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MAJOR ARTICLE

The Humoral Immune Profiles of Infants Before and After Severe Primary Respiratory Syncytial Virus A and B Infection

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Background. Infants are at risk of severe respiratory syncytial virus (RSV) infection. We characterized the humoral immune response of infants with primary RSV infection.

Methods. Term infants hospitalized for RSV acute respiratory infection (ARI) or non-RSV ARI (controls) were enrolled from November 2018 through March 2020 at 5 pediatric medical institutions. Adult controls were women aged 18–45 years without acute RSV infection. Acute and convalescent sera were tested for homologous and heterologous neutralizing antibodies (NtAbs), competitive antibodies (CAs) to sites Ø, II, IV, and I on the fusion (F) glycoprotein, and anti-postF and 27-amino acid peptide (p27) immunoglobulin G (IgG). Geometric mean titer or CA concentrations of acute and convalescent sera were compared between and within groups.

Results. Sixty-six infants (49 RSV infected and 17 controls) were enrolled. Median age was 76 (interquartile range [IQR], 45–179) days and 151 (IQR, 72–207) days for the RSV and control groups, respectively. NtAb and CA at hospitalization were low among infant groups. Postinfection, RSV/A induced robust homologous and heterologous NtAb responses while RSV/B caused a robust NtAb response only to RSV/B. RSV/A infection generated significant CA rise to sites IV and II, while RSV/B infection resulted in only site II CA rise. Rises in postF and p27 IgG were not detected. Postinfection RSV antibody levels in infants were markedly lower compared to those in control adult women.

Conclusions. RSV-infected infants had low preinfection levels of protective antibodies. Infants infected with RSV/A compared to RSV/B generated a more robust NtAb response, highlighted by a broader CA response to sites II and IV.

Keywords. RSV; infants; primary infections; immune responses; neutralizing and competitive antibodies.

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infection (ARI) in infants and young children [1]. Initial (primary) infection with RSV usually occurs before age 2 years, and reinfection is common throughout life [2]. Infants <12 months of age are at increased risk of severe RSV infection, often resulting in hospitalization [3]. RSV is classified into subgroups RSV/A and RSV/B based on variation in the attachment (G) gene [4] and other viral genes [5, 6]. Viruses from both subgroups can co-circulate, although usually 1 subgroup dominates in each RSV season [7]. The G and fusion (F) surface glycoproteins of RSV are the only 2 surface proteins capable of inducing a neutralizing antibody (NtAb) response [8]. However, F protein is highly conserved and thus has been the major antigen for RSV vaccine development [9].

Two monoclonal antibodies (mAbs) with long half-lives are US Food and Drug Administration approved and recommended for all infants <8 months of age to prevent severe RSV infection [10]. Live attenuated RSV vaccines are in development for infants and young children [11]. Other vaccines such as mRNA preF [12] are recommended for select adults, and vector-based preF [13] is under evaluation in children. Understanding the

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breadth of humoral immune responses to primary RSV infection is a benchmark for interpreting antibody (Ab) response when RSV-naïve infants are vaccinated for the first time with a live attenuated or vector-based vaccine. Limited studies have described the Ab response after primary RSV infection in infants [14–24]. Age at the time of primary RSV infection can attenuate the Ab response, with 4 months being an important transition age [18]. Few studies have focused on the Ab response to the major antigenic form of F or preF [17, 21, 24], and fewer reports describe the F site-specific serum Ab responses after primary RSV infection [18].

In this report, we describe the robustness and breadth of the Ab response in infants with primary infection based on their infecting genotype, RSV/A/Ontario (RSV/A/ON) or RSV/B/Buenos Aires (RSV/B/BA), and age. Infants with non-RSV ARI served as controls while women of childbearing age (18–45 years) served as an adult reference group to better understand the magnitude of the Ab response generated in infants after primary RSV infection.

METHODS

Study Design

A prospective longitudinal study was conducted to evaluate Ab response in infants hospitalized with their first RSV infection. Term infants <12 months of age without a known immunodeficiency and hospitalized for an RSV ARI were enrolled from November 2018 through March 2020 at 5 of 7 US pediatric medical institutions (Cincinnati, Ohio; Houston, Texas; Kansas City, Missouri; Pittsburgh, Pennsylvania; and Seattle, Washington) comprising the New Vaccine Surveillance Network (NVSN), which is an active, prospective, population-based surveillance network for acute respiratory illness [7]. Infants at hospitalization had a midturbinate swab specimen tested by quantitative polymerase chain reaction for RSV and other respiratory viruses [7]. Acute (within 7 days of illness onset) and convalescent (4–6 weeks after symptom onset) blood samples, as well as demographic and clinical data from electronic medical records and parent interviews, were collected. The control group was term infants aged <12 months hospitalized for a non-RSV ARI. Infants were excluded if they received any blood product including palivizumab within 90 days prior to enrollment, were born prematurely (<37 weeks' gestation), or had a known immunodeficiency [25]. Each site processed blood samples after collection and sera were stored at −30°C. All sera were sent to the Houston site for RSV Ab testing.

The Ab profile of the women aged 18–45 years served as an adult reference for comparison of infant immune responses following primary RSV infection. These women were enrolled in a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surveillance study in the greater Houston area and had no evidence of RSV illness at enrollment [26]. A single blood sample at enrollment was collected from March 2020 through July 2020 when RSV was not circulating locally [27].

Ethics Statement

This study was reviewed and approved by the Centers for Disease Control and Prevention and all NVSN sites' institutional review boards (IRBs) for the primary RSV infection study, and from the Baylor College of Medicine IRB for the women of childbearing age surveillance study (see 45 Code of Federal Regulations [C.F.R.] part 46; 21 C.F.R. part 56). All legal guardians of participants for the primary RSV infection study and all women of the childbearing age study provided written consent.

RSV-Specific Microneutralization Assay

Heat-inactivated serum samples were analyzed for NtAb against prototypic (RSV/A/Tracy and RSV/B/18537) and contemporaneous (RSV/A/ON and RSV/B/BA) strains using qualified microneutralization assays as described previously [28, 29]. The lower limit of detection was 2.5 $\log_2$. Serum samples with no detectable NtAb titers were assigned a value of 2 $\log_2$.

