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Evaluation of neutralizing antibodies on respiratory syncytial virus in Japanese mother-infant pairs after COVID-19 pandemic.

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Abstract

Respiratory Syncytial Virus (RSV) is the most common cause of acute lower respiratory tract infection in young children globally. Following the COVID-19 pandemic, RSV infections have become more prevalent. Consequently, a new vaccine targeting RSV infections in pregnant women has been introduced worldwide. To estimate the effectiveness of this new vaccine for pregnant women, we investigated neutralizing antibodies against RSV in samples taken from 51 mothers and their babies. The prevalence rate of neonatal antibodies, defined as a titer of ≥ 16, was 39.2%. We found no significant differences in neonatal neutralizing antibodies based on factors, such as sex, gestational age at birth, birth weight and presence of siblings, neonatal problem and usage of palivizumab. Neonatal neutralizing antibodies were equal to or higher than those of their mother. A new RSV vaccine targeting all pregnant women is promising, as approximately 60% of neonates had low antibody titers against RSV. However, predicting low antibody titer against RSV remains challenging. Moreover, our findings indicate efficient transmission of RSV antibodies from babies to their mothers.

Keywords: Neutralizing antibodies, Respiratory syncytial virus, Mother, Neonate.

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Introduction

Respiratory Syncytial Virus (RSV) is the most common cause of acute lower respiratory infection in young children around the world. RSV infections especially cause severe respiratory diseases among children under 6 months old [1-3]. In Japan, around one-fourth of all patients with RSV <2 years were hospitalized, about 90% of whom did not have an underlying risk factor. In 2017-2018, three to four out of every 100 Japanese children <6 months were hospitalized for RSV [4]. The prevalence of RSV decreased during the COVID-19 pandemic. However, RSV infections have been prevalent thereafter in Japan. Recently, a new vaccine for pregnant women has been introduced worldwide, including in Japan [5]. To assess the effectiveness of the RSV vaccine, we investigated the situation of antibody retention for RSV among pregnant women and transmissions from mothers to their babies.

Materials and Methods

Participants

We enrolled pregnant women, who were admitted for their pregnancies at Kawasaki medical school hospital from March, 2023 to February, 2024. We obtained their consent and collected blood samples from them and their cord blood at delivery. We also checked their gestation age at delivery and their ages. Furthermore, we investigated their babies' sex, Apgar scores at 5 minutes, outcomes and birth weights.

Measurement of neutralizing antibody on Respiratory Syncytial Virus (RSV)

We assayed serum neutralizing antibodies on RSV in a micro titration system using standard techniques previously reported [6]. The dilutions were started at 1:4 and up to 1:320 and we assessed more than 1:16 as enough antibody titer to protect against RSV infections based on a previous report [7].

Statistical methods

Graph pad prism 5 (Graph pad software Inc., San Diego, CA, USA) was used for statistical analysis. Differences between the two groups were analyzed using chi-square test, student's t-test, fisher's exact test, or Mann Whitney U-test and the 95% confidence interval was determined. p-values of <0.05 were considered significant.

Results

Participants

From March, 2023 to February, 2024, a total of 51 children and their 51 mothers who were admitted to Kawasaki Medical School Hospital during the investigation period were enrolled.

Characteristics of the maternal and infant participants

Table 1 shows the characteristics of the maternal and infant participants. Among the 51 maternal participants, the mean and median gestation at delivery was 37.5 and 38 weeks, respectively. The mean and median age of the mothers was 29.8 and 29 years old, respectively.

Among the 51 infants participants, 31 (60.8%) were male and 20 (39.2%) were female. Among them, 15 (29.4%) were born at <37 weeks, indicating preterm delivery. None had Apgar scores of less than seven points at 5 minutes. Regarding their outcomes, 38 (74.5%) was normal. However, nine (17.7%) had congenital malformations or anomalies, one (2.0%) had developmental delays and three (5.9%) had other neonatal problems. Among the total babies, 15 (29.4%) had low birth weights, including one very low birth weight baby. Nine

