

Respiratory syncytial virus neutralizing antibodies in cord blood, respiratory syncytial virus hospitalization, and recurrent wheeze

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Background: Respiratory syncytial virus (RSV) hospitalization is associated with wheeze.

Objective: To examine the influence of maternally derived RSV neutralizing antibodies in cord blood on RSV hospitalization and recurrent wheeze in infancy.

Methods: Among children from the Danish National Birth Cohort, we selected a subcohort of 459 randomly selected children, 408 children with RSV hospitalization, 408 children with recurrent wheeze, and all 289 children who experienced both RSV hospitalization and recurrent wheeze. The influence of cord blood RSV neutralizing antibodies was examined as predictors for (1) RSV hospitalization, (2) RSV hospitalization after recurrent wheeze, (3) recurrent wheeze, and (4) recurrent wheeze after RSV hospitalization.

Results: Neutralizing antibody levels were inversely associated with RSV hospitalization in infants below 6 months of age (adjusted incidence rate ratio [IRR], 0.74; 95% CI, 0.62-0.87), and also inversely associated with RSV hospitalization in infants with recurrent wheeze (IRR, 0.83; 0.71-0.97). In contrast, neutralizing antibody levels were directly associated with an increased risk of recurrent wheeze in infants below 6 months of age (IRR, 1.28; 1.04-1.57) and with an increased risk of recurrent wheeze after RSV hospitalization in infants below 6 months of age (IRR, 1.44; 1.10-1.90).

Conclusion: Maternally derived RSV neutralizing antibodies protect infants against RSV hospitalization, and also when the infant has recurrent wheeze. However, high maternally derived RSV neutralizing antibody levels were associated with an increased risk of recurrent wheeze. (J Allergy Clin Immunol 2009;123:1003-1010.)

Key words: Cord blood, maternally derived antibodies, neutralizing, respiratory syncytial virus, recurrent wheeze

Within the first year after severe respiratory syncytial virus (RSV) hospitalization, as many as 20% of the children are rehospitalized because of wheezing,¹ and RSV acute lower respiratory tract infection (ALRI) has been associated with abnormal pulmonary function, wheezing, and asthma in children.^{2,3} However, a family history of asthma predisposes children to develop severe RSV ALRI.^{4,5} Thus, studies indicate an association between RSV hospitalization, wheezing, and asthma, but it is not clear whether severe RSV infection causes wheezing, or whether the RSV infection becomes more severe in children who are predisposed to wheeze. Earlier studies showed that high titers of maternally derived respiratory syncytial virus antibodies were inversely associated with the incidence⁶⁻¹² and severity^{7,13} of RSV infection during the first 6 months of life, and incomplete transfer of maternally derived RSV antibodies has been implicated in the increased risk of severe RSV infection in preterm infants.¹⁴ Studies of passively administered polyclonal^{15,16} or humanized monoclonal antibody against RSV has been shown to reduce RSV ALRI¹⁵ or hospitalizations¹⁵⁻¹⁷ among premature infants and children with chronic lung disease. A recent study found that in premature infants, preventing RSV decreased the incidence of recurrent wheezing by 50%.¹⁸

If severe RSV infection causes wheezing, the prevention of severe RSV infection would decrease the incidence of wheezing. We hypothesized that a high level of maternally derived RSV neutralizing antibodies would be associated with a decrease in the incidence of RSV hospitalization and a decrease in the incidence of recurrent wheeze in infancy. Thus, the current study examined the influence of maternally derived RSV neutralizing antibodies on the risk of RSV hospitalization and recurrent wheeze.

