical specificity was evaluated by concordance studies on matched specimens, which compared each method with a reference standard assay, the

Xpert Xpress CoV-2/Flu/RSV plus (Cepheid, Sunnyvale, CA), with further RSV subtyping performed by UW Virology. There was 100% result concordance compared to negative specimens for both RSV A and RSV B. Additionally, included in each validation plate is a control that has no template, called a “no template controls” (NTC). All NTC specimens failed to show any amplification of viral targets or RNase P in either assay.”

Statistical methods

To describe our study population, we first conducted descriptive analyses of demographics, baseline RSV antibody titers, RSV illness outcomes, and illness characteristics. However, we did not perform hypothesis testing since our intent was not to make direct comparisons between groups or make inference to a population.

We estimated overall and age-specific RSV incidence rates stratified by age group, for each 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 restricted our analysis to participants who contributed >5 days of follow-up from the date of their first nasal swab collection. Correlated measurements between household members were accounted for using generalized estimating equations (GEE) stratified by age group using an independence working correlation structure. Wald-type confidence intervals were constructed using distribution- and correlation structure-robust standard error estimates. To estimate the overall incidence rate, we calculated the geometric mean of the estimated monthly incidence rates over the months during which RSV was detected. We estimated monthly incidences separately by subtype using the months during which RSV A (September 1, 2022 to May 31, 2023) and RSV B (October 1, 2022 to May 31, 2023) were detected. For combined RSV A/B incidence estimates, we used the period during which either subtype was detected (September 1, 2022 to May 31, 2023).

We calculated the nonparametric coefficient of determination (R^2) to evaluate the extent to which RSV neutralizing antibody titers could be predicted from binding antibody titers. We also estimated the added value of binding antibody titers for predicting neutralizing antibody titers relative to using demographic characteristics alone.¹⁹ We used the SuperLearner package in R to predict neutralizing antibody titers, incorporating a diverse set of base learners to optimize predictive performance. The ensemble included the following base learners:

- SL.ranger: Random forest (via the ranger package)
- SL.mean: Sample mean (intercept-only model, serving as a simple benchmark)
- SL.glm: Generalized linear model (logistic regression)
- SL.glmnet: Penalized regression (lasso and elastic net via the glmnet package)
- SL.xgboost: Extreme gradient boosting (via the xgboost package)

Using proportional hazards (PH) regression, we assessed the association between baseline $\log_{10}$ -transformed RSV binding antibody levels and time to symptomatic RSV during the analytic period. 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 restricted our analysis to participants who contributed >5 days of follow-up starting from the date of their baseline blood draw appointment. We fit stratified PH models to estimate overall and age-specific hazard ratios (HRs) (Supplementary Table 13). We adjusted for potential confounders identified *a priori* using a directed acyclic graph (Supplementary Figure 9). Model fits accounted for possible within-household correlation and included a baseline hazard stratified by two-week intervals to account flexibly for temporal trends in community transmission. Wald-type confidence intervals were constructed using robust standard error estimates. Among pediatric participants, we repeated the above analysis using $\log_{10}$ -transformed RSV neutralizing antibody titers as the exposure of interest. We used the standardized antibody titers to obtain comparable titer-specific HR estimates. To investigate a possibly nonlinear association between antibody titers and risk of symptomatic RSV, we also repeated the above analysis using discretized titer categories (very low; low; moderate; high; very high) and performed isotonic regression as a post-hoc correction to enforce monotonicity.⁷ See Supplementary Table 12 for the range of each titer category. Based on the PH analysis using the discretized antibody variables, we estimated covariate-adjusted cumulative incidence, which were plotted across time since baseline blood draw as an estimate of the absolute incidence.

To complement the PH analysis, we conducted a nonparametric variable importance analysis for 500 bootstrap replicates 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), where AUC was used as a unit-independent measure of predictive ability on a scale of 0-1.^{40,41} 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. Repeated sample splitting across 10 different seeds was used to ensure valid testing of null importance while limiting variance inflation.^{8,9} This approach enables a direct comparison of antibodies that are quantified differently. We restricted the variable importance analysis to our pediatric study population in whom both antibodies were measured.

For the PH analysis, we conducted a complete-case analysis. This approach is valid 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 3). All hypothesis tests were two-sided, and confidence intervals were constructed to achieve nominal level 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).¹ The variable importance analysis was implemented using the R package survML with Cox PH regressions.⁸

List of Supplementary Tables/Figures

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Supplementary Table 1. Baseline characteristics of CASCADIA study population stratified by site (n=3237 individuals; 1188 households).

Supplementary Table 2. Baseline characteristics of CASCADIA study population stratified by RSV binding antibody titer levels ($\log_{10}$ -AU/mL) above the median, equal to or below the median, and missing values (n=3237 individuals; 1188 households).

Supplementary Table 3. Illness characteristics among participants with symptomatic RSV A/B infections stratified by age group and subtype (n=305).

Supplementary Table 4. Frequency of symptom reporting by week among participants with symptomatic RSV A infections (n=247).

Supplementary Table 5. Frequency of symptom reporting by week among participants with symptomatic RSV B infections (n=63).

Supplementary Table 6. Illness characteristics among participants with RSV A/B infections regardless of symptom status stratified by age group (n=328).

Supplementary Table 7. Symptom reporting by care-seeking status during symptomatic RSV A/B infections (n=305).

Supplementary Table 8. Summary of nonparametric coefficient of determination values using demographic characteristics alone or in combination with baseline RSV pre-F antibody titers to predict baseline neutralizing antibody titers among pediatric participants (n=1355).

Supplementary Table 9. Standard deviation-standardized hazard ratios of the association between baseline antibody titers and RSV A/B illness.

Supplementary Table 10. Hazard ratios of the association between baseline binding antibody titers ($\log_{10}$ -AU/mL) and RSV A/B infection (regardless of symptom status).

Supplementary Table 11. Hazard ratios of the association between baseline neutralizing antibody titers ($\log_{10}$ -IU/mL) and RSV A/B infection (regardless of symptom status).

Supplementary Figure 1. Study flow diagram showing participants followed during the first respiratory virus season for inclusion in the analysis.

Supplementary Figure 2. Participant timelines for (a) RSV A and (b) RSV B symptomatic infections stratified by age group.

Supplementary Figure 3. Monthly RSV A/B illness incidence rates per 1,000 person-days stratified by age group.

Supplementary Figure 4. Mean RSV relative cycle threshold (Crt) value of first positive swab stratified by adult versus pediatric participants among multipathogen testing swab results (n=278).

Supplementary Figure 5. Mean RSV relative cycle threshold (Crt) value of first positive swab stratified by co-detection status among multipathogen testing swab results (n=278).

Supplementary Figure 6. Mean RSV relative cycle threshold (Crt) values over time among participants with RSV A/B illnesses (n=278) including those with repeat Crt measurements among multipathogen testing swab results (n=55).

Supplementary Figure 7. Baseline RSV pre-F antibody titers ($\log_{10}$ -AU/mL) stratified by continuous age in years.

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Supplementary Figure 8. Directed acyclic graph for the association between baseline antibody titers and RSV infection.

Supplementary Table 12. Summary of discretized antibody titer categories.

Supplementary Table 13. Summary of proportional hazards regression models to generate overall, pediatric subpopulation, and age-group-specific hazard ratios.

Supplementary Table 14. Symptomatic RSV A/B outcomes with baseline antibody titer measurements included in complete case analysis where infections occurred >5 days from enrollment.

Supplementary Table 1. Baseline characteristics of CASCADIA study population stratified by site (n=3237 individuals; 1188 households).^a

	Oregon (N=1631)	Washington (N=1606)	Overall (N=3237)
Overall household characteristics (regardless of enrollment status)			
Household density			
Lives alone	18 (1.10%)	6 (0.37%)	24 (0.74%)
2-4 people	1218 (74.68%)	1275 (79.39%)	2493 (77.02%)
5+ people	89 (23.85%)	323 (20.11%)	712 (22.00%)
Number of children in household			
No children	56 (3.43%)	31 (1.93%)	87 (2.69%)
1 child	458 (28.08%)	395 (24.60%)	853 (26.35%)
2-4 children	1092 (66.95%)	1160 (72.23%)	2252 (69.57%)
5+ children	19 (1.16%)	18 (1.12%)	37 (1.14%)
Household income			
Below study median (<\$100,000)	730 (44.76%)	353 (21.98%)	1083 (33.46%)
Study median (\$100,000-\$124,999)	424 (26.00%)	373 (23.23%)	797 (24.62%)
Above study median (≥\$125,000)	412 (25.26%)	842 (52.43%)	1254 (38.74%)
Prefer not to say	59 (3.62%)	36 (2.24%)	95 (2.93%)
Enrolled household member characteristics			
Number of fully enrolled participants in household			
Median [Min, Max]	3.00 [1.00, 8.00]	3.00 [1.00, 7.00]	3.00 [1.00, 8.00]
Children in household (yes/no)			
Yes	1487 (91.17%)	1547 (96.33%)	3034 (93.73%)
Children <5 years attend daycare (yes/no)			
Yes	521 (31.94%)	451 (28.08%)	972 (30.03%)
Individual characteristics			
RSV illness			
Negative	1507 (92.40%)	1425 (88.73%)	2932 (90.58%)
Positive	124 (7.60%)	181 (11.27%)	305 (9.42%)
Baseline binder antibody titer (log₁₀-AU/mL)			
Median [Min, Max]	5.20 [1.48, 6.78]	5.21 [1.48, 6.86]	5.21 [1.48, 6.86]
Missing	136 (8.34%)	105 (6.54%)	241 (7.45%)
Age group			
6 mo-1 year	62 (3.80%)	38 (2.37%)	100 (3.09%)