Maternal participants	
Gestation at delivery week	
Mean	37.5 ± 2.2
Median (range)	38 (33–41)
Age	
Mean	29.8 ± 5.3
Median (range)	29 (20-39)
Infant participants	
Sex no./total no.(%)	
Male	31/51 (60.8)
Female	20/51 (39.2)
Gestational age at birth no./total no.(%)	
24 to <28 week	0/51 0.0)
28 to <34 week	2/51 (3.9)
34 to <37 week	13/51 (25.5)
37 to <42 week	36/51 (70.6)
≥ 42 week	0/51 (0.0)
Apgar score, 5 min	
<4-no./total no.(%)	0/51 (0.0)
4 to <7-no./total no.(%)	0/51 (0.0)
7 to 10-no./total no.(%)	51/51 (60.8)
Median (range)	9 (9–9)
Outcome-no./total no.(%)	
Normal	38/51 (74.5)
Congenital malformation or anomaly	9/51 (17.7)
Developmental delay-no./total no.(%)	1/51 (2.0)
Other neonatal problems	3/51 (5.9)
Extremely low birth weight, ≤ 1000 g-no./total no.(%)	0/51 (0.0)
Very low birth weight, >1000 to 1500 g-no./total no.(%)	1/51 (2.0)
Low birth weight, >1500 g to 2500 g-no./total no.(%)	15/51 (29.4)
Usage of palivizumab	9/51 (17.7)
Presence of siblings	16/51 (31.4)

Table 1. Characteristics of the maternal and infant participants.

(17.7%) infants received palivizumab and 16 (31.4%) had siblings.

Maternal neutralizing antibody on Respiratory Syncytial Virus (RSV)

Maternal neutralizing antibody titers against RSV are shown in Table 2. The Geometric Mean Titer (GMT) was 7.9 and the antibody prevalence rate, defined as an antibody titer of ≥ 16, was 21.6%. Mothers aged ≥ 35 years had a GMT of 5.7 and an antibody prevalence rate of 16.7%, while mothers aged <35 years had a GMT of 8.5 and an antibody prevalence rate of 23.1%. Mothers who gave birth at <37 weeks had a GMT of 6.4 and an antibody prevalence rate of 6.7%, while those who gave birth at ≥ 37 weeks had a GMT of 8.8 and an antibody prevalence rate of 27.8%.

Mothers who delivered by cesarean section had a GMT of 7.7 and an antibody prevalence rate of 14.3%, while those who had other types of delivery had a GMT of 8.2 and an antibody prevalence rate of 27.8%. Mothers with a history of previous deliveries had a GMT of 8.4 and an antibody prevalence rate of 17.7%, while those without a history of previous deliveries had a GMT of 7.6 and an antibody prevalence rate of 23.5%. No significant differences in GMT and antibody prevalence among these categories were observed (Table 2).

Neonatal neutralizing antibody on Respiratory Syncytial Virus (RSV)

Table 3, shows neonatal neutralizing antibody titers against RSV. The GMT was 10.6 and the antibody prevalence rate, defined as an antibody titer of ≥ 16, was 39.2%. Neonates had a GMT of 9.9 and an antibody prevalence rate of 35.5%, while female neonates had a GMT of 11.7 and an antibody prevalence rate of 45.0%. Neonates born at less than 37 weeks had a GMT of 9.6 and an antibody prevalence rate of 40.0%, while those born at 37 weeks or more had a GMT of 11.1 and an antibody prevalence rate of 38.9%. Neonates with siblings had a GMT of 12.7 and an antibody prevalence rate of 41.2%, while those without siblings had a GMT of 9.8 and an antibody prevalence rate of 38.2%.

Neonates with any problems, including congenital malformations or anomalies, developmental delays and other neonatal problems had a GMT of 13.5 and an antibody prevalence rate of 50.0%, while those without such problems had a GMT of 9.8 and an antibody prevalence rate of 35.9%. Neonates who received palivizumab had a GMT of 10.4 and an antibody prevalence rate of 37.5%, while those who did not receive palivizumab had a GMT of 10.7 and an antibody prevalence rate of 37.8%. No significant difference in GMT and antibody prevalence among these categories was observed (Table 3).

Neutralizing antibody on RSV	**Total (N=51)**		
Geometric mean titer	7.9		
Antibody prevalence rate*	21.6% (11/51)		
Mother of 35-year-old and above	Yes	No	p-value
Geometric mean titer	5.7 (n=12)	8.5 (n=39)	p=0.30
Antibody prevalence rate*	16.7% (2/12)	23.1% (9/39)	p=1.0
Gestational age at birth	<37 week	≥37 week	
Geometric mean titer	6.4 (n=15)	8.8 (n=36)	p=0.10
Antibody prevalence rate*	6.7% (1/15)	27.8% (10/36)	p=0.14
Type of delivery	**Cesarean section**	**Normal or vacuum**	
Geometric mean titer	7.4 (n=21)	8.2 (n=30)	p=0.94
Antibody prevalence rate*	14.3% (3/21)	27.8% (8/30)	p=0.50
Past history of delivery	**Yes**	**No**	
Geometric mean titer	8.4 (n=17)	7.6 (n=34)	p=0.54
Antibody prevalence rate*	17.7% (3/17)	23.5% (8/34)	p=0.73
Note= *: ≥ 16 of antibody titer.			

