Illness Severity, Viral Shedding, and Antibody Responses in Infants Hospitalized with Bronchiolitis Caused by Respiratory Syncytial Virus

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The relationships between host factors, viral shedding, illness severity, and antibody response in respiratory syncytial virus (RSV)–induced bronchiolitis are poorly defined. These relationships were prospectively evaluated in 77 infants hospitalized with RSV bronchiolitis in multicenter, double-blind, placebo-controlled trials of RSV immunoglobulin therapy. Severity of illness was influenced by age and host risk factors but was not influenced by RSV neutralizing antibody titer or by the amount of virus in nasal secretions at enrollment. Virus recovery in nasal secretions was variable but was highest at enrollment. Viral shedding was not influenced by primary diagnosis, antibody titer, age, or duration of acute respiratory illness before enrollment. In intubated patients, the amounts of virus recovered in nasal secretions and endotracheal aspirates were highly correlated. A serum neutralizing antibody response was seen in 64% of subjects who received placebo. The response was not influenced by age, primary diagnosis, amount of virus recovered, or severity of illness but was suppressed by preexisting antibody.

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection (LRTI) in infants and children, and RSV infections occur in predictable epidemics every year. By age 2 years, almost all children have experienced at least 1 RSV infection, and 50% have been infected ≥2 times [1]. Hospitalization rates are estimated to be 3% among infants <1 year of age and are disproportionately higher among the very youngest infants, those born just before or during the RSV infection season [2–4]. Infants with congenital heart disease (CHD) or bronchopulmonary dysplasia (BPD) or who are born prematurely are at particular risk for severe bronchiolitis or pneumonia caused by RSV infection [5–8]. The clinical characteristics of illness in each of these populations have been well described elsewhere [5–8]. Other nuances of the natural history of primary RSV infection are less clear. These include the relationships of illness severity and antibody response to age, underlying condition(s), levels of maternally acquired RSV serum antibody at the time of clinical illness, and quantity of virus being shed. A better understanding of these interrelationships is important to the development of RSV vaccines and other intervention strategies against RSV illness.

We participated in placebo-controlled multicenter trials that used immunoglobulin preparations enriched for high titers of antibodies to RSV (RSVIG) (RespiGam; MedImmune) as therapy for previously healthy or high-risk infants hospitalized with RSV LRTI. Although, as has been reported elsewhere [9, 10], these studies did not show that RSVIG has a therapeutic benefit, they provided an opportunity to explore the interrelationship of host factors, virus replication, and antibody responses in primary RSV LRTIs.

Methods

Enrollment. Seventy-seven infants <2 years of age who had been hospitalized with RSV bronchiolitis at Vanderbilt University Hospital were enrolled in 2 multicenter, double-blind, placebo-controlled therapeutic trials of RSVIG (1990–1994) [9, 10]. Table 1 shows the demographic characteristics of the populations at enrollment. Of the enrolled subjects, 70% were white and 30% were black.

The first study included 33 otherwise healthy infants (18 of whom received placebo and 15 of whom received RSVIG) with RSV LRTIs. Subjects had exhibited symptoms of acute LRTI for ≤4 days and had initial respiratory illness scores >2.5 (twice daily scoring of illness severity was done as described elsewhere [9]). The second study included 44 infants (22 of whom received placebo and 22 of whom received RSVIG) who were at higher risk for severe LRTI with RSV.
Table 1. Demographic characteristics of 77 infants hospitalized at Vanderbilt University with respiratory syncytial virus (RSV) bronchiolitis.

<table>
<thead>
<tr>
<th>Previous health status</th>
<th>No. of patients</th>
<th>Sex, male/female</th>
<th>Mean age, days (range)</th>
<th>No. of patients in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>33</td>
<td>19/14</td>
<td>59 (15–217)</td>
<td>18</td>
</tr>
<tr>
<td>CHD</td>
<td>18</td>
<td>8/10</td>
<td>163 (28–677)</td>
<td>8</td>
</tr>
<tr>
<td>CHD alone</td>
<td>14</td>
<td>7/7</td>
<td>172 (28–677)</td>
<td>7</td>
</tr>
<tr>
<td>CHD and BPD</td>
<td>3</td>
<td>1/2</td>
<td>165 (97–227)</td>
<td>1</td>
</tr>
<tr>
<td>CHD and prematurity</td>
<td>1</td>
<td>0/1</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>BPD</td>
<td>11</td>
<td>7/4</td>
<td>212 (72–357)</td>
<td>6</td>
</tr>
<tr>
<td>BPD alone</td>
<td>3</td>
<td>3/0</td>
<td>178 (72–313)</td>
<td>1</td>
</tr>
<tr>
<td>BPD and prematurity</td>
<td>8</td>
<td>4/4</td>
<td>224 (128–357)</td>
<td>5</td>
</tr>
<tr>
<td>Prematurity &lt; 32 weeks</td>
<td>15</td>
<td>4/11</td>
<td>164 (54–388)</td>
<td>8</td>
</tr>
</tbody>
</table>