METHODS

We designed a case-cohort study that included randomly selected children, children with RSV hospitalization, children with recurrent wheeze, and children with both RSV hospitalization and recurrent wheeze. We used data

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Abbreviations used

ALRI: Acute lower respiratory tract infection

DNBC: Danish National Birth Cohort

IRR: Incidence rate ratio

RSV: Respiratory syncytial virus

Maternally derived

RSV neutralizing

antibodies: Maternally derived respiratory
syncytial virus neutralizing
antibodies in cord blood

from The Danish National Birth Cohort (DNBC, www.bsmb.dk)¹⁹ and the RSV database and followed the children from birth to 18 months of age.

The RSV database

Based on registration data of Danish laboratories testing hospitalized patients for RSV in Denmark, we established a database of patients tested for RSV between January 1996 and May 2003 (the RSV database). The information gathered includes date and result of the RSV test and the patient's personal identification number (central person registry number), which serves as a key reference to the individual citizen in all public registries in Denmark. The RSV database has been validated using information from The Danish National Patient Registry,²⁰ which registers all inpatient hospitalizations in Denmark; it was found to cover 96% of hospitalizations with a positive RSV test result.²¹

Throughout the study period, antigen testing by immunofluorescence or ELISA techniques was used for routine tests of RSV infection in hospitalized patients in Denmark.

The DNBC

The DNBC consecutively and prospectively recruited pregnant women in the period from 1997 to 2003. All women who spoke Danish and intended to carry their pregnancy to term were invited to participate when they came to their general practitioner for the first antenatal consultation. Participation involved 4 structured computer-assisted telephone interviews performed by trained interviewers at approximately gestational weeks 12 and 30 (interviews 1 and 2) and when the child was 6 and 18 months old (interviews 3 and 4). Interviews collected information on health, lifestyle, and socioeconomic status of the parents. For the child, data regarding feeding habits, diseases, medication, vaccinations, motor and cognitive development, anthropometry, and day care attendance was obtained, and age at onset was registered by using 2-week intervals. For example, when the mother informed the interviewer that her child had physician-diagnosed recurrent wheezing or asthma, she was asked, "Did your child wheeze the first 2 weeks after birth?" "Did your child wheeze from 2 to 4 weeks after birth?" and so on. Her answers were registered separately for each period. This procedure took place at both the 6-month postpartum interview and the 18-month postpartum interview. We used the 7th day of the first 2-week period in which the mother said that her baby had physician-diagnosed wheeze as the day of onset of wheeze. The women were called as many as 4 times for each interview. Thus, although interviews were missed, very few women actively denied participation. Blood samples were collected from the pregnant women at weeks 12 and 24 of gestation, and a cord blood sample was obtained at birth. Because information on RSV hospitalization was gathered separately in the RSV database, interviewers were blind to information about RSV-confirmed hospitalizations.

Outcomes

Information on RSV hospitalization before 18 months of age was obtained from the RSV database. Information on wheezing was obtained from the 3rd and 4th interview from the DNBC. In these 2 interviews, the mother was asked whether her child had experienced any wheezing episodes, and if so, how many,

and whether a doctor had verified the diagnosis. The child was categorized as having recurrent wheeze if the child had ≥ 3 episodes of wheezing and a physician's diagnosis of asthmatic bronchitis or asthma on the basis of clinical examination, a definition used in previous studies.^{3,5} The age at the first episode of wheezing was used to describe the age at onset of recurrent wheeze.

Background factors

Data on date of birth, sex, breast-feeding, number of children below 12 years of age in the home ("siblings"), maternal occupation, smoking, asthma, and atopic dermatitis was obtained from the interviews. Data on gestational age, birth weight, and nonatopic chronic conditions in the child (intrauterine growth retardation, low birth weight [<2500 g], cystic fibrosis, chronic lung disease, chronic heart disease, immune suppression, Down syndrome or other chromosomal disorders, cerebral palsy, or neuromuscular disease) was obtained from the Danish National Patient Registry.²² Prematurity was defined as a gestational age of <259 days.