Competitive Antibody Assays to Antigenic Sites on the F Protein

NtAb activity in serum comes from varying concentrations of competitive antibodies (CAs), and understanding the relationship between CAs and NtAbs in primary RSV infection will aid in interpreting responses to live replicating virus. CA assays were used to measure Abs that bound to 4 antigenic sites on the F protein of RSV/A (F_A). The source of F_A was sucrose purified RSV/A/Bernett. Serum concentrations of CA for D25 (site Ø), 131-2A (site I), palivizumab (site II), and 101F (site IV) that competed with the binding of biotinylated mAbs to their respective antigenic sites were measured as described previously [30]. A 4-parameter logistic regression model was used to calculate the CA concentrations (μg/mL) that resulted in 50% inhibition. The lower limit of detection was 1.0 μg/mL for sites I, II, IV, and Ø, and negative samples were assigned a value of 0.5 μg/mL. See supplementary materials for anti-p27 IgG and post-F IgG Enzyme Linked Immunosorbent assays, and real-time reverse transcription polymerase chain reaction for the detection of RSV/A and RSV/B.

Statistical Analyses

Demographic characteristics and clinical outcomes were compared between infants with non-RSV ARI and infants with RSV ARI using the Mann–Whitney *U* test or Welch's t-test for continuous variables or Fisher exact test for categorical variables. Descriptive statistics are presented for the demographic characteristics of the adult reference group (women of childbearing age). Assay outcomes for both infant and adult cohorts are summarized as geometric mean titers (GMTs) or geometric mean concentrations (GMCs) with 95% confidence intervals (CIs). Estimation of serum NtAb titer at birth by infection

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status was done using a first-order decay model and an NtAb half-life of 40 days [30, 31]. Only infants aged <6 months with a detectable NtAb titer were included in the analysis. No formal statistics were conducted to compare RSV Ab levels between women of childbearing age and infants with ARI. To contextualize infant ARI Ab levels to adult levels, fold change was calculated using the ratio of adult to infant Ab concentrations. Post hoc analyses using linear regression and mixed-effects models were conducted to assess differences in mean of log-transformed titers or concentrations for the following comparisons: (1) RSV ARI (RSV/A and RSV/B) groups versus non-RSV ARI group; (2) acute versus convalescent paired samples within ARI groups, including postF immunoglobulin G (IgG) binding Ab to NtAb titer ratio; and (3) infants aged <4 months versus ≥4 months within ARI groups. Associations between F site-specific CA concentrations and NtAb titers were assessed using Pearson correlation coefficients and visualized with scatterplots. Statistical significance was defined as P value <.05. Statistical analyses were performed using Stata version 164 software (StataCorp, LLC).

RESULTS

Sixty-six infants <12 months old were enrolled; 49 were hospitalized with an RSV ARI and 17 with a non-RSV ARI (control) (Table 1). The median age of all infants was 87 days; 54.5% were male, 45.5% Hispanic, and 77.3% White. The median age of infants in the non-RSV ARI group was approximately twice the median age of infants in the RSV/A and RSV/B ARI groups, although not significantly different. In general, the demographic characteristics between groups were comparable except that the RSV/B ARI group had a higher proportion of infants <4 months old compared to non-RSV ARI (77.8% vs 41.2%, $P < .05$) and a significantly lower proportion of Hispanic infants (22.2% vs 70.6%, $P < .01$). A higher percentage of infants in the RSV/A ARI group were born to a parent who smoked or used e-cigarettes compared to non-RSV ARI (96.6% vs 64.7%, $P < .01$).

In the women of childbearing age reference cohort (n = 29), the mean age was 34.8 years; 20.7% were Hispanic, and 65.5% were White (Table 2).

RSV-Specific Serum Neutralizing, F Site-Specific Competitive, and Binding Antibodies at Hospitalization

The Ab profiles in the acute serum samples of infants in the RSV/A and RSV/B ARI groups were compared to that of the non-RSV ARI control group (Table 3). Acute serum NtAb titers against strains representing prototypic (RSV/A/Tracy and RSV/B/18537) and contemporaneous (RSV/A/ON and

Table 1. Demographic Characteristics of Infants <1 Year of Age by Respiratory Syncytial Virus Infection Status

			RSV Subgroup Infection		
Characteristic	Non-RSV ARI (n = 17)	RSV ARI[a] (n = 49)	RSV/A[b] (n = 29)	RSV/B[b] (n = 18)	Overall[c] (N = 66)
Age, d, median (IQR)	151 (72–207)	76 (45–179)	69 (54–179)	76 (34–112)	87 (54–196)
Age <4 mo (<121 d)	7 (41.2%)	34 (69.4%)	19 (65.5%)	**14 (77.8%)***	41 (62.1%)
Gestational age, wk, median (IQR)	39 (38–40)	38 (37–39)	39 (37–39)	38 (37–39)	39 (37–39)
Sex, male	11 (64.7%)	25 (51.0%)	16 (55.2%)	9 (50.0%)	36 (54.5%)
Ethnicity, Hispanic	12 (70.6%)	18 (36.7%)[d]	13 (44.8%)[d]	**4 (22.2%)****	30 (45.5%)[d]
Race					
White	13 (76.5%)	38 (77.6%)	23 (79.3%)	14 (77.8%)	51 (77.3%)
Black/African American	2 (11.8%)	6 (12.2%)	3 (10.3%)	2 (11.1%)	8 (12.1%)
Multiracial	1 (5.9%)	3 (6.1%)	2 (6.9%)	1 (5.6%)	4 (6.1%)
Unknown	1 (5.9%)	2 (4.1%)	1 (3.4%)	1 (5.6%)	3 (4.5%)
Birthweight, g, mean (SD)	3203.3 (492.7)	3296.8 (622.0)	3416.1 (630.7)	3069.6 (584.8)	3272.4 (588.6)
Low birthweight (≤2500 g)	2 (11.8%)	3 (6.3%)[e]	0 (0.0%)[e]	3 (16.7%)	5 (7.7%)[e]
Length of hospital stay, d, mean (SD)	5.4 (12.4)	3.6 (3.4)	3.2 (2.2)	4.4 (4.9)	4.1 (6.9)
≥1 underlying condition[f]	2 (11.8%)	3 (6.1%)	1 (3.4%)	1 (5.6%)	5 (7.6%)
Breastfed	16 (94.1%)	41 (83.7%)	26 (89.7%)	14 (77.8%)	57 (86.4%)
Children <5 y in household	10 (58.8%)	29 (59.2%)	19 (65.5%)	8 (44.4%)	39 (59.1%)
Parents smoked cigarettes or e-cigarettes	11 (64.7%)[g]	44 (89.8%)	**28 (96.6%)****	14 (77.8%)	55 (83.3%)[g]

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ARI, acute respiratory infection; IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation.