	Oregon (N=1631)	Washington (N=1606)	Overall (N=3237)
2-4 years	127 (7.79%)	106 (6.60%)	233 (7.20%)
5-12 years	420 (25.75%)	513 (31.94%)	933 (28.82%)
13-17 years	183 (11.22%)	168 (10.46%)	351 (10.84%)
18-50 years	839 (51.44%)	781 (48.63%)	1620 (50.05%)
Sex assigned at birth			
Female	992 (60.82%)	907 (56.48%)	1899 (58.67%)
Gender			
Male	622 (38.14%)	683 (42.53%)	1305 (40.32%)
Female	957 (58.68%)	857 (53.36%)	1814 (56.04%)
Transgender	25 (1.53%)	21 (1.31%)	46 (1.42%)
Other	27 (1.66%)	45 (2.80%)	72 (2.22%)
Race			
American Indian or Alaska Native	10 (0.61%)	4 (0.25%)	14 (0.43%)
Asian	64 (3.92%)	174 (10.83%)	238 (7.35%)
Black or African American	45 (2.76%)	31 (1.93%)	76 (2.35%)
Native Hawaiian or other Pacific Islander	2 (0.12%)	3 (0.19%)	5 (0.15%)
White	1304 (79.95%)	1142 (71.11%)	2446 (75.56%)
Multiracial	151 (9.26%)	199 (12.39%)	350 (10.81%)
Other	39 (2.39%)	39 (2.43%)	78 (2.41%)
Hispanic			
Yes	165 (10.12%)	114 (7.10%)	279 (8.62%)
Health insurance			
Employer-sponsored health insurance	1327 (81.36%)	1398 (87.05%)	2725 (84.18%)
Individual health insurance	73 (4.48%)	44 (2.74%)	117 (3.61%)
Government insurance program	177 (10.85%)	106 (6.60%)	283 (8.74%)
None	13 (0.80%)	12 (0.75%)	25 (0.77%)
Other	18 (1.10%)	25 (1.56%)	43 (1.33%)
Overall health (self-reported)			
Poor/fair	47 (2.88%)	34 (2.12%)	81 (2.50%)
Good/very good	968 (59.35%)	871 (54.23%)	1839 (56.81%)
Excellent	616 (37.77%)	701 (43.65%)	1317 (40.69%)
Any smoking (yes/no)			
Yes	32 (1.96%)	21 (1.31%)	53 (1.64%)
Comorbidities (self-reported)			
Asthma	257 (15.76%)	211 (13.14%)	468 (14.46%)

	Oregon (N=1631)	Washington (N=1606)	Overall (N=3237)
Chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)	2 (0.12%)	5 (0.31%)	7 (0.22%)
Hypertension	81 (4.97%)	67 (4.17%)	148 (4.57%)
Immunocompromised	30 (1.84%)	29 (1.81%)	59 (1.82%)
Other ^b	558 (34.21%)	453 (28.21%)	1011 (31.23%)

^a Percentages of missing data are shown if variable missingness is $\geq 5\%$.

^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.

Supplementary Table 2. Baseline characteristics of CASCADIA study population stratified by RSV binding antibody titer levels ($\log_{10}$ -AU/mL) above the median, equal to or below the median, and missing values (n=3237 individuals; 1188 households).^a

	RSV binding antibody titers			
	>Median (N=1498)	≤Median (N=1498)	Missing (N=241)	Total (N=3237)
Overall household characteristics (regardless of enrollment status)				
Enrollment site				
Oregon, USA	739 (49.33%)	756 (50.47%)	136 (56.43%)	1631 (50.39%)
Washington, USA	759 (50.67%)	742 (49.53%)	105 (43.57%)	1606 (49.61%)
Household density				
Lives alone	10 (0.67%)	14 (0.93%)	0 (0%)	24 (0.74%)
2-4 people	1144 (76.37%)	1154 (77.04%)	195 (80.91%)	2493 (77.02%)
5+ people	343 (22.90%)	324 (21.63%)	45 (18.67%)	712 (22.00%)
Number of children in household				
No children	47 (3.14%)	40 (2.67%)	0 (0%)	87 (2.69%)
1 child	380 (25.37%)	406 (27.10%)	67 (27.80%)	853 (26.35%)
2-4 children	1055 (70.43%)	1027 (68.56%)	170 (70.54%)	2252 (69.57%)
5+ children	15 (1.00%)	19 (1.27%)	3 (1.24%)	37 (1.14%)
Household income				
Below study median (<\$100,000)	501 (33.44%)	492 (32.84%)	90 (37.34%)	1083 (33.46%)
Study median (\$100,000-	372 (24.83%)	370 (24.70%)	55 (22.82%)	797 (24.62%)

	RSV binding antibody titers			
	>Median (N=1498)	≤Median (N=1498)	Missing (N=241)	Total (N=3237)
\$124,999)				
Above study median (≥\$125,000)	579 (38.65%)	587 (39.19%)	88 (36.51%)	1254 (38.74%)
Prefer not to say	45 (3.00%)	43 (2.87%)	7 (2.90%)	95 (2.93%)
Enrolled household member characteristics				
Number of fully enrolled participants in household				
Median [Min, Max]	3.00 [1.00, 8.00]	3.00 [1.00, 8.00]	3.00 [2.00, 8.00]	3.00 [1.00, 8.00]
Children in household (yes/no)				
Yes	1387 (92.59%)	1407 (93.93%)	240 (99.59%)	3034 (93.73%)
Children <5 years attend daycare (yes/no)				
Yes	437 (29.17%)	416 (27.77%)	119 (49.38%)	972 (30.03%)
Individual characteristics				
Age group				
6 mo-1 year	11 (0.73%)	64 (4.27%)	25 (10.37%)	100 (3.09%)
2-4 years	60 (4.01%)	111 (7.41%)	62 (25.73%)	233 (7.20%)
5-12 years	305 (20.36%)	499 (33.31%)	129 (53.53%)	933 (28.82%)
13-17 years	172 (11.48%)	167 (11.15%)	12 (4.98%)	351 (10.84%)
18-50 years	950 (63.42%)	657 (43.86%)	13 (5.39%)	1620 (50.05%)
Sex assigned at birth				
Female	870 (58.08%)	881 (58.81%)	148 (61.41%)	1899 (58.67%)
Gender				
Male	607 (40.52%)	612 (40.85%)	86 (35.68%)	1305 (40.32%)
Female	839 (56.01%)	832 (55.54%)	143 (59.34%)	1814 (56.04%)
Transgender	23 (1.54%)	20 (1.34%)	3 (1.24%)	46 (1.42%)
Other	29 (1.94%)	34 (2.27%)	9 (3.73%)	72 (2.22%)
Race				
American Indian or Alaska Native	3 (0.20%)	8 (0.53%)	3 (1.24%)	14 (0.43%)
Asian	122 (8.14%)	107 (7.14%)	9 (3.73%)	238 (7.35%)

	RSV binding antibody titers			
	>Median (N=1498)	≤Median (N=1498)	Missing (N=241)	Total (N=3237)
Black or African American	45 (3.00%)	25 (1.67%)	6 (2.49%)	76 (2.35%)
Native Hawaiian or other Pacific Islander	3 (0.20%)	2 (0.13%)	0 (0%)	5 (0.15%)
White	1132 (75.57%)	1147 (76.57%)	167 (69.29%)	2446 (75.56%)
Multiracial	136 (9.08%)	166 (11.08%)	48 (19.92%)	350 (10.81%)
Other	41 (2.74%)	32 (2.14%)	5 (2.07%)	78 (2.41%)
Hispanic				
Yes	138 (9.21%)	119 (7.94%)	22 (9.13%)	279 (8.62%)
Health insurance (not mutually exclusive)				
Employer-sponsored health insurance	1239 (82.71%)	1280 (85.45%)	206 (85.48%)	2725 (84.18%)
Individual health insurance	57 (3.81%)	53 (3.54%)	7 (2.90%)	117 (3.61%)
Government insurance program	144 (9.61%)	115 (7.68%)	24 (9.96%)	283 (8.74%)
None	13 (0.87%)	11 (0.73%)	1 (0.41%)	25 (0.77%)
Other	24 (1.60%)	18 (1.20%)	1 (0.41%)	43 (1.33%)
Any smoking (yes/no)				
Yes	29 (1.94%)	24 (1.60%)	0 (0%)	53 (1.64%)
Overall health (self-reported)				
Poor/fair	50 (3.34%)	29 (1.94%)	2 (0.83%)	81 (2.50%)
Good/very good	950 (63.42%)	810 (54.07%)	79 (32.78%)	1839 (56.81%)
Excellent	498 (33.24%)	659 (43.99%)	160 (66.39%)	1317 (40.69%)
Comorbidities (self-reported)				
Asthma	277 (18.49%)	173 (11.55%)	18 (7.47%)	468 (14.46%)
Chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)	5 (0.33%)	2 (0.13%)	0 (0%)	7 (0.22%)
Hypertension	92 (6.14%)	55 (3.67%)	1 (0.41%)	148 (4.57%)
Immunocompromised	36 (2.40%)	21 (1.40%)	2 (0.83%)	59 (1.82%)
Other ^b	532 (35.51%)	453 (30.24%)	26 (10.79%)	1011 (31.23%)

a Percentages of missing data are not shown since variable missingness was <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.