RSV seasonality and susceptibility in the newborn infant

In Denmark, the RSV season occurs from November to April, peaking in January and February²³; 97% of the RSV-positive test results in the RSV database were from samples between November to April. Infants born in the last 3 months before the epidemic and during the first half of the epidemic have the lowest titers of maternally derived RSV neutralizing antibodies.⁷ Hence, children in the current study were considered to be more susceptible to severe RSV infection if they were born between August and January, and the analyses were adjusted for this seasonal variation.

Age groups

Because passively acquired antibodies to RSV have a half-life of approximately 4 to 5 weeks, the influence of maternally derived antibodies is expected to be limited at 6 months of age. To study the interaction between age and titers of maternally derived antibodies, data were analyzed in 3 age groups: 0 to 5 months, 6 to 11 months, and 12 to 18 months of age.

RSV neutralizing antibody assay

We used a microneutralization assay modified from one described earlier,²⁴ performed in 96-well microtiter plates. With each set of test plates, there was a control plate that contained 3 columns of known positive and negative controls diluted out 2-fold, and 2 columns for a back titer for the virus. Each of the test plates contained 4 patient sera samples (done in duplicate) diluted out 2-fold across the 96-well plate. Sera were first serially diluted in 2% FBS in minimal essential medium in the test plates, followed by the addition of 15 to 25 plaque-forming units of virus per well. The serum virus mixture was allowed to incubate for 1.5 hours on a rocker at 37.0°C. A total of 25,000 Hep-2 cells per well in 10% FBS minimal essential medium were then added and allowed to incubate for 6 days; plates were observed daily for visible cytopathic effects. Then the medium/virus/serum mixture was gently aspirated, and the cells were stained with a crystal violet fixative. After 24 hours, the wells were washed with water, allowed to dry, and read under a microscope. The titer was obtained as the reciprocal of the dilution from the last row where there was no cytopathic effect seen.

Case-cohort design

Study base. Among 51,701 children in the DNBC with a date of birth between December 3, 1998, and May 2, 2003, and interview 3 and/or interview 4 and a cord-blood sample, we identified 2562 children with RSV hospitalization and 6153 children with recurrent wheeze.

Sampling of groups. To study the influence of maternally derived RSV neutralizing antibodies on RSV hospitalization, recurrent wheeze after RSV hospitalization, recurrent wheeze, and RSV hospitalization after recurrent wheeze, we selected from the study base 4 groups of children:

1. Group A: 459 children randomly selected among the cohort of 51,701 children in the DNBC with a date of birth between December 3, 1998, and May 2, 2003, and interview 3 and/or interview 4 and a cord-blood sample.
2. Group B: 408 randomly selected children among those with RSV hospitalization.
3. Group C: 408 randomly selected children among those with recurrent wheeze.
4. Group D: all 289 children with both RSV hospitalization and recurrent wheeze. This group was subsequently divided into group D1 (recurrent wheeze after RSV) and D2 (RSV after recurrent wheeze).

The sizes of the groups were based on power calculations aiming to detect an odds ratio of 1.5, with power = 0.8 at the 5% significance level.

Comparisons. 1. Group B (RSV hospitalized children) was compared with group A (randomly selected children) to study the effect of maternally derived RSV neutralizing antibodies on the incidence of RSV hospitalization. 2. Group D2 (children with RSV after recurrent wheeze) was compared with group C (children with recurrent wheeze) to study the effect of maternally derived RSV neutralizing antibodies on the incidence of RSV hospitalization after recurrent wheeze. 3. Group C (children with recurrent wheeze) was compared with group A (randomly selected children) to study the effect of maternally derived RSV neutralizing antibodies on the incidence of recurrent wheeze. 4. Group D1 (children with recurrent wheeze after RSV) was compared with group B (children with RSV hospitalization) to study the effect of maternally derived RSV neutralizing antibodies on the incidence of recurrent wheeze after RSV hospitalization.