[a]Includes 2 RSV-infected infants whose RSV subgroup was not determined.

[b]Statistical significance of the comparison between RSV/A or RSV/B ARI groups and the non-RSV ARI group in medians, means, or proportions was assessed using Mann–Whitney U test, Welch's t-test, or Fisher exact test, respectively; *$P < .05$, **$P < .01$.

[c]Infants were enrolled from Cincinnati (n = 4), Houston (n = 35), Kansas City (n = 2), Pittsburgh (n = 3), and Seattle (n = 22).

[d]Two RSV/A-infected infants missing information on ethnicity.

[e]One RSV/A-infected infant missing information on birthweight.

[f]Indicator for ≥1 underlying condition comprised of: Down syndrome/genetic conditions (2 non-RSV, 1 RSV/B, 1 RSV/A), endocrine conditions (1 RSV/B), airway disorders (1 RSV untyped), cardiovascular/heart conditions (2 non-RSV, 1 RSV/B), neurologic/neuromuscular conditions (1 RSV/A, 1 RSV/B), respiratory/lung conditions (1 non-RSV).

[g]One non-RSV infant missing information on whether parents smoked.

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RSV/B/BA) genotypes were comparable between non-RSV ARI and RSV ARI groups. All infants regardless of RSV infection status had low levels of acute RSV-specific NtAb titers, F site-specific CAs, and anti-postF and anti–27-amino acid peptide (p27) IgG Abs.

Table 2. Demographic Characteristics of Reference Group of Women of Childbearing Age

Characteristic	Women of Childbearing Age (n = 29)
Age at enrollment, y, mean (SD)	34.8 (8.3)
Age at enrollment, y, median (IQR)	36.0 (27.0–42.0)
Ethnicity: Hispanic, No. (%)	6 (20.7)
Race, No. (%)	
Asian	4 (13.8)
Black or African American	4 (13.8)
Multiracial	1 (3.4)
White	19 (65.5)
Declined to answer	1 (3.4)
Comorbid health conditions[a], No. (%)	
None	19 (59.4)
Cardiovascular disease	1 (3.1)
Lung disease (including asthma)	6 (18.8)
Metabolic disease	2 (6.3)
Other	4 (12.5)

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]Number of women with each comorbid condition.

RSV-Specific Serum Neutralizing and F Site-Specific Competitive Antibodies in Women of Childbearing Age

RSV Ab activity in women of childbearing age served as an adult reference for comparison with infant responses. RSV-specific NtAb titers as well as F site-specific CAs are shown in Table 4. RSV NtAb titers in women of childbearing age at enrollment, as compared to those of RSV ARI and non-RSV ARI infants (Table 3), were higher, with adult NtAb titers being 4.5- to 7.1-fold higher against RSV/A and 5.0- to 26.3-fold higher for RSV/B. Similarly, F site-specific CAs were higher in adults, and the mean fold increase ranged from 19.4 to 29.9 for site Ø, compared with 6.2 to 9.1 for site II and 4.1 to 7.7 for site IV.

Estimated Serum Neutralizing Antibody at Birth

Since there was no significant difference in acute Ab levels at the time of hospitalization, we next estimated the infants' serum NtAb titer by infection status at birth using a first-order decay model (Table 5). This approach allowed us to infer baseline Ab levels and assess susceptibility. We hypothesized that the non-RSV ARI group will have higher NtAbs compared to

Table 3. Respiratory Syncytial Virus (RSV)–Specific Acute Serum Antibody Titer or Concentration at Hospitalization by RSV Infection Status in Infants <1 Year of Age

				RSV Subgroup ARI	
Assay Category	Assay Target	Non-RSV ARI (n = 17)	RSV ARI[a] (n = 48)	RSV/A[b] (n = 29)	RSV/B[b,c] (n = 17)
MN assay, GMT [95% CI]	RSV/A/ON	31.4 [16.1–61.0]	32.0 [23.4–43.7]	30.1 [19.3–47.1]	38.4 [23.8–62.1]
	RSV/A/Tracy	19.2 [10.7–34.5]	19.3 [14.0–26.7]	18.2 [11.9–28.1]	23.6 [13.3–41.7]
	RSV/B/BA	34.0 [15.2–76.1]	41.2 [27.4–61.8]	32.8 [19.6–54.9]	68.0 [32.9–140.8]
	RSV/B/18537	22.2 [10.6–46.2]	30.4 [20.4–45.3]	27.4 [15.9–47.2]	42.6 [22.5–80.5]
F_A site-specific CA assay (μg/mL), GMC [95% CI]	Site Ø	1.7 [.8–3.8]	1.2 [.8–1.8]	1.1 [.6–1.9]	1.5 [.7–3.3]
	Site II	3.8 [1.6–8.8]	4.8 [3.0–7.8]	4.2 [2.2–8.2]	5.6 [2.4–13.2]
	Site IV	3.2 [1.5–7.0]	4.9 [3.4–6.9]	4.3 [2.6–7.0]	6.0 [3.6–10.3]
	Site I	1.7 [1.0–3.0]	1.6 [1.2–2.1]	1.5 [1.0–2.2]	1.9 [1.2–2.9]
ELISA (μg/mL), GMT [95% CI]	Anti-postF IgG	627.8 [224.2–1757.7]	554.0[d] [387.1–792.8]	498.0[e] [304.5–814.5]	709.5 [387.1–1300.3]
ELISA (ng/mL), GMT [95% CI]	Anti-p27 IgG	5358.7[f] [4076.1–7044.9]	4524.0[g] [3721.6–5499.5]	4497.0[h] [3607.1–5606.3]	4454.2 [2937.2–6754.9]
PostF IgG binding Ab to NtAb titer ratio, GM [95% CI]	RSV/A/ON	20.0 [7.5–53.3]	17.2[d] [12.1–24.3]	16.4[e] [9.7–27.9]	18.5 [11.0–30.9]
	RSV/A/Tracy	32.7 [11.5–93.1]	28.7[d] [20.7–39.7]	27.5[e] [16.9–44.7]	30.1 [18.0–50.3]
	RSV/B/BA	18.5 [6.7–51.2]	13.0[d] [9.2–18.4]	14.9[e] [8.8–25.5]	10.4 [6.5–16.7]
	RSV/B/18537	28.3 [9.7–82.5]	17.4[d] [11.9–25.6]	17.1[e] [9.4–31.2]	16.7 [9.8–28.4]

Abbreviations: Ab, antibody; ARI, acute respiratory infection; CA, competitive antibody; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; F_A, Fusion protein of RSV/A; GM, geometric mean; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; MN, microneutralization; NtAb, neutralizing antibody; p27, 27-amino acid peptide; RSV, respiratory syncytial virus.