Supplementary Table 3. Illness characteristics among participants with symptomatic^a RSV A/B infections stratified by age group and subtype (n=305).

Illness characteristic	RSV A (n=247)					RSV B (n=63)				
	6 mo-1 year (n=19)	2-4 years (n=49)	5-12 years (n=84)	13-17 years (n=12)	18-50 years (n=83)	6 mo-1 year (n=6)	2-4 years (n=9)	5-12 years (n=24)	13-17 years (n=7)	18-50 years (n=17)
RSV relative cycle threshold (C_{rt}) value of first positive swab^b										
Median [Min, Max]	13.98 [8.79, 23.35]	15.45 [4.91, 27.03]	17.56 [4.62, 27.91]	17.93 [9.84, 26.85]	21.29 [7.68, 27.86]	15.29 [10.80, 29.48]	17.81 [12.13, 26.09]	20.61 [9.770, 27.75]	20.22 [13.08, 25.17]	19.64 [12.85, 26.63]
Missing	2 (10.53%)	7 (14.29%)	9 (10.71%)	1 (8.33%)	9 (10.84%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.88%)
Symptom reported (yes/no)^c										
<i>Rhinorrhea</i>	19 (100.00%)	47 (95.92%)	77 (91.67%)	12 (100.00%)	71 (85.54%)	6 (100.00%)	8 (88.89%)	20 (83.33%)	7 (100.00%)	16 (94.12%)
<i>Cough</i>	16 (84.21%)	47 (95.92%)	71 (84.52%)	10 (83.33%)	54 (65.06%)	5 (83.33%)	8 (88.89%)	19 (79.17%)	5 (71.43%)	10 (58.82%)
<i>Sore throat</i>	2 (10.53%)	13 (26.53%)	38 (45.24%)	6 (50.00%)	50 (60.24%)	0 (0.00%)	1 (11.11%)	8 (33.33%)	5 (71.43%)	9 (52.94%)
<i>Fatigue</i>	7 (36.84%)	13 (26.53%)	21 (25.00%)	1 (8.33%)	45 (54.22%)	0 (0.00%)	1 (11.11%)	5 (20.83%)	2 (28.57%)	6 (35.29%)
<i>Headache</i>	1 (5.26%)	5 (10.20%)	25 (29.76%)	3 (25.00%)	38 (45.78%)	0 (0.00%)	1 (11.11%)	3 (12.50%)	2 (28.57%)	5 (29.41%)
<i>Fever</i>	8 (42.11%)	19 (38.78%)	16 (19.05%)	2 (16.67%)	16 (19.28%)	2 (33.33%)	3 (33.33%)	7 (29.17%)	1 (14.29%)	1 (5.88%)
<i>Myalgia</i>	1 (5.26%)	5 (10.20%)	9 (10.71%)	0 (0.00%)	16 (19.23%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (14.29%)	2 (11.76%)
<i>Shortness of breath</i>	5 (26.32%)	3 (6.12%)	6 (7.14%)	1 (8.33%)	13 (15.66%)	2 (33.3%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	2 (11.76%)
Missed work, school, or daycare (yes/no)	6 (31.58%)	15 (30.61%)	17 (20.24%)	2 (16.67%)	13 (15.66%)	2 (33.33%)	3 (22.22%)	3 (8.33%)	2 (28.57%)	2 (11.76%)
Any care seeking (yes/no)^d	5 (26.32%)	8 (16.33%)	9 (10.71%)	1 (8.33%)	9 (10.84%)	1 (16.67%)	2 (22.22%)	1 (4.17%)	0 (0.00%)	2 (11.76%)

^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. Five participants had unique RSV A and B illness episodes during the follow-up period, however, we only report results for their incident RSV illness episode.

^b Open Array relative cycle threshold (Crt) values are ~10 cycles lower than conventional RT-qPCR CT values (Crt of 5 would be equivalent to a CT ~15). For comparability, Crt 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.

Supplementary Table 4. Frequency of symptom reporting by week among participants with symptomatic RSV A infections (n=247).^a

Symptom	Days -7 to -1 (n = 177)^b	Day 0 (n = 236)	Days 1 to 7 (n = 169)	Days 8 to 14 (n = 197)
Rhinorrhea	27 (15.25%)	189 (80.08%)	83 (49.11%)	56 (28.43%)
Cough	27 (15.25%)	155 (65.68%)	78 (46.15%)	38 (19.29%)
Sore throat	11 (6.21%)	83 (35.17%)	24 (14.20%)	10 (5.08%)
Fatigue	8 (4.52%)	56 (23.73%)	28 (16.57%)	12 (6.09%)
Headache	6 (3.39%)	52 (22.03%)	16 (9.47%)	12 (6.09%)
Fever	7 (3.95%)	40 (16.95%)	13 (7.69%)	11 (5.58%)
Myalgia	3 (1.69%)	18 (7.63%)	7 (4.14%)	7 (3.55%)
Shortness of breath	1 (0.56%)	16 (6.78%)	7 (4.14%)	5 (2.54%)
Other	1 (0.56%)	2 (0.85%)	4 (2.37%)	4 (2.03%)
None	139 (78.53%)	20 (8.47%)	67 (39.64%)	132 (67.01%)

^a Five participants had unique RSV A and B illnesses during the same season at different times.

^b Denominators reflect instances of completed symptom surveys instead of unique illness episodes.

Supplementary Table 5. Frequency of symptom reporting by week among participants with symptomatic RSV B infections (n=63).^a

Symptom	Days -7 to -1 (n = 44)^b	Day 0 (n = 55)	Days 1 to 7 (n = 41)	Days 8 to 14 (n = 53)
Rhinorrhea	11 (25.00%)	48 (87.27%)	10 (24.39%)	11 (20.75%)
Cough	5 (11.36%)	37 (67.27%)	9 (21.95%)	9 (16.98%)
Sore throat	2 (4.55%)	3 (5.45%)	1 (2.44%)	0 (0.00%)
Fatigue	2 (4.55%)	9 (16.36%)	3 (7.32%)	1 (1.89%)
Headache	3 (6.82%)	7 (12.73%)	0 (0.00%)	1 (1.89%)
Fever	1 (2.27%)	10 (18.18%)	2 (4.88%)	3 (5.66%)
Myalgia	2 (4.55%)	2 (3.64%)	0 (0.00%)	0 (0.00%)
Shortness of breadth	2 (4.55%)	3 (5.45%)	1 (2.44%)	0 (0.00%)
Other	0 (0.00%)	1 (1.82%)	2 (4.88%)	1 (1.89%)
None	36 (81.82%)	0 (0.00%)	26 (63.41%)	38 (71.70%)

^a Five participants had unique RSV A and B illnesses during the same season at different times.

^b Denominators reflect instances of completed symptom surveys instead of unique illness episodes.

Supplementary Table 6. Illness characteristics among participants with RSV A/B infections regardless of symptom status^a stratified by age group (n=328).

Illness characteristic	6 mo-1 year (n=24)	2-4 years (n=57)	5-12 years (n=114)	13-17 years (n=20)	18-50 years (n=113)	Overall (n=328)
RSV relative cycle threshold (C_{rt}) value of first positive swab^b						
Median [Min, Max]	13.93 [8.79, 24.71]	15.82 [4.91, 27.03]	18.98 [4.62, 27.91]	18.82 [9.84, 26.85]	21.80 [7.68, 27.86]	18.86 [4.62, 27.91]
Missing	2 (8.33%)	7 (12.28%)	9 (7.89%)	1 (5.00%)	9 (7.96%)	28 (8.54%)
Symptom reported (yes/no)^c						
<i>Rhinorrhea</i>	24 (100%)	55 (96.49%)	98 (85.96%)	19 (95.00%)	86 (76.11%)	282 (85.98%)
<i>Cough</i>	21 (87.50%)	54 (94.74%)	89 (78.07%)	15 (75.00%)	64 (56.64%)	243 (74.09%)
<i>Sore throat</i>	2 (8.33%)	14 (24.56%)	47 (41.23%)	11 (55.00%)	58 (51.33%)	132 (40.24%)
<i>Fatigue</i>	7 (29.17%)	14 (24.56%)	25 (21.93%)	3 (15.00%)	50 (44.25%)	99 (30.18%)
<i>Headache</i>	1 (4.17%)	6 (10.53%)	29 (25.44%)	5 (25.00%)	42 (37.17%)	83 (25.30%)
<i>Fever</i>	10 (41.67%)	21 (36.84%)	24 (21.05%)	3 (15.00%)	17 (15.04%)	75 (22.87%)
<i>Myalgia</i>	1 (4.17%)	5 (8.77%)	11 (9.65%)	1 (5.00%)	18 (15.93%)	36 (10.98%)
<i>Shortness of breath</i>	7 (29.17%)	3 (5.26%)	8 (7.02%)	1 (5.00%)	15 (13.27%)	34 (10.37%)
Missed work, school, or daycare (yes/no)	7 (29.17%)	17 (29.82%)	20 (17.54%)	4 (20.00%)	15 (13.27%)	63 (19.21%)
Any care seeking (yes/no)^d	6 (25.00%)	9 (15.79%)	10 (8.77%)	1 (5.00%)	11 (9.73%)	37 (11.28%)

^a Includes both symptomatic and asymptomatic infections.