Table 2. Maternal neutralizing antibody on Respiratory Syncytial Virus (RSV).

Neutralizing antibody on RSV	**Total (N=51)**
Geometric mean titer	10.6
Antibody prevalence rate*1	39.2% (20/51)

Sex	**Male**	**Female**	**p-value**
Geometric mean titer	9.9 (n=31)	11.7 (n=20)	p=0.36
Antibody prevalence rate*1	35.5% (11/31)	45.0% (9/20)	p=0.50
Gestational age at birth	<37 week	≥37 week	
Geometric mean titer	9.6 (n=15)	11.1 (n=36)	p=0.26
Antibody prevalence rate*1	40.0% (6/15)	38.9% (14/36)	p=0.94
Low birth weight (2500 g or <2500 g)	**Yes**	**No**	
Geometric mean titer	14.6 (n=16)	9.2(n=35)	p=0.07
Antibody prevalence rate*1	50.0% (8/16)	34.3% (12/35)	p=0.29
Siblings	Yes	No	
Geometric mean titer	12.7 (n=17)	9.8 (n=34)	p=0.58
Antibody prevalence rate*1	41.2% (7/17)	38.2% (13/34)	p=0.83
Neonatal problems*2	Yes	No	
Geometric mean titer	13.5 (n=12)	9.8 (n=39)	p=0.35
Antibody prevalence rate*1	50.0% (6/12)	35.9% (14/39)	p=0.38
Usage of palivizumab	Yes	No	
Geometric mean titer	10.4 (n=16)	10.7 (n=37)	p=0.92
Antibody prevalence rate*1	37.5% (6/16)	37.8% (14/37)	p=0.98
Note=*1: ≥ 16 of antibody titer; *2: Congenital malformation or anomaly, developmental delay, or other neonatal problems.			

Table 3. Neonatal neutralizing antibody on Respiratory Syncytial Virus (RSV).

Comparison between maternal and neonatal neutralizing antibodies against RSV

A comparison between maternal and neonatal neutralizing antibodies against RSV is shown in Table 4. The GMT and antibody prevalence rates among mothers and neonates were 7.9%, 10.6%, 21.6% and 39.2%, respectively. The differences in maternal $\log_2$ antibody titers against RSV compared to their babies' titers were as follows: 17.7% of mothers had a titer that was -2 $\log_2$ lower than their babies' titers, 37.3% of mothers had a titer that was -1 $\log_2$ lower than their babies' titers, 37.3% of mothers had a titer equal to their babies' titers, 5.9% of mothers had a titer that was +1 $\log_2$ higher than their babies' titers, none of the mothers had a titer that was +2 $\log_2$ higher than their babies' titers. Therefore, no significant difference in GMT and antibody prevalence between mothers and their babies was observed. Almost all maternal antibody titers were equal to or less than their babies' titers (Table 4).

Neutralizing antibody on RSV	**Mothers (N=51)**	**Neonates (N=51)**	**p-value**
Geometric mean titer	7.9	10.6	p=0.14
Antibody prevalence rate*1	21.6% (11/51)	39.2% (20/51)	p=0.05
Differences in maternal log2 antibody titers˚2 of RSV from their babies' titers˚2			
Mean ± SD	-0.67 ± 0.80		
-2	17.7% (8/51)		
-1	37.3% (19/51)		
0	39.2% (20/51)		
1	5.9% (3/51)		
2	0.0% (0/51)		
Note=*1: ≥ 16 of antibody titer; *2: Congenital malformation or anomaly, developmental delay, or other neonatal problems			

Table 4. Comparison between maternal and neonatal neutralizing antibody against Respiratory Syncytial Virus (RSV).

Discussion

In our study, we collected 51 samples for neutralizing antibodies against RSV from mothers and their babies. Regarding maternal neutralizing antibodies, the antibody prevalence rate was 21.6%. No significant difference in the GMT and antibody prevalence rates among different maternal ages, gestational ages, or delivery types was observed. Yildiz et al., reported that the positive rate of anti-RSV antibody levels of puerperants measured by ELISA kits was 46.5% among puerperants in Istanbul, Turkey, 2016 [8].