NOTE: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; RSVIG, RSV immunoglobulin.

disease [10]. Infants in the high-risk study had received a diagnosis of CHD or BPD or had been born prematurely (at < 32 weeks of gestation). “CHD” was defined as the presence of a cardiac anomaly either with pulmonary hypertension or requiring chronic digitalis and/or diuretic therapy. We defined “BPD” as the need for supplemental oxygen within 6 months of study enrollment in infants born at < 35 weeks of gestation who required mechanical ventilation in the neonatal period and subsequent supplemental oxygen for > 1 month. Subjects who exhibited acute LRTI symptoms for ≤ 4 days and had received an initial respiratory illness score of > 1.0. For purposes of analysis, a primary diagnosis of CHD was assigned to infants who had CHD and ≥ 1 other high-risk condition. In infants without CHD, BPD, if present, was the primary diagnosis assigned. Prematurity (PM) was the risk factor assigned to infants who had neither CHD nor BPD (see table 1 for details).

Exclusion criteria for both studies included any previously diagnosed immunodeficiency, cystic fibrosis, reactive airways disease or asthma, poorly controlled congestive heart failure before the current hospital admission, renal failure, ventilator dependency at the time of enrollment, life expectancy < 6 months, apnea without evidence of LRTI, previous reaction to blood products, receipt of immunoglobulin therapy in the preceding 2 months, enrollment in an intravenous RSV prophylaxis protocol; or receipt of ribavirin treatment in the preceding month.

Detection of RSV antigen in nasal washings (NWs) by ELISA (Testpak; Abbott) was required for enrollment, and subsequent confirmation of RSV infection by viral culture was required for continuation in the study.

Study design—clinical. Enrolled subjects were randomly assigned in a double-blind fashion at a ratio of 1:1 to receive intravenous RSVIG (MedImmune) or albumin placebo. Enrollment and follow-up of subjects was performed according to the overall study design of these multicenter trials [9, 10]. While hospitalized, infants were evaluated twice daily to establish a respiratory illness score, and daily NWs (and endotracheal tube [ET] aspirates, for intubated patients) were obtained for use in quantitative viral cultures. Serum samples and NWs were obtained at enrollment, at 24 h after enrollment, and at 8 weeks after enrollment for analysis of immune responses, per the study protocol. Suplemental studies of viral shedding and serologic response were performed at the Vanderbilt site as described below; for these studies, additional serum samples were collected before and after the subsequent RSV infection season.

Interventions related to patient care (e.g., use of bronchodilators, supplemental oxygen, ventilatory support, and ribavirin) and decisions regarding discharge were left to the discretion of each patient’s primary care physician. Outcome measures of illness severity included the sum of the respiratory illness scores for up to 13 days after enrollment, length of time in which supplemental oxygen was required, and length of time in which ventilatory support was needed.

A subset of 42 patients were evaluated at the start of the subsequent RSV season, and 34 of these patients were followed up through the season for serologic evidence of duration of immunity, reinfection, and rehospitalization. No attempt was made to isolate RSV a second time from patients who became ill.

Study design—laboratory. RSV isolation and identification were done as described elsewhere [9]. Titers in specimens were measured immediately on collection, without prior freezing. Available isolates from all 4 RSV seasons were identified as subgroup A or B viruses by immunofluorescence, using group-specific monoclonal antibodies (MAbs) 92-11C and 102-10B (courtesy of L. Anderson, Centers for Disease Control and Prevention, Atlanta). MAbs were used at a 1:4000 dilution in PBS cell scrapings from HEp-2 cells infected with the RSV isolate that was to be tested. Goat anti-mouse IgG antibody (Bartels) and then Evans blue counterstain were applied, and immunofluorescent cells were identified. No attempt was made to characterize viruses by strain variation.