Statistics

We estimated the association between maternally derived RSV neutralizing antibodies and the 4 different case definitions using 4 separate multivariable Cox regression analyses. The estimates for the associations are reported as incidence rate ratios (IRRs) with 95% CIs, corrected for the case-cohort design by using a robust estimation of variance^{25,26} and adjusted for potential confounders. The possible confounders were sex, premature birth, breast-feeding, nonatopic chronic disease, maternal atopic dermatitis, maternal recurrent wheeze, children below 12 years of age in the home, maternal smoking and occupation, and RSV seasonality.^{7,14,27-32} Further adjustment for breast-feeding did not change the estimates presented (data not shown, available on request).

The anti-RSV antibody titer values expressed to the log base 2 were included in a multivariable model (1) as a categorical variable categorized according to 20% percentile values (3.5-6, 6.5, 7-7.5, 8-8.5, and ≥ 9) and (2) as a continuous variable.

RESULTS

The geometric mean of maternally derived RSV neutralizing antibodies in 1418 cord blood samples (3 samples had insufficient quantity for the analysis) was 7.83 (SD, 1.60; range, 3.5-16; percentiles, 10%, 6; 25%, 6.5; 50%, 7.5; 75%, 9; 90%, 10). The results of the multivariable analysis for the 4 comparisons are as follows.

Comparison 1: Group A (randomly selected) with B (RSV hospitalized)

There were 326 and 456 children from groups B and A, respectively, who were included in this analysis (Fig 1); 6 children from the subcohort (group A) were hospitalized with RSV during follow-up, so the total number became 332 case children (N) and 456 control children from the randomly selected subcohort (Nsub). The titer of maternally derived RSV neutralizing antibodies was inversely associated with RSV hospitalizations, and the age group analysis revealed that the effect was limited to infants below 6 months of age (Table I). For every log₂ increase in titer, there

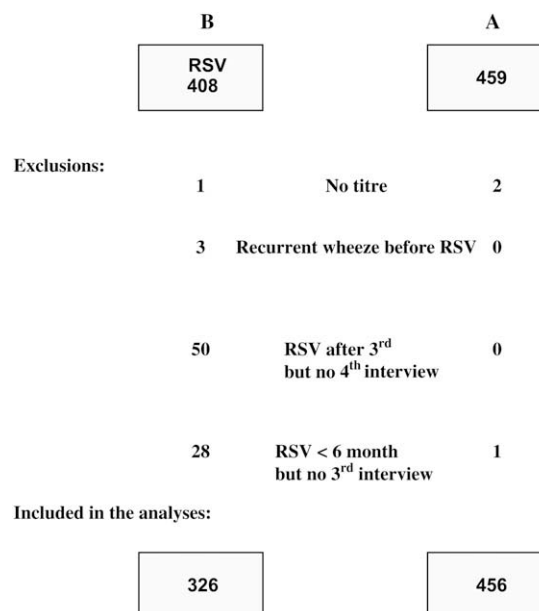


FIG 1. Illustration of the exclusion procedure for the comparison of group B (children with RSV hospitalization) versus group A (randomly selected children). This comparison examined the effect of maternally derived RSV antibodies on the incidence of RSV hospitalization.

was a significant 26% decrease in the incidence of RSV hospitalization in infants below 6 months of age.

Comparison 2: Group C (recurrent wheezers) with D2 (recurrent wheezers already before RSV hospitalization)

There were 135 and 206 children from groups D2 and C, respectively, included in this analysis (Fig 2). Among children with recurrent wheeze, the titer of maternally derived RSV neutralizing antibodies was inversely associated with RSV hospitalization (Table II). The age group analysis showed that the protective effect was most pronounced among infants 6 to 11 months old, because few of the youngest children had recurrent wheeze. Among infants age 6 to 11 months, every log₂ increase in titer was associated with a significant 17% decrease in incidence of RSV hospitalization. If analyzed by titer category, all categories were significantly protective compared with the lowest titer category (20% percentile; titer value ≤ 6).