^b Open Array relative cycle threshold (C_{rt}) values are ~10 cycles lower than conventional RT-qPCR CT values (C_{rt} of 5 would be equivalent to a CT ~15). For comparability, C_{rt} 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.

Supplementary Table 7. Symptom reporting by care-seeking status during symptomatic^a RSV A/B infections (n=305)

Symptom reported (yes/no) ^b	No care-seeking (n=268)	Care-seeking (n=37)	Overall (n=305)
Rhinorrhea	244 (91.04%)	36 (97.30%)	280 (91.80%)
Cough	205 (76.49%)	36 (97.30%)	241 (79.02%)
Sore throat	115 (42.91%)	16 (43.24%)	131 (42.95%)
Fatigue	78 (29.10%)	21 (56.76%)	99 (32.46%)
Headache	68 (25.37%)	14 (37.84%)	82 (26.89%)
Fever	54 (20.15%)	19 (51.35%)	73 (23.93%)
Myalgia	28 (10.45%)	7 (18.92%)	35 (11.48%)
Shortness of breath	21 (7.84%)	12 (32.43%)	33 (10.82%)

^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. 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.

^b 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.

Supplementary Table 8. Summary of nonparametric coefficient of determination (R^2) values using demographic characteristics alone or in combination with baseline RSV pre-F antibody titers to predict baseline neutralizing antibody titers among pediatric participants (n=1355).

Group	R^2 of demographic characteristics	Additional R^2 gained with binding antibody titers
Pediatric overall	0.13 (95% CI: 0.08, 0.23)	0.52 (95% CI: 0.44, 0.60)
<5 years	0.07 (95% CI: 0.01, 0.32)	0.72 (95% CI: 0.59, 0.82)

Supplementary Table 9. Standard deviation-standardized hazard ratios of the association between baseline antibody titers and RSV A/B illness.^{a,b}

Age Group	Binding Antibody		<i>P</i> value	Neutralizing Antibody		<i>P</i> value
	Hazard Ratio	95% CI		Hazard Ratio	95% CI	
Pediatric participants (6 mo-17 yrs)	0.69	0.60, 0.80	4.08*10 ⁻⁷	0.59	0.48, 0.71	1.22*10 ⁻⁷
6 mo-1 yr	0.67	0.51, 0.90	6.95*10 ⁻³	0.74	0.47, 1.18	2.03*10 ⁻¹
2-4 yrs	0.74	0.63, 0.87	1.93*10 ⁻⁴	0.63	0.49, 0.82	5.87*10 ⁻⁴
5-12 yrs	0.45	0.32, 0.64	8.21*10 ⁻⁶	0.43	0.31, 0.60	7.09*10 ⁻⁷
13-17 yrs	1.42	0.79, 2.56	2.43*10 ⁻¹	1.14	0.66, 1.98	6.39*10 ⁻¹

^a Antibody titers are standardized by dividing by the standard deviation. The hazard ratio (HR) represents the estimated difference in the hazard of symptomatic RSV illness for any two groups differing by one standard deviation in antibody titers, with the higher titer group having a lower hazard of symptomatic RSV illness when the HR is less than 1.

^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 two-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 1 for details.

Supplementary Table 10. Hazard ratios of the association between baseline binding antibody titers (log₁₀-AU/mL) and RSV A/B infection (regardless of symptom status).^a

Age Group	RSV A			RSV B		
	Hazard Ratio	95% CI	<i>P</i> value	Hazard Ratio	95% CI	<i>P</i> value
Overall	0.70	0.57, 0.85	2.84*10 ⁻⁴	0.65	0.50, 0.85	1.70*10 ⁻³
Pediatric participants (6 mo-17 yrs)	0.69	0.57, 0.84	2.75*10 ⁻⁴	0.64	0.49, 0.84	1.49*10 ⁻³
6 mo-1 yr	0.59	0.40, 0.88	8.77*10 ⁻³	0.57	0.29, 1.10	9.27*10 ⁻²
2-4 yrs	0.82	0.66, 1.02	7.81*10 ⁻²	0.54	0.38, 0.79	1.18*10 ⁻³
5-12 yrs	0.35	0.24, 0.51	3.38*10 ⁻⁸	1.15	0.59, 2.24	6.75*10 ⁻¹
13-17 yrs	1.53	0.57, 4.13	4.01*10 ⁻¹	1.51	0.77, 2.94	2.27*10 ⁻¹
Adult participants (18-50 yrs)	0.75	0.39, 1.43	3.81*10 ⁻¹	0.83	0.13, 5.39	8.47*10 ⁻¹

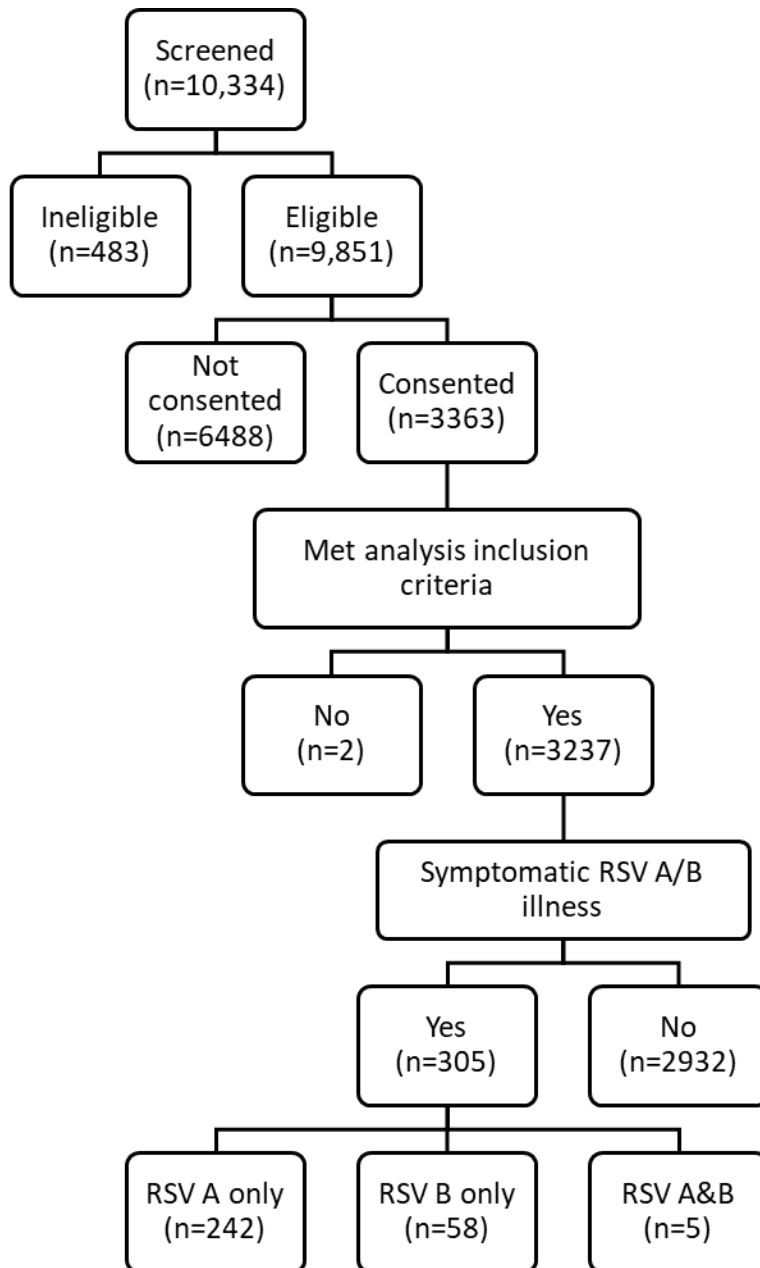
^a Includes both symptomatic and asymptomatic infections. Cox proportional hazard models were adjusted for age group, school/daycare attendance, and immunocompromised status; clustered by household ID to account for correlated data between household members; and stratified by two-week enrollment intervals 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 1 for details.