[a]Includes 2 infants infected with RSV whose RSV subgroup was not determined.

[b]Statistical significance of difference in means of the log-transformed titers or concentrations between RSV/A or RSV/B ARI groups and the non-RSV ARI group was assessed using post hoc comparisons from a linear regression analysis. No significant differences were observed in any of the assay serologic results.

[c]Acute serum sample of an RSV/B-infected infant (age 1 month) not available.

[d]Acute serum sample was depleted for the 4 RSV-infected infants listed in footnote e.

[e]Acute serum sample was depleted for 4 RSV/A-infected infants (age 0, 1, 2, and 8 months).

[f]Acute serum sample had insufficient volume for a non-RSV ARI infant (age 3 months).

[g]Acute serum sample had insufficient volume for 2 RSV/A-infected infants listed in footnote h.

[h]Acute serum sample had insufficient volume for 2 RSV/A-infected infants (age 0 and 1 month).

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RSV ARI at birth, as there was no difference in Ab activity at hospitalization. However, infants in the non-RSV ARI group were older than those in the RSV ARI groups, which influenced Ab levels [32, 33]. The estimated GMTs at birth were significantly lower for the RSV/A ARI group compared to the non-RSV ARI group, potentially increasing their susceptibility to RSV infection and subsequent hospitalization. Interestingly, GMTs at birth against contemporaneous and prototypic RSV strains in the non-RSV ARI group were generally above the upper bound of the 95% CI for women of childbearing age, except for RSV/B/18537. In contrast, GMTs at birth for both RSV ARI groups largely fell within the women's 95% CI, again except for RSV/B/18537, which was below the lower bound (Table 4). The higher Ab levels for RSV/A observed in the non-RSV ARI group suggest that these infants received a relatively higher transfer of maternal Abs, which may have contributed to protection against RSV illness.

Acute and Convalescent RSV-Specific Serum Antibody Responses by Infection Status

Non-RSV ARI

Of 17 participants with non-RSV ARI, 13 had paired acute and convalescent serum samples. In these 13 paired samples, the RSV-specific convalescent serum Ab responses were comparable to the levels detected in the acute samples (Table 6).

Table 4. Respiratory Syncytial Virus–Specific Serum Antibody Titer or Concentration in Women of Childbearing Age Reference Group

Assay Category	Assay Target	Women of Childbearing Age (n = 29)
MN assay, GMT [95% CI]	RSV/A/ON	172.6 [136.7–217.8]
	RSV/A/Tracy	129.5 [98.7–170.0]
	RSV/B/BA	337.0 [263.7–430.6]
	RSV/B/18537	583.9 [401.9–848.4]
F_A site-specific CA assay (μg/mL), GMC [95% CI]	Site Ø	32.9 [27.3–39.7]
	Site II	34.7 [28.8–41.7]
	Site IV	24.7 [20.6–29.5]

Sera were collected from women of childbearing age (18–45 years) from March 2020 through July 2020.

Abbreviations: CA, competitive antibody; CI, confidence interval; F_A, Fusion protein of RSV/A; GMC, geometric mean concentration; GMT, geometric mean titer; MN, microneutralization; RSV, respiratory syncytial virus.

RSV/A ARI

Among infants with RSV/A ARI, 21 of 29 had paired acute and convalescent serum samples available to evaluate posthospitalization Ab profile (Table 6). These infants were presumed to be infected with RSV/A/ON, the only circulating RSV/A genotype during the study period. A significant increase in NtAb titers occurred against RSV/A/ON and RSV/A/Tracy, along with significant heterologous response to the contemporaneous RSV/B/BA genotype, but not to the prototypic RSV/B/18537 strain. Statistically significant CA increases in GMCs were detected against sites II, IV, and I, but not against site Ø. By 4–6 weeks post–RSV/A ARI, CA levels for sites IV and II were 40%–50% of those in women of childbearing age. Binding IgG Abs to postF and p27 did not increase. The postF binding Ab to NtAb ratio decreased for RSV/A/ON, RSV/A/Tracy, and RSV/B/BA, indicating enhanced NtAb potency after infection.

RSV/B ARI

Of 17 participants with RSV/B ARI, 14 paired acute and convalescent serum samples were available to evaluate the RSV-specific serum Ab responses (Table 6). These infants had a statistically significant serum NtAb increase limited to RSV/B/BA and RSV/B/18537. Unlike primary infection with RSV/A/ON, primary infection with RSV/B/BA did not induce a significant NtAb rise against the heterologous RSV/A subgroup. A modest, nonsignificant rise in CA was observed only to site II, with levels at 4–6 weeks reaching approximately 30% of those observed in women of childbearing age. Binding IgG Abs to postF and p27 did not increase. The postF binding Ab to NtAb ratio decreased for RSV/B/BA and RSV/B/18537, indicating enhanced NtAb potency after infection.

Table 5 Estimation of Neutralizing Antibody Titers at Birth in Infants <6 Months of Age Based on a First-Order Antibody Decay Model

Assay Category	Assay Target	Non-RSV ARI (n = 12)	RSV/A ARI[a] (n = 21)	RSV/B ARI[a] (n = 13)
MN assay, GMT [95% CI]	RSV/A/ON	468.2 [151.9–1443.2]	**164.1* [117.2–229.7]**	207.7 [132.4–325.7]
	RSV/A/Tracy	255.3 [94.3–690.8]	**100.0* [72.2–138.6]**	143.0 [90.8–225.1]
	RSV/B/BA	624.9 [229.2–1703.9]	**206.7** [153.9–277.7]**	426.5 [227.1–801.1]
	RSV/B/18537	361.0 [154.3–844.4]	**166.8* [103.6–268.7]**	250.3 [154.9–404.4]

The estimated neutralizing antibody titer at birth (N_0) was based on a first-order decay model, $N_0 = N(t) \cdot e^{kt}$, given a neutralizing antibody half-life of 40 days (decay constant $k = \ln(2)/40$), the neutralizing antibody titer at hospitalization ($N(t)$; excluding titers <3.0 $\log_2$), and age in days (t).