Comparison 3: Group A (randomly selected) with C (recurrent wheezers)

There were 388 and 456 children from groups C and A, respectively, included in this analysis (Fig 3); 30 children from the subcohort (group A) developed recurrent wheeze during follow-up, so the total number became 418 case children and 456 control children. Comparing randomly selected children against those with recurrent wheeze, the titer of maternally derived RSV neutralizing antibodies was associated with an increase in the risk of recurrent wheeze, and the age group analysis showed that this effect was limited to infants below 6 months of age (Table III). Every log₂ increase in titer was associated with a significant 28% increase in the incidence of recurrent wheeze.

TABLE I. Titer of maternally derived RSV neutralizing antibodies and the incidence rate ratio of RSV hospitalization among children below 6 months of age; RSV hospitalized infants were compared with randomly selected infants

Maternally derived RSV neutralizing antibodies titer	Birth to 5 mo	
	N (Nsub)	IRR (95% CI)*
0-6	48 (49)	Reference
6.5	25 (45)	0.40 (0.18-0.92)
7.0-7.5	57 (98)	0.57 (0.29-1.10)
8-8.5	35 (84)	0.41 (0.20-0.85)
9+	32 (118)	0.27 (0.13-0.57)
All	197 (394)	0.74 (0.62-0.87)†

N, Number of cases; Nsub, number of children in subcohort.

*The estimates are adjusted for sex, premature birth, nonatopic chronic disease, maternal atopic dermatitis, maternal asthma, season, children below 12 years of age in the home ("siblings"), maternal smoking and occupation, and RSV seasonality.

†Test for trend when titers were analyzed as a continuous variable—that is, per 1 unit increase in titer.

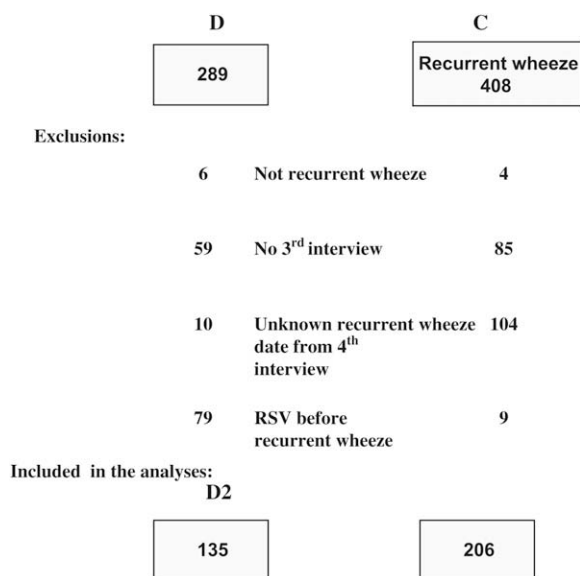
TABLE II. Titer of maternally derived RSV neutralizing antibodies and the incidence rate ratio of RSV hospitalization after recurrent wheeze in infancy; infants who experienced RSV hospitalization after physician-diagnosed recurrent wheezing were compared with randomly selected infants with physician-diagnosed recurrent wheeze

Maternally derived RSV neutralizing antibodies titer	Birth to 5 mo		6-11 mo	
	N (Nsub)	IRR (95% CI)*	N (Nsub)	IRR (95% CI)*
0-6	2 (7)	Reference	16 (18)	Reference
6.5	6 (8)	2.74 (0.28-27.0)	4 (18)	0.20 (0.05-0.76)
7.0-7.5	4 (16)	0.49 (0.05-4.71)	9 (31)	0.23 (0.08-0.68)
8-8.5	3 (19)	0.30 (0.03-2.99)	15 (54)	0.26 (0.09-0.76)
9+	8 (31)	0.63 (0.08-4.92)	25 (57)	0.25 (0.10-0.64)
Total	23 (81)	0.87 (0.61-1.23)†	69 (158)	0.74 (0.59-0.93)†

N, Number of cases; Nsub, number of children in subcohort. A subcohort member can be present in both age groups.