Supplementary Table 11. Hazard ratios of the association between baseline neutralizing antibody titers (log₁₀-IU/mL) and RSV A/B infection (regardless of symptom status).^a

Age Group	RSV A			RSV B		
	Hazard Ratio	95% CI	<i>P</i> value	Hazard Ratio	95% CI	<i>P</i> value
Pediatric participants (6 mo-17 yrs)	0.36	0.23, 0.55	2.51*10 ⁻⁶	0.62	0.32, 1.19	1.50*10 ⁻¹
6 mo-1 yr	0.62	0.22, 1.76	3.71*10 ⁻¹	0.30	0.08, 1.17	8.23*10 ⁻²
2-4 yrs	0.52	0.30, 0.90	1.99*10 ⁻²	0.34	0.12, 0.95	3.95*10 ⁻²
5-12 yrs	0.18	0.09, 0.36	7.00*10 ⁻⁷	0.81	0.32, 2.08	6.66*10 ⁻¹
13-17 yrs	0.49	0.12, 2.09	3.37*10 ⁻¹	3.17	0.80, 12.62	1.01*10 ⁻¹

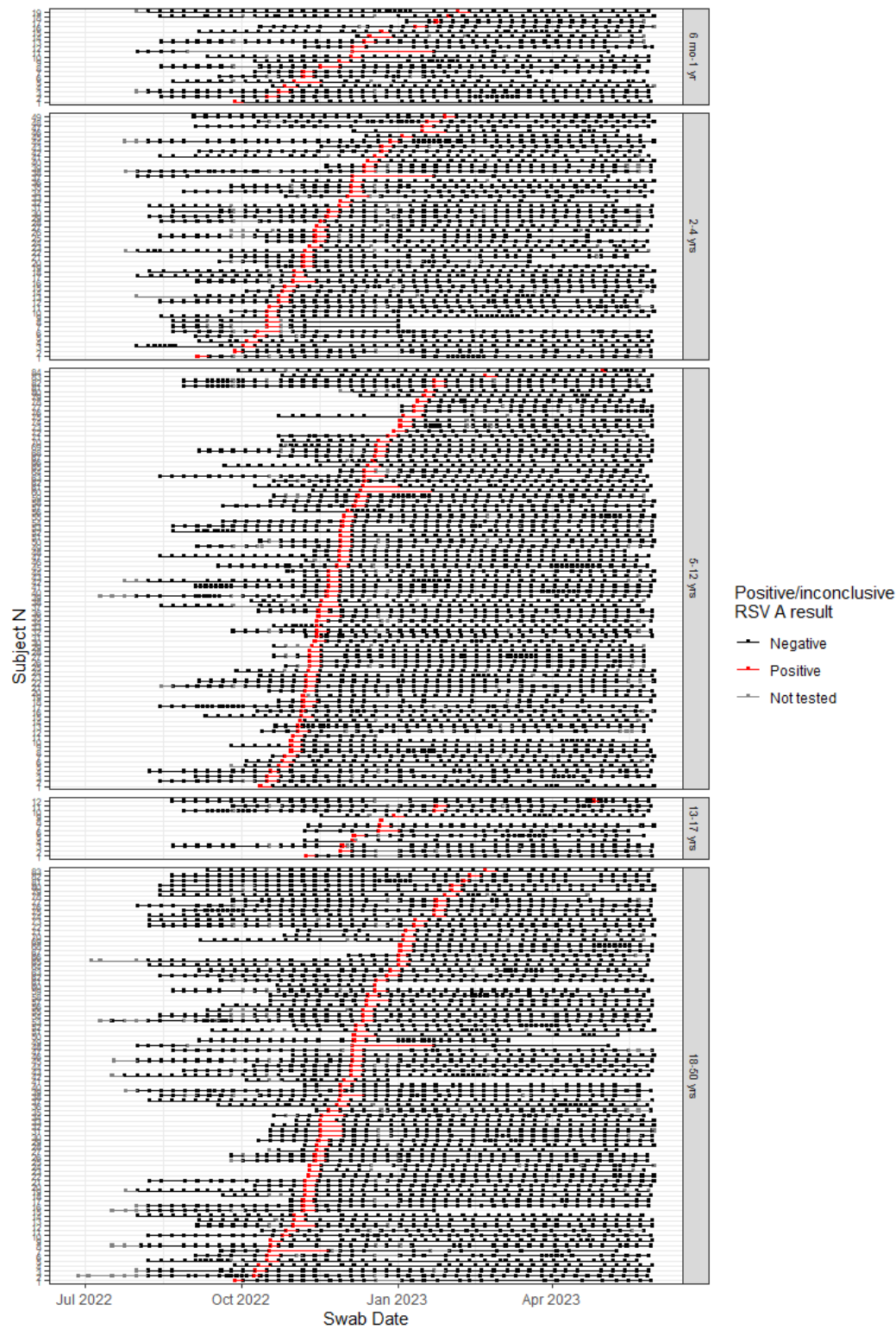
^a Includes both symptomatic and asymptomatic infections. Cox proportional hazard models were adjusted for age group, school/daycare attendance, and immunocompromised status; clustered by household ID to account for correlated data between household members; and stratified by two-week enrollment intervals 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 1 for details.

Supplementary Figure 1. Study flow diagram showing participants followed during the first respiratory virus season for inclusion in the analysis.

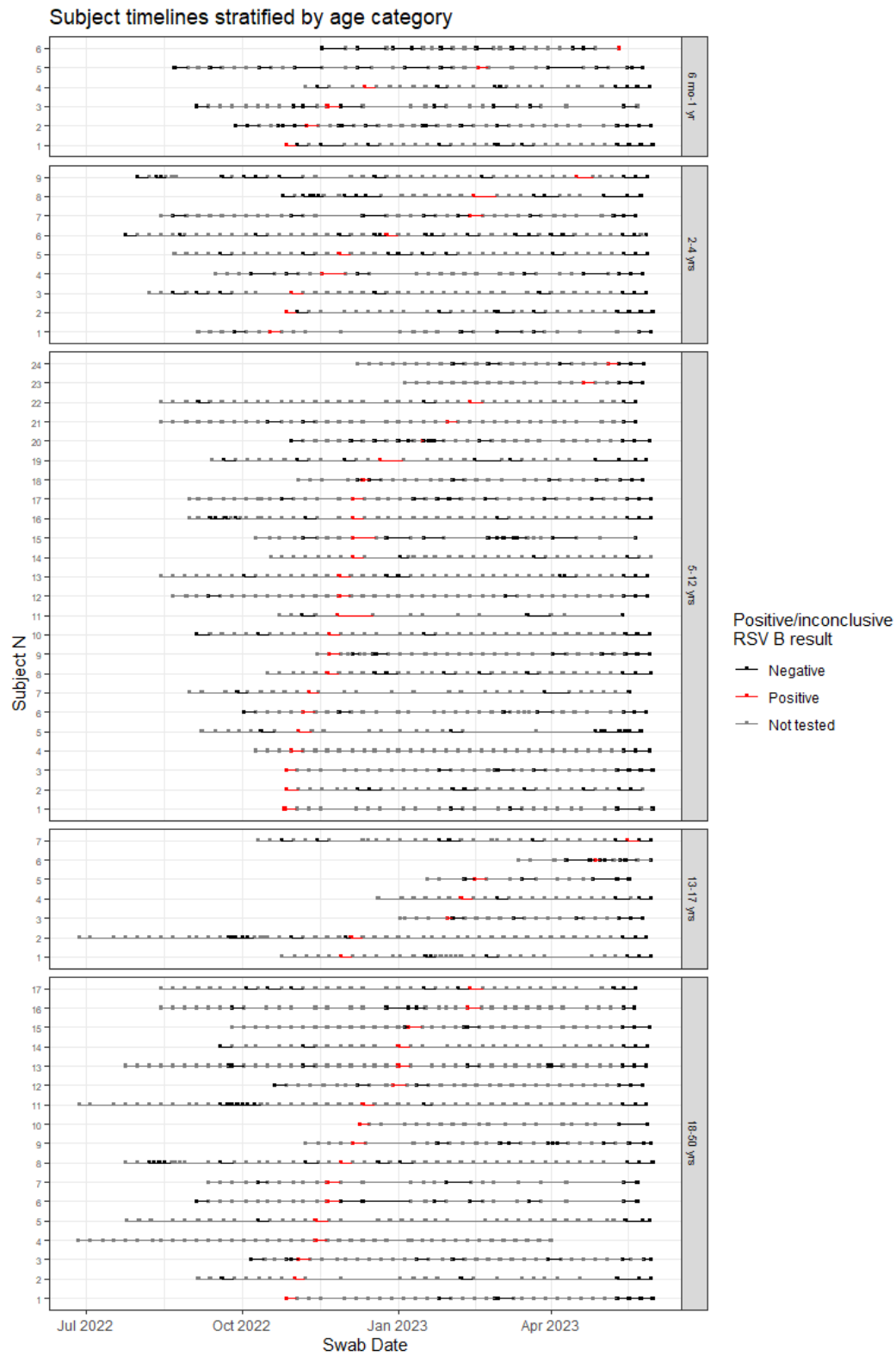


Supplementary Figure 2. Participant timelines for (a) RSV A and (b) RSV B symptomatic infections stratified by age group.