Measurement of RSV was done with fresh NWs and ET specimens by plaque assay and reported as plaque-forming units per milliliter, as described elsewhere [11]. Serum neutralizing antibody titers were determined by a 60% plaque-reduction neutralization assay [11]. The starting dilution for serum antibody determinations was 1:20. Antibody responses are reported only for placebo recipients. Antibody titers at 8 weeks were corrected for decay from the time of infection (estimated half-life, 21 days) of passively acquired maternal antibody in infants < 6 months old. A ≥ 4-fold increase in corrected serum antibody levels or seroconversion from negative to positive for RSV at 8 weeks after enrollment was considered to be evidence of antibody response to infection.

IgA and IgG antibody responses in serum and NWs to RSV F and Gα proteins (courtesy of E. Walsh, University of Rochester, Roch-
Ester, NY, and Wyeth Lederle Vaccines) were determined by a kinetic ELISA previously developed for influenza and adapted to detection of antibodies to the F and GA proteins [12]. The dilutions used were 1:20 for serum antibody determinations and 1:4 for NW antibody determinations. A kinetic ELISA value of 5 milli-optical destiny/min was considered to be evidence of the presence of specific antibody. Total IgA was determined to ensure that the specimens had measurable IgA, but the values were not corrected for total IgA. Data for these ELISA determinations are more fragmentary than neutralization results because of a lack of sample availability.

Statistical analysis. Descriptive and exploratory graphical analyses were used to investigate the distribution of demographic characteristics and to identify outlying data. Two children >600 days old were excluded from the analysis of age influence. We used χ² or Fisher’s exact tests, as appropriate, for contingency table analyses. The mean amount of virus recovered from NWs over time was analyzed by 1-way analysis of variance (ANOVA). Univariate comparisons of continuous variables were made with a t test and a nonparametric Mann-Whitney test. Results were consistent, and we report the P values for t tests (P < .05 was considered significant). We compared relationships by using Pearson’s correlation and scatter plot. Best-fit regression analysis was used to determine the best models for illness severity. Analysis was done by using SPSS Interactive Graphics for Windows, version 10.0.5, and SAS for Windows (SAS Institute), version 8.0.

Results

Factors influencing illness severity. Severity of illness at study entry could not be analyzed in terms of risk status, because the severity-of-illness entry criteria for the study involving otherwise healthy infants and the high-risk study differed. Although the illness criterion for admission to the low-risk trial included a severity score of 2.5 on entry, the traditional high-risk groups of BPD and CHD were each identified by ≥1 independent criteria as having a more-severe course of illness (table 2). CHD had the strongest association with severe illness, as has been reported elsewhere [3, 8]. The younger a child was when acquisition of RSV occurred, the more severe was the course of illness during hospitalization, by several criteria (table 2). However, the severity of illness, as judged by total illness score, had no correlation with serum neutralizing antibody titer at enrollment (figure 1A) or titer of RSV in NWs (figure 1B).

RSV isolates could be retrieved for serotyping into subgroups A and B from only 21 subjects; 16 (76%) of 21 virus isolates were of group A, and 5 (24%) were of group B. Too few isolates were available for severity of illness to be analyzed by strain, although RSV A strains are reported to cause more-severe illness [13].

Factors influencing viral shedding. The quantity of RSV recovered from NWs at trial entry was not influenced by serum antibody titer (figure 2A) and did not vary by age (figure 2B). Within 48 h of trial entry, the mean amount of virus recovered from the NWs of patients receiving RSVIG and patients receiving place-

<table>
<thead>
<tr>
<th>Illness severity criterion</th>
<th>Age (P)</th>
<th>Congenital heart disease (P)</th>
<th>Bronchopulmonary dysplasia (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of illness scores</td>
<td>NA</td>
<td>+ (.03)</td>
<td>NA</td>
</tr>
<tr>
<td>Days receiving supplementary oxygen</td>
<td>− (.08)</td>
<td>+ (.02)</td>
<td>+ (&lt;.001)</td>
</tr>
<tr>
<td>Days receiving ventilatory support</td>
<td>− (.023)</td>
<td>+ (.086)</td>
<td>NA</td>
</tr>
<tr>
<td>Total days in hospital</td>
<td>− (.073)</td>
<td>+ (.003)</td>
<td>+ (.01)</td>
</tr>
</tbody>
</table>

NOTE. NA, no strong association after correction for other factors; −, inverse correlation, by best-fit regression model, after correction for other factors; +, positive correlation, by best-fit regression model, after correction for other factors.