This rate is higher than that in our study. However, because the methods of measurement for RSV antibodies and the region and time of the studies were different, a direct comparison between this report and ours is not straightforward. In fact, Suara et al., reported that RSV-neutralizing-antibody titers in sera of mothers and newborns were significantly different between those residing in the Gambia and Houston [9]. Therefore, it is important to conduct surveys and comparisons in various terms and places in the future.

We also investigated neonatal neutralizing antibodies against RSV, finding that their antibody prevalence rate was 39.2%. No significant difference was observed in the GMT and antibody prevalence rates among different sexes, gestational ages at birth, birth weights and presence of siblings, neonatal problems and usage of palivizumab. According to the previously mentioned study by Yildiz et al., the positive rate of anti-RSV antibodies in infants at birth was 61.5%, which was higher than our data. They also reported no significant differences in the level of natal antibodies among gender, frequency of gravidity, delivery type, gestational week and birth weight, similar to our study [8].

In comparison between maternal and neonatal neutralizing antibodies against RSV, no significant difference was observed in GMT and antibody prevalence rates. However, the mean difference in maternal $\log_2$ antibody titer of RSV was less than zero, indicating that neonatal antibody titers were higher than maternal ones for each mother-neonate pair. Chu et al., and Langley et al., reported that the cord-to-maternal RSV antibody transfer ratio was 1.03 and 1.15, respectively, indicating a similar tendency in our results [9].

There are some limitations to our study. First, we exclusively utilized the neutralizing antibody method to evaluate immunity against RSV. Other studies have employed ELISA kits to measure IgG for RSV [8-11], which are recognized for their high sensitivity and specificity [12]. However, neutralizing antibodies play an important role in preventing infection by rendering the virus non-infectious or less pathogenic [13]. Therefore, the neutralizing antibodies may reflect the ability to prevent infections. However, it is necessary to compare the effectiveness of these two methods, neutralizing antibodies and Enzyme-Linked Immunosorbent Assay (ELISA), in preventing RSV infections.

We considered a neutralizing antibody titer of ≥ 16 as positive, following past reports [7]. However, to better understand the relationship between neutralizing antibody levels and the severity of RSV infections, it would be valuable to collect samples from children with RSV infections and assess the effectiveness of different antibody levels in preventing severe RSV infections. Second, our data was collected from a single medical center. Immunity to RSV infections can vary significantly among different regions and over time [9]. Despite the global impact of RSV infections, collaborative efforts with other regions using standardized methods would allow for meaningful comparisons in the future [14].

Third, our study only sampled infants at birth. Research by Yildiz et al., indicates that the levels of IgG in infants decrease by the 6^{th} month compared to those at birth. Given that infants under 6 months are at higher risk for severe RSV infections, future studies should consider monitoring antibody levels up to at least 6 months after birth to better understand protective immunity over time [8].

Conclusion

We investigated neutralizing antibodies against RSV in Japanese mother-infant pairs after the COVID-19 pandemic. The antibody prevalence rate among mothers was 21.6%, while among their babies it was 39.2%. Despite investigating various factors affecting neonates, we did not find a significant difference in neutralizing antibodies against RSV, making it challenging to predict low levels of these antibodies. Furthermore, nearly all babies had neutralizing antibody titers at birth that were equal to or higher than those of their mothers. This suggests that an RSV vaccine targeting all pregnant women could be effective in preventing severe RSV infections in early infants.

Declaration

Ethics aspects

Informed consent was obtained from the children or their parents. The study protocol was approved by the ethics committee of Kawasaki medical school, Kurashiki, Japan, on 1 August, 2023 (no. 5370-04).

Author's contribution

Conceptualization done by Daisuke Yoshioka, Sachie Ono, Yuto Yasui, Atsushi Kato, Satoko Ogita, Tomoaki Tokutomi. Masumi Miura, Takahiro Eitok and Hideo Enoki. Formal analysis done by Tomohiro Oishi; writing, review and editing by Koichiro Shimoya and Takashi Nakano; writing-original draft by Tomohiro Oishi. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The raw data supporting the conclusions of this article will be

made available by the corresponding author, Tomohiro Oishi on request.

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Conflicts of interest

The authors declare no conflicts of interest.

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