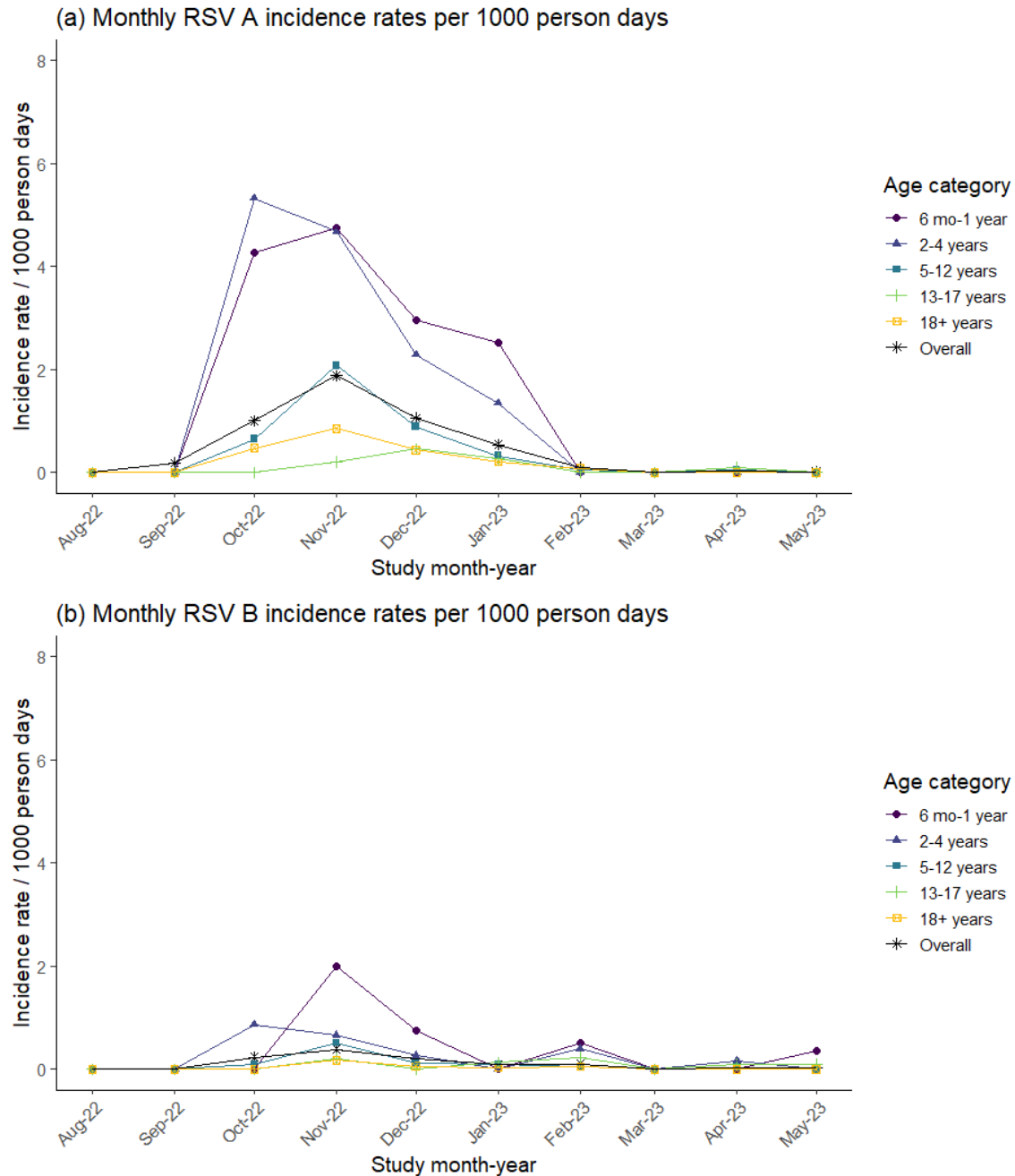
(a) Participants with symptomatic RSV A infections



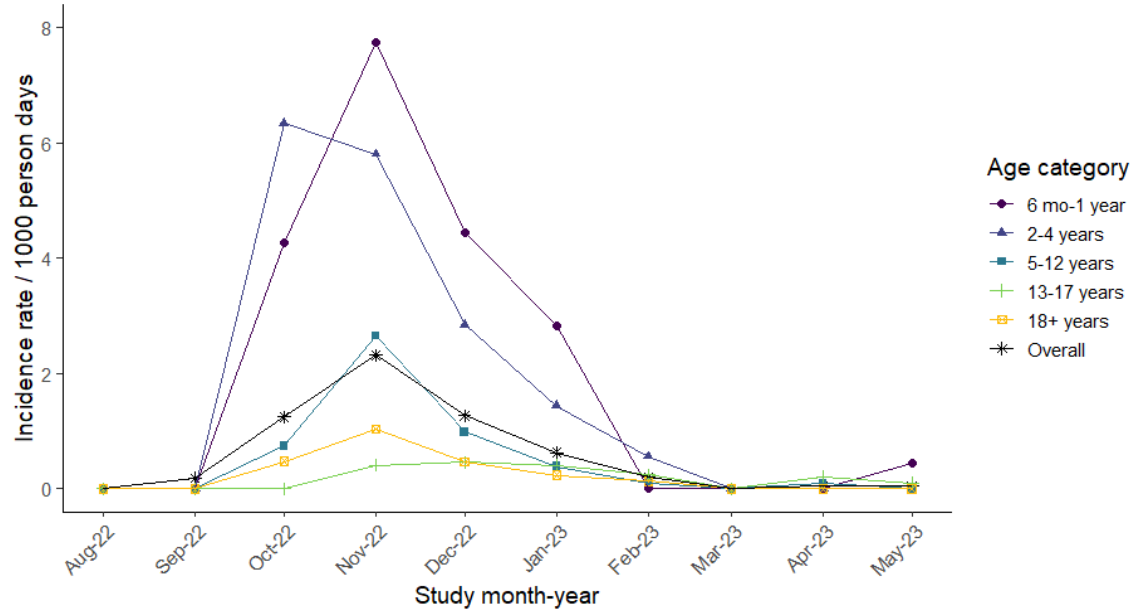
(b) Participants with symptomatic RSV B infections



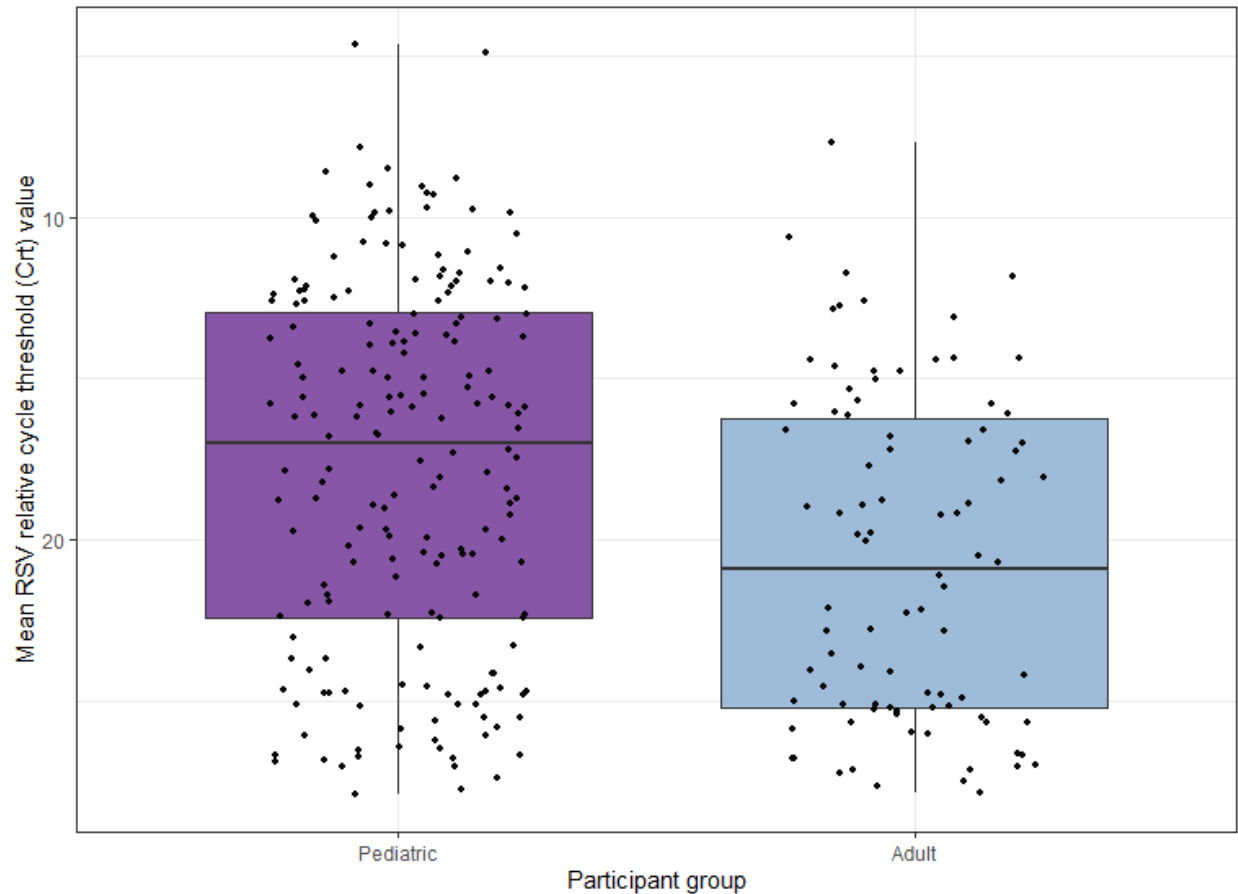
Supplementary Figure 3. Monthly RSV A/B illness incidence rates per 1,000 person-days stratified by age group. Plots show monthly RSV incidence rates per 1,000 person days from August 2022 to May 2023 for the overall study population and by age group for (a) RSV A, (b) RSV B, and (c) RSV A/B combined.