Table 2. Relationship between respiratory illness severity and host factors in 77 children hospitalized at Vanderbilt University with respiratory syncytial virus bronchiolitis.

![Figure 1. Relationships between total illness score (sum of twice daily scoring on a 1–5 scale [9], in which 5 is the most severe [e.g., requiring intubation]), serum neutralizing antibody titer (A), and quantity of respiratory syncytial virus (RSV) recovered from nasal secretions (B) at enrollment. Illness was scored during hospitalization for up to 13 days.](https://academic.oup.com/jid/article-abstract/185/8/1011/813012)
bo was 10-fold lower than entry levels (figure 3), a significant difference, by ANOVA, for both placebo ($P = 0.017$) and RSVIG ($P = 0.015$) groups. We compared the quantity of RSV shed in NWs and ET aspirates in a subset of 16 intubated patients. In this group, NW RSV titers were highly variable but strongly correlated with ET titers in individual patients (figure 4; $P < 0.001$).

Factors influencing enrollment antibody titers. Antibody titers at enrollment were lower, although not significantly so, in the BPD and PM groups, in which patients might have been expected to have less transplacental antibody (figure 5A). Antibody titers at entry were inversely correlated with age, as would be expected, since younger children have relatively higher levels of residual maternal antibody (figure 5B). At entry, 64% of the infants were seronegative. At 24 h after entry, a difference in neutralizing titers was seen between placebo and RSVIG groups, and the expected rise in titers among the RSVIG recipients occurred, to a mean titer of $1:1000$. However, no changes in neutralizing antibody titers were seen in the placebo group at 24 h after enrollment—indicating that this arm of the immune defense was not yet operational—and there was no evidence of consumption of antibody through binding to antigen.

Evaluation of antibody response to infection. The increase in antibody levels at 8 weeks could only be assessed in the placebo group. Of 33 infants in the placebo group, 21 (64%) had an increase in neutralizing antibody titers. Numbers were too small to make any correlations with risk groups. The responses were not influenced by titer of virus at enrollment, severity of illness, or age. The presence of maternally derived neutralizing antibody in the enrollment sample was associated with fewer antibody responses: only 2 (25%) of 8 seropositive children made a response in whom preexisting antibody was present, compared with 19 (76%) of 25 seronegative children ($P = 0.015$). The number of children with neutralizing antibody responses was not smaller among the 17 children $< 90$ days of age at trial enrollment than among the 16 children $> 90$ days of age (65% vs. 63%, respectively).

Table 3 shows the numbers of placebo recipients with serum and mucosal IgA and IgG neutralizing antibodies to F and G proteins. No single response exceeded the seroconversion rate seen with neutralizing antibodies. The frequency of increases in IgG antibody to F protein was significantly diminished by the presence of neutralizing antibody ($P = 0.028$), but this comparison was not statistically significant when the analysis was controlled for age. Increases in the levels of IgG antibody to G protein were not significantly diminished in association with age in days or preexisting maternal antibody. One-third of placebo reci-

Figure 2. Relationships between quantity of respiratory syncytial virus (RSV) recovered, serum neutralizing antibody titer (A), and age in days (B) at enrollment. No significant interactions between these variables were seen.

Figure 3. The quantity of respiratory syncytial virus (RSV) recovered from nasal secretions decreased significantly after enrollment in both placebo (○) and RSV immunoglobulin (RSVIG; △) groups. A significant decrease, by 1-way analysis of variance, was seen in the mean level between 0 and 1 and between 1 and 2 days after enrollment in both groups.
Patients had mucosal IgA responses. Mucosal responses were not influenced by age or preexisting neutralizing antibody. By the subsequent autumn, 6–8 months after vaccination, more than two-thirds of available subjects were seronegative, and one-half were reinfected in the subsequent RSV season. None were rehospitalized.