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; GMT, geometric mean titer; MN, microneutralization; RSV, respiratory syncytial virus.

[a]Statistical significance of difference in means of the log-transformed titers between RSV/A or RSV/B ARI groups and the non-RSV ARI group was assessed using post hoc comparisons from a linear regression analysis; *$P < .05$, **$P < .01$.

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Table 6. Acute and Convalescent Antibody Response by Respiratory Syncytial Virus Infection Status in Infants <12 Months of Age

		Non-RSV ARI (n = 13)		RSV/A ARI (n = 21)		RSV/B ARI (n = 14)	
Assay Category	Assay Target	Acute	Convalescent[a]	Acute	Convalescent[a]	Acute	Convalescent[a]
MN assay, GMT [95% CI]	RSV/A/ON	28.8 [12.7–65.1]	28.0 [10.1–77.5]	33.1 [20.6–53.1]	**82.0* [61.2–109.7]**	34.5 [19.4–61.1]	58.0 [31.5–106.7]
	RSV/A/Tracy	17.3 [8.6–34.9]	15.6 [7.0–34.7]	20.2 [12.4–32.9]	**50.8* [38.4–67.2]**	21.0 [10.6–41.7]	29.7 [18.3–48.3]
	RSV/B/BA	27.3 [10.5–70.6]	31.2 [10.2–94.8]	37.1 [20.3–67.9]	**139.0* [103.5–186.7]**	60.9 [25.5–145.4]	**215.3* [95.7–484.4]**
	RSV/B/18537	18.8 [8.1–43.5]	18.8 [8.0–44.3]	28.5 [15.0–54.0]	44.5 [30.1–65.8]	42.0 [19.5–90.4]	**84.0* [41.4–170.4]**
F_A site-specific CA assay (μg/mL), GMC [95% CI]	Site Ø	1.3 [.5–3.3]	0.8 [.4–1.6]	1.2 [.6–2.3]	1.5[b] [.7–3.0]	1.3 [.5–3.0]	0.6 [.4–1.1]
	Site II	2.9 [1.0–8.5]	3.1 [1.0–9.1]	5.3 [2.4–11.7]	**17.0* [15.4 18.8]**	4.8 [1.7–13.6]	10.1 [5.8–17.6]
	Site IV	3.4 [1.4–8.3]	3.2 [1.2–8.3]	5.8 [3.5–9.8]	**10.0* [8.9–11.3]**	5.6 [3.0–10.7]	5.7 [3.1–10.7]
	Site I	1.6 [.8–3.3]	1.5 [.8–2.8]	1.8 [1.1–2.8]	**3.8* [3.2–4.5]**	1.7 [1.0–3.0]	1.5 [.9–2.5]
ELISA (μg/mL), GMT [95% CI]	Anti-postF IgG	683.4 [166.7–2802.2]	683.4[c] [242.4–1926.6]	608.9 [300.2–1235.1]	608.9[d] [325.8–1137.9]	624.1 [312.5–1246.7]	512.0 [230.0–1140.0]
ELISA (ng/mL), GMT [95% CI]	Anti-p27 IgG	6120.4 [4752.7–7881.6]	6755.2 [4196.9–10873.0]	4553.7 [3368.9–6155.2]	5588.3[e] [4069.5–7674.0]	4205.0 [2705.3–6535.8]	2392.0 [380.3–15044.1]
PostF IgG binding Ab to NtAb titer ratio, GM [95% CI]	RSV/A/ON	26.9 [8.0–91.0]	25.4[c] [6.9–93.7]	18.2 [8.4–39.8]	**6.6[d,]* [4.0–10.7]**	18.1 [10.2–32.0]	8.8 [4.6–17.1]
	RSV/A/Tracy	44.0 [12.1–159.6]	47.9[c] [15.6–147.3]	30.6 [15.0–62.7]	**10.8[d,]* [5.9–19.8]**	29.7 [16.7–52.9]	17.2 [8.7–34.2]
	RSV/B/BA	30.2 [10.2–89.1]	25.4[c] [6.9–93.4]	17.1 [8.0–36.5]	**4.5[d,]*** [2.5–7.8]**	10.2 [6.0–17.6]	**2.4*** [1.2–4.8]**
	RSV/B/18537	45.3 [13.5–151.7]	44.0[c] [15.8–122.2]	23.6 [10.7–52.3]	15.0[d] [7.5–30.1]	14.9 [8.5–26.0]	**6.1* [3.0–12.5]**

Abbreviations: Ab, antibody; ARI, acute respiratory infection; CA, competitive antibody; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; F_A, Fusion protein of RSV/A; GM, geometric mean; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; MN, microneutralization; NtAb, neutralizing antibody; p27, 27-amino acid peptide; RSV, respiratory syncytial virus.

[a]Statistical significance of difference in means of the log-transformed titers or concentrations between acute and convalescent paired samples for each ARI group was assessed using post hoc comparisons from a linear mixed-effects model for repeated measures; *$P < .05$, **$P < .01$, ***$P < .001$.

[b]One convalescent sample for an RSV/A ARI infant (age 0 months) had insufficient volume for F site-specific competitive antibody assay against site Ø.

[c]One convalescent sample was depleted for non-RSV ARI infant (age 1 month).

[d]The acute serum sample was depleted for 3 RSV/A ARI infants (age 0, 1, and 8 months), and the convalescent sample of 1 RSV/A ARI infant (age 1 month), and both the acute and convalescent samples were depleted for 1 RSV/A ARI infant (age 2 months).

[e]The acute sample had insufficient volume for 2 RSV/A ARI infants (age 0 and 1 months).