*The estimates are adjusted for sex, premature birth, nonatopic chronic disease, maternal atopic dermatitis, maternal asthma, season, children below 12 years of age in the home ("siblings"), maternal smoking and occupation, and RSV seasonality.

†Test for trend when titers were analyzed as a continuous variable—that is, per 1 unit increase in titer.

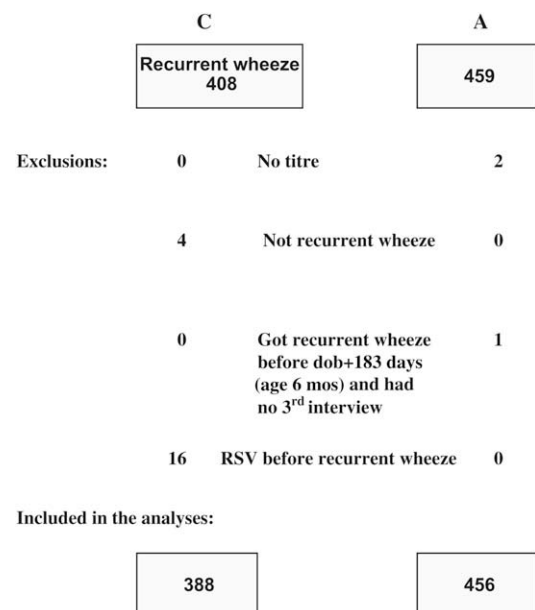
**FIG 2.** Illustration of the exclusion procedure for the comparison of group C (children with recurrent wheeze) versus group D (children with RSV hospitalization and recurrent wheeze). This comparison examined the effect of maternally derived RSV antibodies on the incidence of RSV hospitalization after recurrent wheeze.

Comparison 4: Group B (RSV hospitalization) with D1 (recurrent wheezing after RSV hospitalization)

There were 79 and 304 children from groups D1 and B, respectively, included in this analysis (Fig 4). Among children with RSV hospitalization, the titer of maternally derived RSV neutralizing antibodies was associated with an increased risk of recurrent wheeze after RSV hospitalization in infants below 6 months of age (Table IV). Every log2 increase in titer was associated with a significant 44% increase in the incidence of recurrent wheeze among infants below 6 months of age.

DISCUSSION

The main findings of the current case-cohort study are that the titer of maternally derived RSV neutralizing antibodies in cord

**FIG 3.** Illustration of the exclusion procedure for the comparison of group C (children with recurrent wheeze) versus group A (randomly selected children). This comparison examined the effect of maternally derived RSV antibodies on the incidence of recurrent wheeze. *dob*, Date of birth.

blood is associated with a decreased risk of RSV hospitalization in healthy infants below 6 months of age, a decreased risk of RSV hospitalization among infants age 6 to 11 months with recurrent wheeze, and an increased risk of recurrent wheeze in children both with and without RSV hospitalization.

The finding of a protective effect of maternally derived RSV neutralizing antibodies on RSV hospitalization is in accordance with earlier studies,^{6-10,14} but to our knowledge, our study is the first to demonstrate a protective effect also in children with recurrent wheeze. The protective effect among infants with recurrent wheeze was found to be significant among infants age 6 to 11

TABLE III. Titer of maternally derived RSV neutralizing antibodies and the incidence rate ratio of recurrent wheeze; infants with physician-diagnosed recurrent wheeze were compared with randomly selected infants

Maternally derived RSV neutralizing antibodies titer	Birth to 5 mo	
	N (Nsub)	IRR (95% CI)*
0-6	7 (49)	Reference
6.5	9 (45)	1.06 (0.31-3.65)
7.0-7.5	18 (98)	1.29 (0.45-3.66)
8-8.5	22 (84)	1.61 (0.57-4.58)
9+	34 (118)	1.99 (0.70-5.61)
Total	90 (394)	1.28 (1.04-1.57)†

N, Number of cases; Nsub, number of children in subcohort. A subcohort member can be present in all 3 age groups.