Discussion

RSV has been the major cause of LRTIs in infants since its recognition >40 years ago. Unfortunately, progress in our understanding of the epidemiology of RSV has not been matched by concomitant development of effective intervention strategies. The use of inactivated RSV vaccines in the 1960s led to exaggerated illness after subsequent natural RSV infection [14–16]; the live vaccines of the 1970s lacked infectivity or were insufficiently attenuated [17–19]; and the effectiveness of ribavirin in treating infection was found to be limited [20]. Monthly prophylaxis with RSV polyclonal and monoclonal gamma globulin preparations against RSV illness is effective in children with BPD [21–23], but it is too costly and inconvenient to be used in otherwise healthy children.

We analyzed data from RSVIG treatment trials to better define the factors associated with increased severity of disease and to identify factors associated with development of a protective immune response. These results will help guide future prevention and intervention strategies.

The lack of a relationship between viral shedding and clinical outcome has been noted [24]. In our study, the virus titer at enrollment was highly variable and in no way predictive of severity of illness at admission or of the course of illness. The amount of virus shed by some children was impressively high (10^7 pfu/mL was not uncommon) when titers of virus in nasal samples were directly measured. The highest virus titers were seen at enrollment and decreased within 48 h of admission. Children in whom virus burden begins to decrease shortly after the onset of an LRTI likely are late in the course of the viral infection. Analogously, children receiving live attenuated RSV vaccines have peak viral shedding on days 6−8 after vaccine administration, and the decline in titer begins on day 9 [25]. Thus, further reduction in virus titer alone may be relatively insignificant in affecting outcome. These observations are consistent with the limited or absent clinical effectiveness of treatment strategies directed at reduction of virus load (e.g., administration of ribavirin or RSVIG) in children hospitalized with RSV bronchiolitis.
[9, 10, 21]. At the postulated time of peak illness, 8–10 days after infection, inflammatory and immune-mediated processes set in motion by the infection may play an important role in determining illness severity. However, neither broad immunosuppression resulting from use of steroids nor bronchodilators have been shown to have any benefit in improving the outcome for children hospitalized with bronchiolitis [26–29].

In intubated children, a subset of our study groups, a close correlation was seen between the amount of virus being shed in the lungs and the amount shed in the nasal passages. Thus, there is no dissociation between viral replication at these 2 respiratory tract sites. Again, even in infants sick enough to require intubation, virus loads were highly variable and were not, on average, higher than the virus loads seen in less ill patients.

A number of factors were associated with more-severe disease after hospitalization. PM and CHD increased the likelihood of more-severe disease (as defined by clinical scoring, duration of supplemental oxygen, and/or need for ventilatory support). Age in days was inversely correlated with duration of supplemental oxygen and need for ventilatory support. These observations support findings of similar, smaller studies [5–7, 30, 31]. Large-scale studies in Canada and Tennessee have further defined the relative importance of host risk factors in determining whether RSV infection leads to hospitalization [3, 32, 33]. In our study, we saw greater severity of RSV infection in children with BPD or CHD, even though the criteria for study enrollment in high-risk groups were less stringent than those for healthy groups.

Inconsistent and poorly sustained systemic and mucosal immune responses to RSV (F and Gα proteins and neutralizing antibody) were observed in our population of children with bronchiolitis. Other investigators have noted poor responses to specific RSV proteins and diminished immunoglobulin class and subclass responses after primary infection in children <1 year of age [34–39]. Neutralizing antibody to RSV is observed less commonly than antibody to specific proteins in young children [40, 41]. Brandenburg et al. [34] reported poor neutralizing antibody responses to RSV infection in infants <6 months old. No correlation was found between parameters of illness severity and antibody response, although details of RSV illness severity were not provided.

In our population of children with RSV bronchiolitis, one-third of placebo recipients had not mounted an antibody response to RSV, as determined by measurement of serum neutralizing antibody, by 8 weeks after infection, and two-thirds of both placebo and RSVIG recipients had no residual antibody 6 months later. Serologic responses were not related to the quantity of RSV shedding or to illness severity in these children. IgG responses to the F protein were diminished in the presence of maternally derived antibody, but this association could not be distinguished from the association with age by multivariate analysis. This is somewhat discrepant with a previous observation suggesting that response to F protein was influenced primarily by age and to G protein by preexisting antibody [41]. Age and preexisting antibody of maternal origin are closely interrelated at the age at which most children have a first RSV infection. One-half of the infants followed up in our studies, whether they received RSVIG or not, were reinfected in the subsequent RSV season, as determined by a 4-fold rise in antibody titers, but none were rehospitalized.