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Table 7. Magnitude of the Convalescent Antibody Response by Infant Age Category and Respiratory Syncytial Virus Infection Status in Infants <12 Months of Age

		Non-RSV ARI		RSV/A ARI		RSV/B ARI	
Assay Category	Assay Target	<4 mo (n = 5)	≥4 mo[a] (n = 8)	<4 mo (n = 15)	≥4 mo[a] (n = 6)	<4 mo (n = 12)	≥4 mo[a] (n = 3)
MN assay, GMT [95% CI][b]	RSV/A/ON	55.7 [9.3–333.7]	18.2 [4.2–79.8]	70.2 [50.6–97.5]	120.8 [62.0–235.5]	60.4 [31.8–114.9]	64.0 [4.0–2003.5]
	RSV/A/Tracy	29.9 [7.1–126.0]	**10.4* [4.0–31.3]**	47.4 [33.0–68.1]	60.4 [35.4–103.2]	32.9 [19.6–55.3]	25.4 [4.0–352.4]
	RSV/B/BA	84.4 [8.4–846.8]	**16.7* [4.2–65.9]**	143.7 [100.2–206.0]	128.0 [61.8–264.9]	228.1 [95.8–542.9]	181.0 [4.0–9357.3]
	RSV/B/18537	45.3 [8.8–233.0]	**10.8* [4.0–30.8]**	53.2 [32.2–87.9]	28.5 [15.7–51.6]	90.5 [43.0–190.7]	57.0 [4.0–1849.7]
F_A site-specific CA assay (μg/mL), GMC [95% CI][b]	Site Ø	1.0 [.5–6.3]	0.7 [.5–1.6]	1.9[c] [.7–4.7]	0.8 [.5–2.8]	0.7 [.5–1.3]	0.5 [.5–.5]
	Site II	8.3 [1.0–68.0]	**1.7** [.5–6.6]**	17.0 [14.9–19.4]	17.0 [14.3–20.3]	10.3 [5.4–19.5]	10.4 [2.1–52.0]
	Site IV	6.8 [1.1–43.4]	**2.0* [.6–7.2]**	10.4 [8.9–12.0]	9.3 [7.3–11.7]	7.0 [4.0–12.2]	2.9 [.5–153.8]
	Site I	2.0 [.6–6.9]	1.2 [.5–3.1]	3.5 [2.9–4.2]	4.7 [3.4–6.6]	1.7 [.9–3.0]	1.2 [.5–13.9]
ELISA (μg/mL), GMT [95% CI]	Anti-postF IgG	1448.2[d] [104.8–20002.2]	469.5 [124.2–1775.3]	633.7[e] [331.3–1212.2]	574.7 [164.2–2011.7]	456.1 [182.4–1140.9]	512.0 [16.4–16027.7]
ELISA (ng/mL), GMT [95% CI]	Anti-p27 IgG	4389.7 [2847.3–6767.7]	8843.9 [4229.7–18491.5]	5180.7 [3859.2–6954.8]	7556.2 [3146.1–18148.4]	2135.7 [238.1–19153.7]	6116.7 [4052.0–9233.5]

Abbreviations: ARI, acute respiratory infection; CA, competitive antibody; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; F_A, Fusion protein of RSV/A; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; MN, microneutralization; p27, 27-amino acid peptide; RSV, respiratory syncytial virus.

[a]Statistical significance of difference in means of the log-transformed titers or concentrations between age categories <4 months and ≥4 months for each ARI group was assessed using post hoc comparisons from a linear regression analysis; $*P < .05$, $**P < .01$.

[b]The lower bound CI was constrained to 4.0 for neutralizing antibody titer and 0.5 μg/mL for F site-specific CA assay.

[c]The convalescent sample for 1 RSV/A ARI infant (age 0 months) had insufficient volume for CA assay against site Ø.

[d]The convalescent sample for 1 non-RSV ARI (age 1 month) had insufficient volume for postF ELISA assay.

[e]The convalescent sample for 2 RSV/A ARI (age 1 and 2 months) had insufficient volume for postF ELISA assay.

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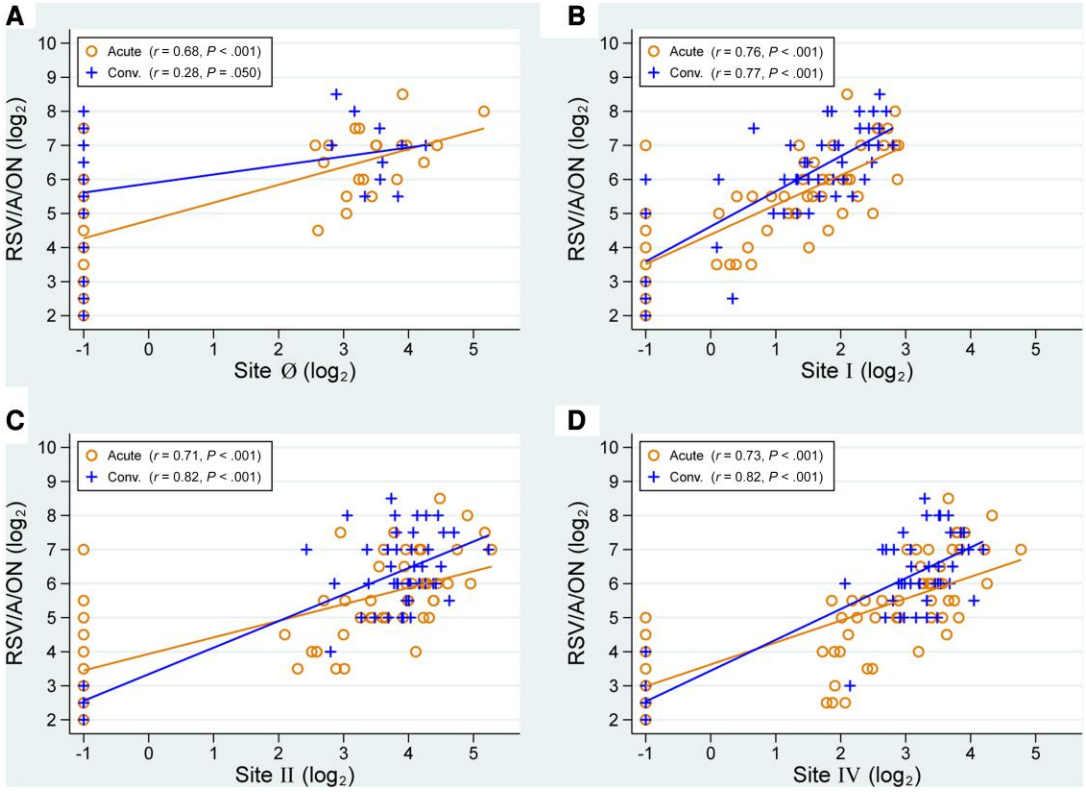


Figure 1 The relationship between respiratory syncytial virus (RSV) subgroup A/Ontario (RSV/A/ON) neutralizing antibody titer and F site-specific competitive antibody concentration in infants with primary RSV infection. Pearson correlation coefficient was performed to assess the relationship between the microneutralization titer (log_2) and the F site-specific competitive antibody concentration (log_2) by antigenic site (sites Ø, I, II, and IV) in the acute (n = 65) and convalescence (n = 50) serum samples in the combined infant acute respiratory infection groups (non-RSV, RSV/A, and RSV/B). *A*, Site Ø, a prefusion antigenic site. *B*, Site I, a postfusion antigenic site. *C*, Site II, shared by both the prefusion and postfusion form of the fusion protein. *D*, Site IV, shared by both the prefusion and postfusion form of the fusion protein.