*The estimates are adjusted for sex, premature birth, non-atopic chronic disease, maternal atopic dermatitis, maternal asthma, season, children below 12 years of age in the home ("siblings"), maternal smoking and occupation, and RSV seasonality.

†Test for trend when titers were analyzed as a continuous variable—that is, per 1 unit increase in titer.

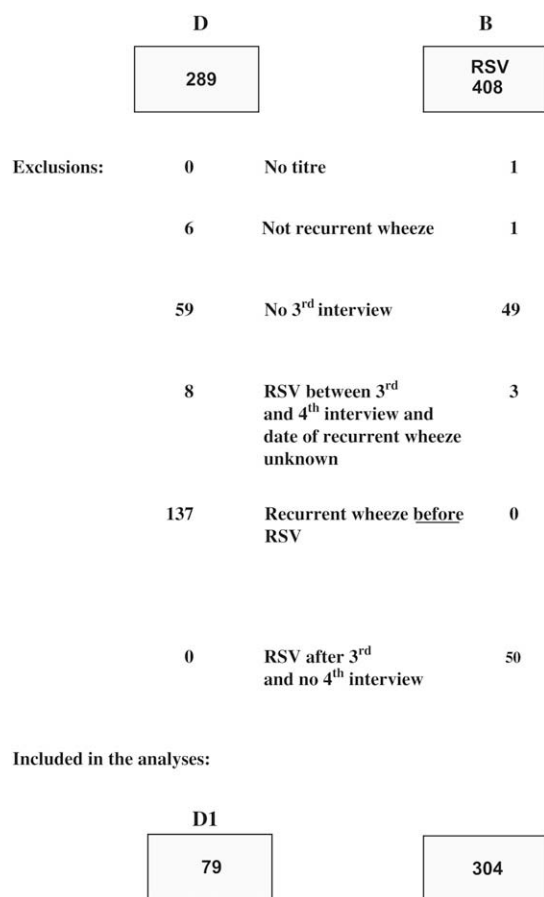
TABLE IV. Titer of maternally derived RSV neutralizing antibodies and the incidence rate ratio of recurrent wheeze after RSV hospitalization; infants with physician-diagnosed recurrent wheezing after RSV hospitalization were compared with infants with RSV hospitalization

Maternally derived RSV neutralizing antibodies titer	0-5 mo	
	N (Nsub)	IRR (95% CI)*
0-6	6 (47)	Reference
6.5	8 (25)	1.82 (0.45-7.37)
7.0-7.5	9 (54)	1.00 (0.27-3.63)
8-8.5	3 (34)	0.60 (0.13-2.80)
9+	16 (31)	4.36 (1.42-13.3)
Total	42 (191)	1.44 (1.10-1.90)†

N, Number of cases; Nsub, number of children in subcohort. A subcohort member can be present in all 3 age groups.

*The estimates are adjusted for sex, premature birth, nonatopic chronic disease, maternal atopic dermatitis, maternal asthma, season, children below 12 years of age in the home ("siblings"), maternal smoking and occupation, and RSV seasonality.

†Test for trend when titers were analyzed as a continuous variable—that is, per 1 unit increase in titer.

**FIG 4.** Illustration of the exclusion procedure for the comparison of group D (children with recurrent wheeze and RSV hospitalization) versus group C (children with recurrent wheeze). This comparison examined the effect of maternally derived RSV antibodies on the incidence of recurrent wheeze after RSV hospitalization.

months; however, even in this Scandinavian atopy high-risk child population, only a few infants experienced recurrent wheeze before the age of 6 months; hence the power of the comparison

among the youngest infants was limited. A possible explanation of this finding is that the children got a milder RSV infection as they were older when infected because of the protection during the first months of life.