Recent vaccine trial data suggest that the most consistent immune response to a live attenuated intranasal vaccine and the best correlate of immunity on rechallenge with vaccine is a serum IgA response to the G protein [42]. In this study, the IgA response to G protein was not as striking. The variation in G protein between group A and group B RSV might account for some of the discrepancy. The serum and mucosal IgA responses seen in this study were not influenced by age or by the presence of maternal antibody, which suggests that there may be a selective response in young children, as was seen in the vaccine trial [42]. In contrast, in some studies, younger infants failed to develop detectable NW secretory antibody to RSV infection more frequently than did older infants [43].

Although the neutralizing antibody assays were not performed in parallel, children who experienced natural infection leading

### Table 3. Serum and mucosal antibody responses in placebo recipients 8 weeks after enrollment in a study in infants hospitalized with respiratory syncytial virus bronchiolitis.

<table>
<thead>
<tr>
<th>Source, serostatus&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Neutralization response, n/N</th>
<th>Against F protein</th>
<th>Against Gα protein</th>
<th>Against F protein</th>
<th>Against Gα protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>19/25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10/17</td>
<td>7/17</td>
<td>4/11</td>
<td>6/16</td>
</tr>
<tr>
<td>Positive</td>
<td>2/8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/5</td>
<td>1/4</td>
<td>1/3</td>
<td>2/4</td>
</tr>
<tr>
<td>Nasal secretions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>ND</td>
<td>8/24</td>
<td>5/24</td>
<td>10/24</td>
<td>9/24</td>
</tr>
<tr>
<td>Positive</td>
<td>ND</td>
<td>1/8</td>
<td>0/8</td>
<td>1/8</td>
<td>2/8</td>
</tr>
</tbody>
</table>

NOTE. ND, not done; n/N, no. of children with response/no. of children in whom response was measured (some responses were not measured in some children because samples were insufficient for testing).

<sup>a</sup>Based on serum neutralizing antibody levels at enrollment.

<sup>b</sup>For comparison between seronegative patients and seropositive patients with responses, P = .015.
to hospitalization were more likely to be seronegative for RSV on presentation (47%) than were healthy children of a similar age (24%) who participated in vaccine trials [42], which suggests that susceptibility to serious illness is based on seronegativity, as reported by Glezen et al. [44].

The failure of some seronegative hospitalized infants to adequately mount and sustain a serum RSV neutralizing antibody response, particularly in the presence of maternally derived antibody, implies that there may be a formidable barrier to effective immunization of young infants against RSV infection. This observation may apply to immune responses to live viral mucosal vaccines in general, even though RSV and other respiratory viruses acquired through vaccination or natural infection replicate well in the mucosa, with no interference from serum antibody. Infants <6 months of age demonstrate reduced serologic responses to live attenuated influenza virus and to rotavirus, in comparison with older children [45, 46].

Serum neutralizing antibody plays a role in protecting an infant against severe RSV infection. The observations of Glezen et al. [44] and passive immunophylaxis studies in humans [21–23] show that a serum neutralizing antibody titer of 1:300 is sufficient to protect young infants against being hospitalized with RSV illness. However, alternative immune mechanisms may be important in preventing RSV illness. A local mucosal antibody response may be sufficient to block cellular entry or intracellular replication of RSV [47, 48], and an early cytotoxic T cell response might favorably influence the course of infection, as is suggested by murine models in which cytotoxic T cells and T helper subsets are important to virus clearance [49] and in which manipulation of the cytokine environment can have an impact on the efficiency of virus clearance, type of pathology, and magnitude of illness [50].

Successful immunization against RSV will require a full understanding of the ontogeny of immune response to respiratory virus antigens in very young children and continued definition of correlates of protection against disease. The lack of correlation between severity of natural infection with RSV in infancy and the amount of virus present or the level of neutralizing antibody in the serum reinforces the need to explore the hypothesis that natural infection with RSV is an immune-modulated disease.

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References