(c) Monthly RSV A/B incidence rates per 1000 person days

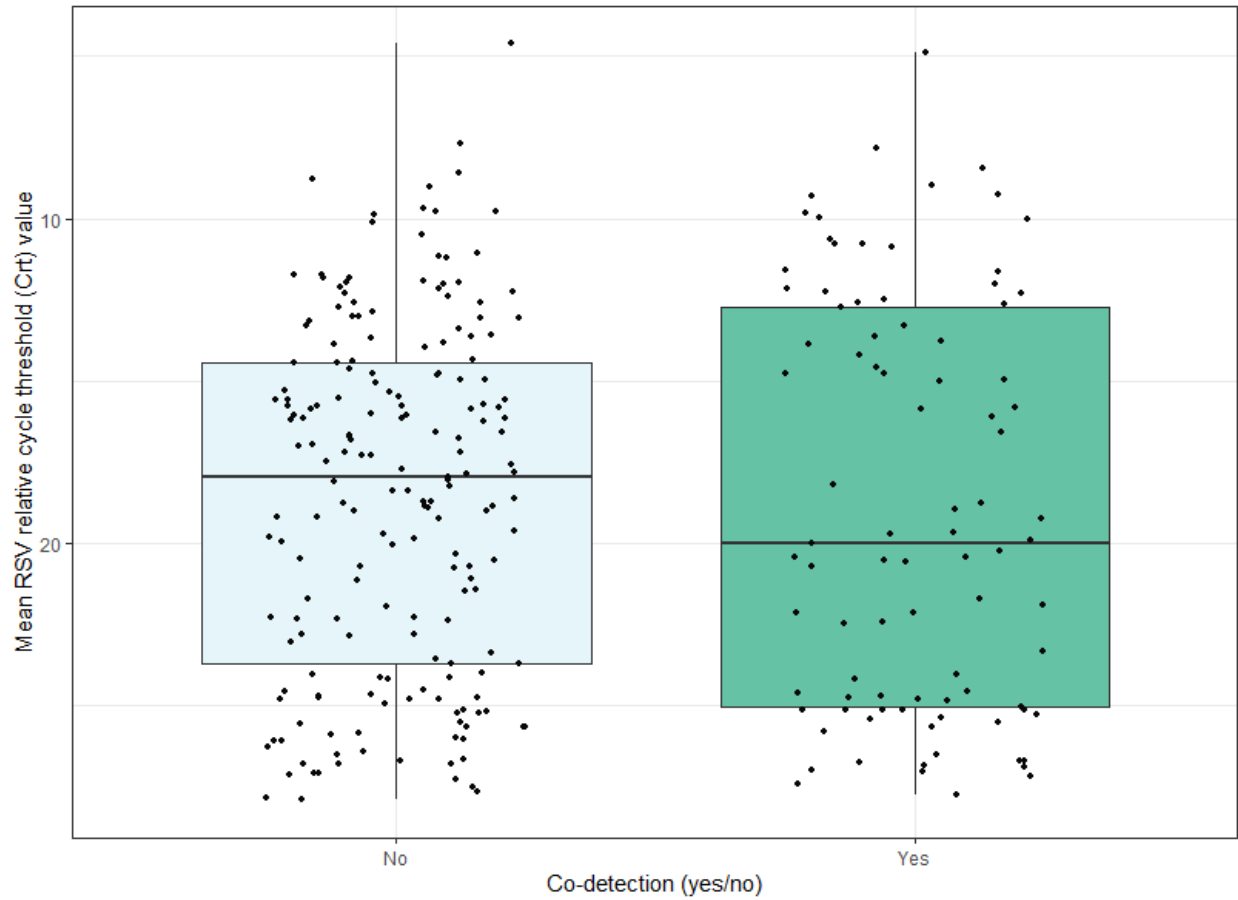


Supplementary Figure 4. Mean RSV relative cycle threshold (C_{rt}) value of first positive swab stratified by adult versus pediatric participants among multipathogen testing swab results (n=278).^a



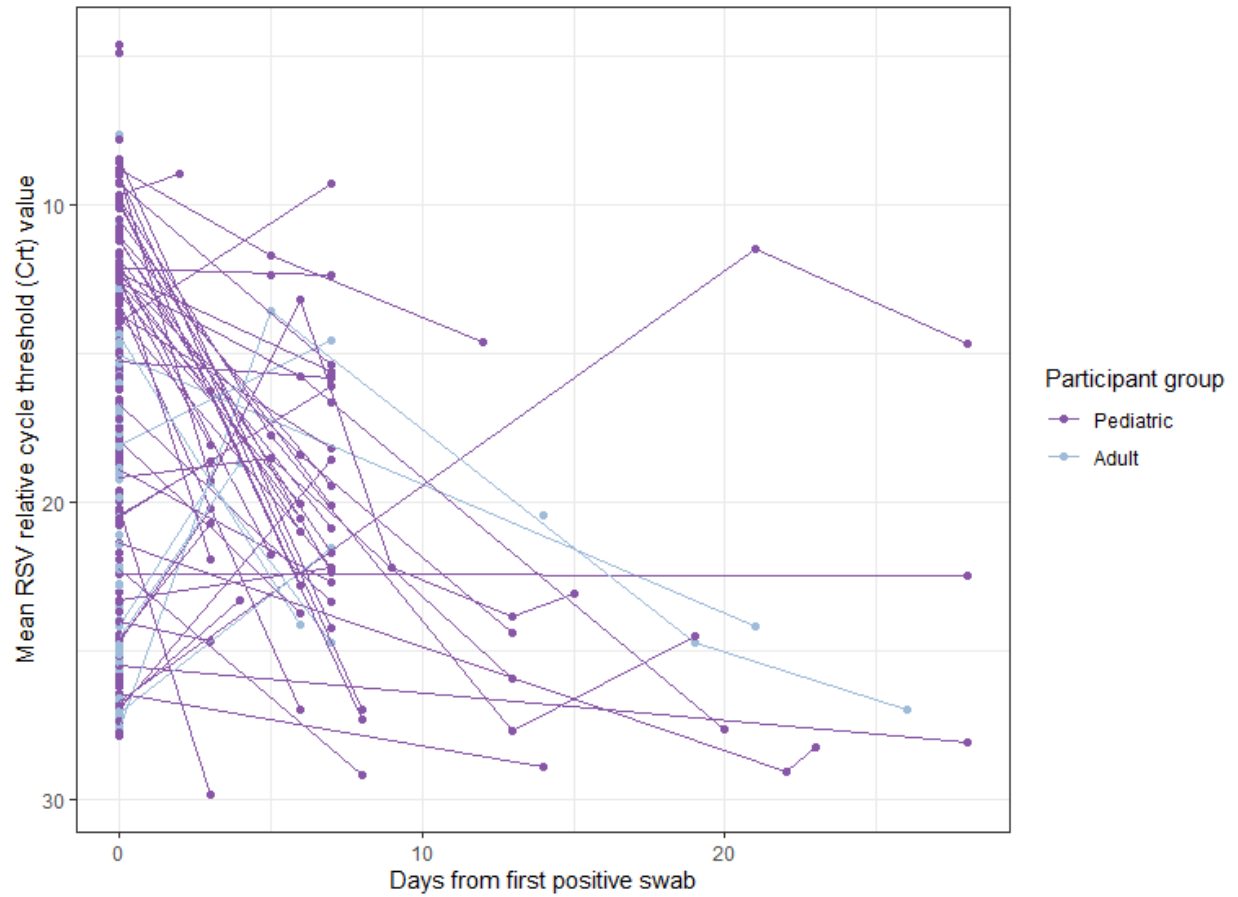
^a Open Array relative cycle threshold (C_{rt}) values are ~10 cycles lower than conventional RT-qPCR CT values (C_{rt} of 5 would be equivalent to a CT ~15). For comparability, C_{rt} values are reported for swabs tested on the multipathogen (“open array”) assay. As such, results are only shown for n=278 participants instead of the n=305 participants who experienced an RSV illness. Data are presented as participant-level C_{rt} values by the dots (n=278), which are overlaid by box 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, 1.5x interquartile range.

Supplementary Figure 5. Mean RSV relative cycle threshold (C_{rt}) value of first positive swab stratified by co-detection status among multipathogen testing swab results (n=278).^a