Convalescent RSV-Specific Antibody Response by Age Category and Infection Status

Non-RSV ARI

We compared convalescent RSV-specific Ab response between infants aged <4 months and infants aged 4 to <12 months (Table 7). We anticipated older infants (4 to <12 months) in the non-RSV ARI group to have lower Ab levels, if the Abs were maternally derived and the infants were not previously infected with RSV. As expected, statistically significant reductions in the NtAb GMTs were observed, with older infants having 20%–35% of titers compared to infants aged <4 months. Similar statistically significant reductions were noted for CA to sites II and IV. Unexpectedly, the anti-p27 IgG Abs increased by about 2-fold.

RSV/A ARI

Higher levels of NtAb GMTs against RSV/A/ON and RSV/A/Tracy were detected in older infants >4 months compared to younger infants ≤4 months (Table 7). Older infants had 1.72- and 1.27-fold higher GMTs than younger infants against RSV/A/ON and RSV/A/Tracy, respectively, although it was not statistically significant. On the other hand, there was a lower NtAb GMT against heterologous strains in older infants, with levels 0.89- and 0.54-fold of the GMTs compared to younger infants against RSV/B/BA and RSV/B/18537, respectively. CA to sites II and IV and anti-postF IgG Ab were comparable between older and younger infant subgroups, while anti-p27 IgG Abs increased by about 1.5-fold.

RSV/B ARI

NtAb GMTs in older infants were 0.79- and 0.63-fold lower compared to younger infants against RSV/B/BA and RSV/B/18537, respectively (Table 7). The NtAb GMTs against heterologous strains (RSV/A/ON and RSV/A/Tracy) were either comparable or 0.25-fold lower in older infants compared to younger infants. Interestingly, CA to site II and anti-postF IgG Abs were similar between the 2 age subgroups, but lower against site IV in older infants. The anti-p27 IgG Ab increased by about 2.9-fold.

Relationship Between RSV-Specific Neutralizing Antibody Titer and F Site-Specific Competitive Antibody Concentration

Statistically significant correlations were observed between serum NtAb titers against RSV/A/ON and CAs to sites Ø, I, II,

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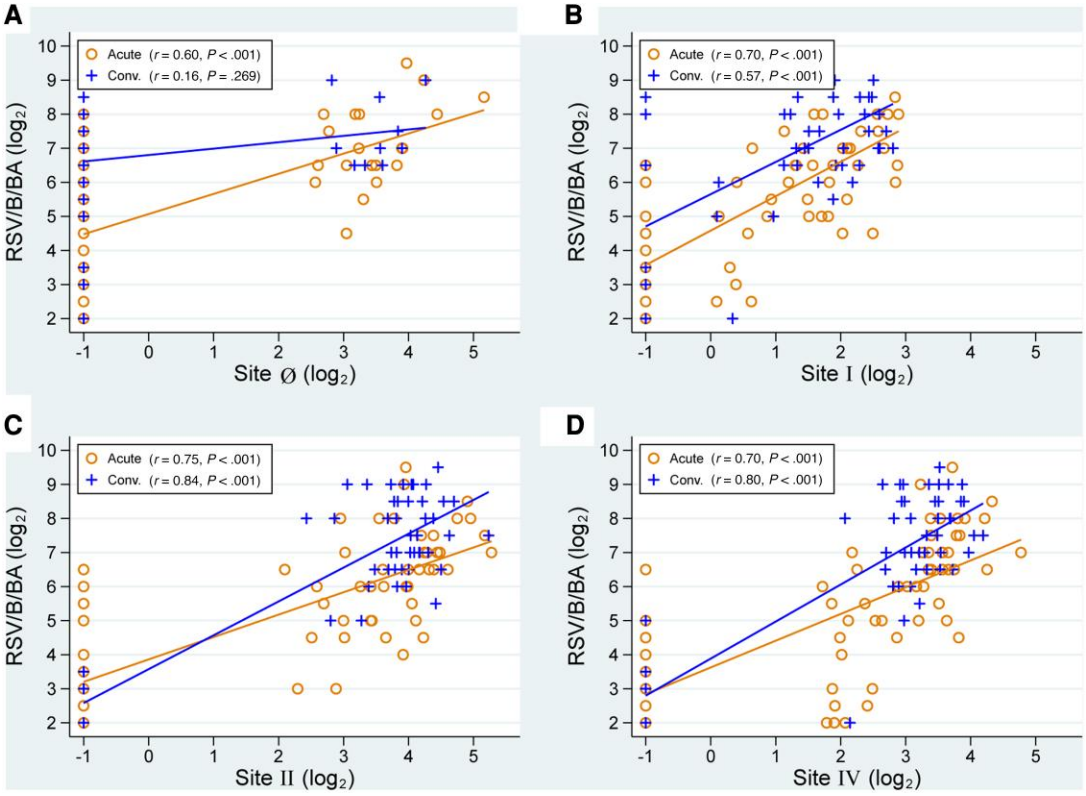


Figure 2. The relationship between respiratory syncytial virus (RSV) subgroup B/Buenos Aires (RSV/B/BA) neutralizing antibody titer and F site-specific competitive antibody concentration in infants with primary RSV infection. Pearson correlation coefficient was performed to assess the relationship between the microneutralization titer (log_2) and the F site-specific competitive antibody concentration (log_2) by antigenic site (sites Ø, I, II, and IV) in the acute (n = 65) and convalescence (n = 50) serum samples in the combined infant acute respiratory infection groups (non-RSV, RSV/A, and RSV/B). *A*, Site Ø, a prefusion antigenic site. *B*, Site I, a postfusion antigenic site. *C*, Site II, shared by both the prefusion and postfusion form of the fusion protein. *D*, Site IV, shared by both the prefusion and postfusion form of the fusion protein.

and IV in acute serum samples (Figure 1*A*–*D*). In convalescent samples, this NtAb correlation was strengthened to sites II and IV, but weakened ($r = 0.28$; $P = .05$) for site Ø.