The association between the titer of maternally derived RSV neutralizing antibodies and the risk of recurrent wheeze has not been examined before. The direct association between antibody level and risk of recurrent wheeze in infants below 6 months of age was a surprising observation because in preterm infants, there are data to suggest that passive immunization against RSV decreases the risk of wheezing.¹⁸ However, we found a significant association in 2 different comparisons, both among infants with recurrent wheeze and among infants with recurrent wheeze after RSV hospitalization. Furthermore, all significant associations were observed in infants below 6 months of age, an age group in which it was most biologically plausible to expect an effect of maternally derived antibodies. In addition, if high levels of maternal antibody may prevent a protective immune response to a primary RSV infection in the first few months of life, this would not explain the observed increase in recurrent wheeze. If indeed the primary RSV infection were not wheezing because of the protection against RSV by high levels of maternally derived RSV neutralizing antibodies, and only RSV infection at a later age presented with wheeze, thus postponing the age of the first wheezing episode, this might strengthen our observation of more recurrent wheeze in these infants.

Our finding might have at least 2 explanations. First, the association between titer of maternally derived RSV neutralizing antibodies and the risk of recurrent wheeze is not necessarily causal. The infants and children with recurrent wheeze might be a selected population of individuals with increased risk of having a familial disposition to wheeze and hypersensitive airways and an increased risk of being exposed to other determinants of wheezing. Hence, many of these infants and children might wheeze despite the highest level of protective immunity against viral infection. Our finding might indicate that some individuals with a strong disposition to wheezing and asthma might not be protected with even high levels of maternal antibodies against airway irritability and inflammation caused by early viral infection.

Second, in human beings, RSV infection appear to stimulate both T_H1 and T_H2 responses.³³ Studies in murine models have shown that previous vaccination, coexisting allergic inflammation, or direct modulation of the cytokine milieu can influence the immune response and symptomatology when infected with RSV.³⁴⁻³⁷ Furthermore, a recent study among HIV-infected children and young adults showed a steep increase in asthma prevalence after highly active antiretroviral therapy, presumably because activated $CD4^+$ and $CD8^+$ T cells and T_H2 inflammatory cytokines IL-4 and IL-13 contributed to pulmonary hypersensitivity.³⁸ Maternal RSV immunization during pregnancy has been described as safe and protective³⁹; however, we know only little about the effect of wild-type RSV infection during pregnancy on the maternal immune system. A previous study found that antenatal sensitization occurs in a third of infants exposed to an RSV epidemic at the appropriate time of gestation and suggested that *in utero* exposure to RSV infection might influence the subsequent immune response on postnatal exposure to RSV.⁴⁰ The majority of RSV infections will not lead to hospitalization but can still provoke a wheezing episode in an infant with hypersensitive airways. This increases the chance for infants included in the current study with recurrent wheezing to be categorized as having recurrent wheeze without any information on a recent RSV infection. Hence, the increased risk of recurrent wheeze and recurrent wheeze after RSV hospitalization in infants with a high titer of maternally derived RSV neutralizing antibodies found in the current study might be partly explained by *in utero* sensitization, possibly via a direct effect of placental transfer of viral proteins or antigens into the T_H2 fetal environment. Because intrauterine conditions have already been found to be determinants of childhood asthma,⁴¹ it seems clear that more fundamental immunologic work is needed to illuminate the association between *in utero* RSV exposure and postnatal risk of recurrent wheeze.

Conclusion

Maternally derived RSV neutralizing antibodies help to protect infants against RSV hospitalization. However, high maternally derived RSV neutralizing antibody levels may increase the risk of developing recurrent wheeze.

Clinical implications: These findings might have implications for the understanding of the pathogenesis of asthma and for future policies of maternal RSV immunization during pregnancy.

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