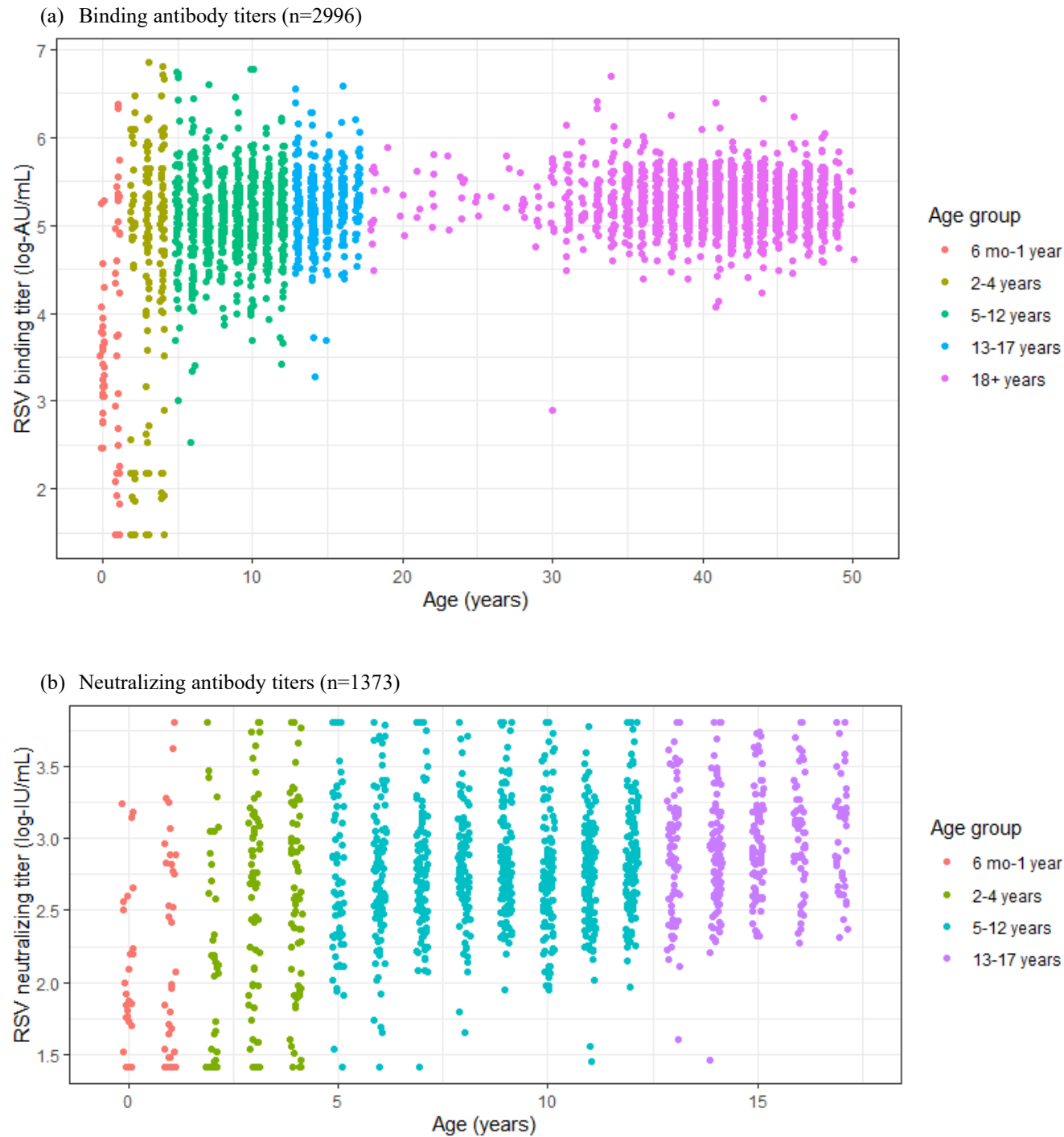
^a Open Array relative cycle threshold (C_{rt}) values are ~10 cycles lower than conventional RT-qPCR CT values (C_{rt} of 5 would be equivalent to a CT ~15). For comparability, C_{rt} values are reported for swabs tested on the multipathogen (“open array”) assay. As such, results are only shown for n=278 participants instead of the n=305 participants who experienced an RSV illness. Data are presented as participant-level C_{rt} values by the dots (n=278), which are overlaid by box 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, 1.5x interquartile range.

Supplementary Figure 6. Mean RSV relative cycle threshold (C_{rt}) values over time among participants with RSV A/B illnesses (n=278) including those with repeat C_{rt} measurements among multipathogen testing swab results (n=55).^a

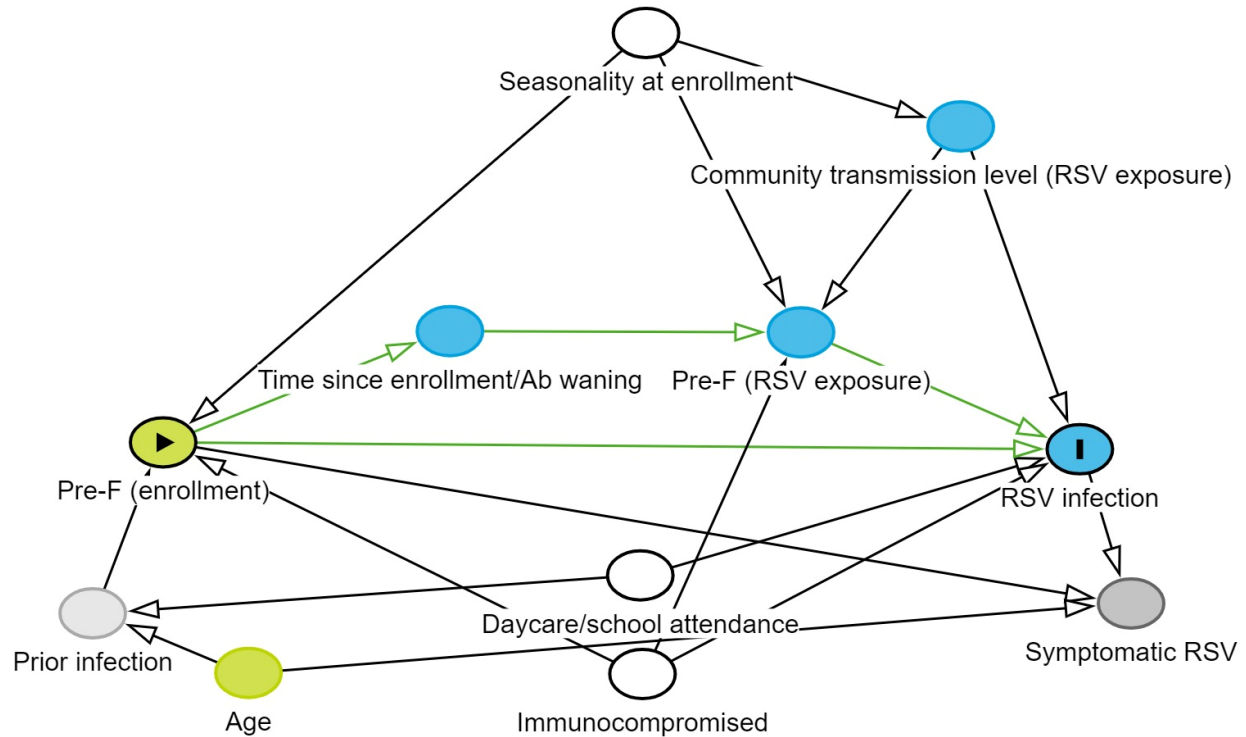


^a Open Array relative cycle threshold (C_{rt}) values are ~10 cycles lower than conventional RT-qPCR CT values (C_{rt} of 5 would be equivalent to a CT ~15). For comparability, C_{rt} values are reported for swabs tested on the multipathogen (“open array”) assay. As such, results are only shown for n=278 participants instead of the n=305 participants who experienced an RSV illness. Data are presented as participant-level C_{rt} values by the dots (n=278); repeated measurements from the same individual are connected using a line.

Supplementary Figure 7. Baseline RSV pre-F antibody titers ($\log_{10}$ -AU/mL) stratified by continuous age in years.



Supplementary Figure 8. Directed acyclic graph for the association between baseline antibody titers and RSV infection.



Supplementary Table 12. Summary of discretized antibody titer categories.

Category	Binding antibody (log ₁₀ -AU/mL)	Neutralizing antibody (log ₁₀ -IU/mL)
Very low	<1.48 (lower limit of quantitation)	< 1.41 (lower limit of quantitation)
Low	≥1.48 & <2.82	≥1.41 & <2.01
Moderate	≥2.82 & <4.17	≥2.01 & <2.61
High	≥4.17 & <5.52	≥2.61 & <3.21
Very high	≥5.52	≥3.21

Supplementary Table 13. Summary of proportional hazards regression models to generate overall, pediatric subpopulation, and age-group-specific hazard ratios.

Model	Population	Description
1	Overall	- Adjusted for age group, school/daycare attendance, and immunocompromised status. - Clustered by household ID to account for correlated data between household members - Stratified by two-week enrollment intervals to account for seasonality.
2	Adult (18-50 years) versus pediatric (6 months-17)	- Adjusted for age group, school/daycare attendance and immunocompromised status. - Interaction term between the log₁₀-transformed pre-F IgG antibody levels and a binary adult variable (yes/no).

	years) subpopulation	• Clustered by household ID to account for correlated data between household members. • Stratified by two-week enrollment intervals to account for seasonality.
3	Pediatric age groups (6 months-1 year; 2-4 years; 5-12 years; 13-17 years)	• Adjusted for school/daycare attendance and immunocompromised status. • Interaction term between the log₁₀-transformed pre-F IgG antibody levels and age group (6 months-1 year; 2-4 years; 5-12 years; 13-17 years; 18-50 years). • Clustered by household ID to account for correlated data between household members. • Stratified by two-week enrollment intervals to account for seasonality.

Supplementary Table 14. Symptomatic RSV A/B outcomes with baseline antibody titer measurements included in complete case analysis where infections occurred >5 days from enrollment.

Age group	Binding antibody measurement available	RSV symptomatic	n
6 mo-1 year	No	No	21
6 mo-1 year	No	Yes	3
6 mo-1 year	Yes	No	55
6 mo-1 year	Yes	Yes	20
2-4 years	No	No	46
2-4 years	No	Yes	12
2-4 years	Yes	No	128
2-4 years	Yes	Yes	38
5-12 years	No	No	115
5-12 years	No	Yes	12
5-12 years	Yes	No	706
5-12 years	Yes	Yes	85
13-17 years	No	No	12
13-17 years	No	Yes	0
13-17 years	Yes	No	320
13-17 years	Yes	Yes	18
18-50 years	No	No	13
18-50 years	No	Yes	0

Age group	Binding antibody measurement available	RSV symptomatic	n
18-50 years	Yes	No	1500
18-50 years	Yes	Yes	94

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