Similar statistically significant relationships between serum NtAb titers against RSV/B/BA and CAs to sites Ø, I, II, and IV were detected in the acute serum samples (Figure 2*A*–*D*). In convalescent samples, these statistically significant relationships were strengthened to sites II and IV, but lost ($r = 0.16$; $P = .269$) for site Ø.

DISCUSSION

We characterized the humoral immune profile of term infants hospitalized with primary RSV/A/ON and RSV/B/BA infection. Primary RSV/A/ON infection induced a homologous and heterologous NtAb response to both prototypic and contemporaneous genotypes, while a primary RSV/B/BA infection induced only a homologous NtAb response. RSV/A/ON infection induced a robust CA response to site II and IV, whereas RSV/B/BA infection produced a limited response restricted to site II. The levels of NtAb and CA generated after primary infection of either genotype were low compared to an adult reference group of women of childbearing age. Women of childbearing age were selected as the adult reference group because (1) adults have mature immune systems that have responded to multiple RSV infections and (2) infants acquire maternal RSV Abs transplacentally at birth that decay over time until infants generate their own Abs after primary RSV infection. These findings have implications in understanding the continued susceptibility of infants to RSV reinfection. Our study can serve as a benchmark for comparing humoral immune response induced by live attenuated or vector-based RSV vaccines currently in development to prevent RSV infection in young children [11, 13]. This is especially relevant considering that our study was conducted prior to the introduction of maternal preF vaccination and the use of nirsevimab or clesrovimab for immunoprophylaxis. As these prevention strategies have the potential to modify Ab response to primary RSV infection, defining the baseline immune profile prior to their broad implementation is essential.

Neutralizing antibodies in the form of polyclonal or monoclonal antibody, whether maternally acquired or systemically

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administered, are the only proven immunological repertoire that can prevent severe RSV infection in infants [34–36]. Our RSV cases were younger than the non-RSV ARI control group, with low enrollment NtAb GMTs (<1:68) against both prototypic (RSV/A/Tracy and RSV/B/18537) and contemporaneous (RSV/A/ON and RSV/B/BA) isolates. We previously demonstrated that low NtAb titers for RSV/A/Tracy and for RSV/B/18537 were associated with increased risk of RSV hospitalization [28]. Consistent with higher NtAbs protecting against severe RSV, we observed that estimated NtAb titers at birth were higher in the non-RSV ARI group compared to the RSV ARI groups.

The ON and BA genotypes have unique 72 and 60 nucleotide duplications in their G genes, respectively [37, 38]. Our study describes for the first time the humoral immune response following primary infection with RSV/A/ON and RSV/B/BA genotypes. BA and ON emerged in 1996 and 2012, respectively, and have become the dominant RSV strains possibly due to a fitness advantage [39, 40]. Prior studies evaluated NtAb responses following RSV infection lacking the G-gene duplication [14, 16] or following the introduction of the BA genotype [41]. We describe for the first time the primary humoral immune response in infants infected with RSV strains carrying a large G-gene duplication.

The F protein has 2 main conformations: preF and postF [42–44]. PreF is metastable and converts to the stable noninfectious postF. Only preF vaccines have been shown to prevent severe RSV [44–46]. Sites Ø and V are unique to preF [47]; nirsevimab targets site Ø and reduces severe RSV [35]. Suptavumab, which targets site V, failed in a phase 3 trial due to RSV/B resistance [48]. Sites II, III, and IV are present in both preF and postF; palivizumab targets site II and clesrovimab targets site IV. Site I, mainly in postF, is associated with mAbs having poor NtAb activity. Antibodies targeting preF sites are most potent [49]. Our study showed that increases in NtAb activity after primary RSV infection were accompanied by rises in CAs to site II and/or site IV. Increased site II CAs were detected after both RSV/A/ON and RSV/B/BA infections, although more pronounced after RSV/A/ON, whereas CA to site IV increased only after RSV/A/ON infection. As with NtAbs, the levels of CA to sites II and IV were lower than those of women of childbearing age. In our study, we did not detect a rise in CA to site Ø after primary RSV infection. This was unexpected and was not attributed to an assay issue since women of childbearing age had the expected levels of CA to site Ø [29]. Interestingly, a statistically significant correlation was observed in the acute sera between NtAb and site Ø CA for both RSV/A/ON and RSV/B/BA. This association was not significant in the convalescent sera but remained highly significant to sites II and IV. Our study is the first comprehensive evaluation of CA responses following primary RSV/A/ON and RSV/B/BA infection. Overall, RSV/A/ON infection induced broader and stronger CA responses than RSV/B/BA. Our study also supports a hierarchy in CA generation in infants that favors site II, followed by site IV, with site Ø likely requiring reinfection for its induction.

Older age at primary RSV infection has been associated with higher NtAb response, with 4 months being an important transition point [18]. Studies have shown steady increase in RSV-F epitope repertoires from early childhood to adulthood [17] and substantial age-dependent differences in RSV-specific immunity in children aged <2 years with a window of vulnerability between 3 and 6 months. Following RSV infection, infants generated cross-reactive F-responses, with minimal maternal blunting [21]. An analysis by Goodwin et al of F-specific Abs from 7 RSV-infected infants revealed that 27%–47% of Abs in the 4 oldest infants recognized both preF and postF, compared to <10% in the 3 youngest infants [24]. In contrast, we observed a bias of CA response toward antigenic sites shared by both preF and postF forms that was consistent with their attenuated NtAb response.

In summary, RSV-infected infants were younger than non-RSV ARI controls at the time of hospitalization and had low levels of protective Abs. Infants infected with RSV/A/ON compared to RSV/B/BA mounted a robust homologous and heterologous NtAb response, mirrored by a broader CA Ab response, although restricted to site II and IV. Humoral Ab response following primary RSV infection was attenuated compared to reference titers in adult women of childbearing age. Defining quantitative and qualitative immune response to RSV/A and RSV/B primary infections in young children is essential for developing and evaluating vaccines for young children.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Data availability. The data underlying this article are available in the article.

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Potential conflicts of interest. All authors: No reported conflicts.

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