CONCISE COMMUNICATION

Half-Life of Human Parainfluenza Virus Type 3 (hPIV3) Maternal Antibody and Cumulative Proportion of hPIV3 Infection in Young Infants

Min-Shi Lee, Paul M. Mendelman, Chithra Sangli, Iksung Cho, Sharon L. Mathie, and Marilyn J. August

During a phase 2 trial of parainfluenza virus type 3 (PIV3) vaccine, sequential serum samples were obtained from infants at 2, 6, 7, 12–15, and 13–16 months of age. Paired serum samples obtained at 2 and 6 months of age were used to estimate the biologic half-life of human PIV3 (hPIV3) maternal antibody in young infants. On the basis of the assumption that hPIV3 maternal antibody decays exponentially and constantly, the biologic half-life was estimated without adjusting for body weight increases. Cumulative proportions of hPIV3 infection in young infants were further estimated after adjusting for maternal antibody decline. A hemagglutination inhibition assay was used to quantify hPIV3 antibody. The mean (95% confidence interval) biologic half-life was estimated to be 51 (42–60) days, on the basis of which cumulative proportions of hPIV3 infection were estimated to be 11% at 6 months of age, 47% at 12–15 months of age, and 50% at 13–16 months of age.

Infants acquire transplacental maternal antibody during their development in utero, which provides young infants with important protection from infectious diseases [1, 2]. On the other hand, maternal antibody in young infants may impede vaccine effectiveness and confound the interpretation of vaccine-induced immune responses [2]. In addition, maternal antibody may confound the verification of virus infection in young infants when detection is based on antibody titers. Thus, there is a need to understand the dynamics of pathogen-specific maternal antibody in young infants [2–8].

Human parainfluenza virus type 3 (hPIV3) infection occurs in early infancy, and hPIV3 is second only to respiratory syncytial virus as a cause of lower respiratory tract disease in infants [9]. During a phase 2 trial of PIV3 vaccine, sequential serum samples were obtained from infants at 2, 6, 7, 12–15, and 13–16 months of age. This study was designed to estimate the half-life of hPIV3 maternal antibody. In addition, cumulative proportions of hPIV3 infection were calculated after adjusting for maternal antibody decline.

Methods

Study population. Healthy infants were enrolled in 3 metropolitan areas (Pittsburgh, Chicago, and Los Angeles). The vaccine was live-attenuated bovine PIV3 [10]. Three treatment groups were included: placebo (n = 66), 10⁴ TCID₅₀ of bovine PIV3 (n = 64), and 10⁶ TCID₅₀ of bovine PIV3 (n = 62). Four doses of study vaccine or placebo were administered at 2, 4, 6, and 12–15 months of age, and serum specimens were obtained at 2, 6, 7, 12–15, and 13–16 months of age. Only the placebo recipients were analyzed in this study, and they included white (36%), black (15%), Hispanic (44%), and “other” (5%) subjects. Information about PIV3-related illness was not collected.

Sero logic assay. Serum antibody titers against hPIV3 were quantified by use of a hemagglutination inhibition (HI) assay [10]. Paired serum samples obtained at 2 and 6 months of age from each individual were tested in the same run, to reduce assay variations. The starting serum dilution was 1:4, and the cutoff level of seropositivity was set at 4. Undetectable HI titer was assigned a level of 2 for the calculation of geometric mean titer (GMT) and half-life of maternal antibody.

Estimating the half-life of hPIV3 maternal antibody. The decline of maternal antibody titers in infants is mainly related to catabolism and the dilution effect of increase in body weight [4, 6, 7]. The biologic and catabolic half-lives are defined, respectively, as the half-lives before and after adjusting for the dilution effect of increase in body weight [6]. Assuming that maternal antibody declines exponentially and constantly, we used paired serum samples obtained at 2 and 6 months of age to estimate the biologic half-life, which represents an overall half-life and is crucial for interpreting the antibody responses in young infants [2–7]. Two methods of data analysis have been used to estimate the biologic half-life of pathogen-specific maternal antibody [3–8]. The first method is longitudinal analysis, which estimates the half-life in each individual [6, 8]. The second method is cross-sectional analysis, which estimates the mean half-life of the population on the basis of the GMT [3–5, 7]. For purposes of comparison, half-life was reported in days, assuming that 1 month is equal to 30 days.

Cumulative proportions of hPIV3 infection in young infants.
obtained the first serum samples when infants were 2 months of age. Most (53 [87%] of 61) of these first samples were obtained during a PIV3 season expected to be low (October through March). Several studies have found that 2-month-old infants have a low risk of acquiring hPIV3 infection [11, 12]. In addition, all the serum samples obtained at 2 months of age in this study tested negative by an in-house hPIV3 IgA assay (Aviron, unpublished data). Therefore, the hPIV3 HI titers at 2 months of age were used as the baseline to adjust for maternal antibody decline. A past hPIV3 infection in placebo recipients was defined on the basis of paired hPIV3 HI titers, as follow: $A_t \geq 4$ (i.e., seropositive) and $A_t \geq 4 \cdot A_2 (0.5)^{t / 30} \text{log}_{10}$ (i.e., HI titers ≥4-fold rise after adjusting the biologic half-life $T$ of maternal antibody), where $A_2$ and $A_t$ represent HI titers at 2 and $t$ (≥2) months of age.

Statistical analysis. HI antibody titers were log-transformed to calculate the GMT and 95% confidence interval (95% CI). The statistical association between 2 nominal or ordinal variables was tested by the χ² test, Fisher’s exact test, or Mantel-Haenszel χ² test for trend, as appropriate. All statistical analyses were performed using Microsoft Excel (version 7.0; Microsoft) or Epi Info 6.02 [13].

Results

Half-life of hPIV3-specific maternal antibody. Among the 45 infants with paired serum samples obtained at 2 and 6 months of age, 2 with undetectable hPIV3 HI titers at 2 months of age were excluded from analysis. In addition, 5 infants may have been infected with hPIV3 before 6 months of age, because their HI titers at 6 months of age were equal to or greater than their HI titers at 2 months of age. Therefore, these 5 infants were also excluded. Figure 1A shows that the HI titers in the 38 eligible infants were distributed normally at 2 months of age but skewed to the left at 6 months of age, because 28 infants (74%) had undetectable HI titers at 6 months of age. On the basis of the longitudinal analysis, the mean (95% CI) biologic half-life of maternal hPIV3 HI antibody in these 38 eligible infants was 57 (50–65) days (table 1). Twenty-eight of the 38 eligible infants had undetectable HI titers at 6 months of age. The mean (95% CI) biologic half-life in these 28 infants was 59 (49–70) days (table 1). The mean (95% CI) biologic half-life in the remaining 10 infants with detectable HI titers at 6
months of age was 51 (42–60) days (table 1). The 10 infants with detectable HI titers at 6 months of age had a higher GMT at 2 months of age (29.9 vs. 10.2) but a shorter mean biologic half-life (51 vs. 59 days) than did the 28 infants with undetectable HI titers at 6 months of age (table 1). Therefore, the longer mean biologic half-life in the 28 individuals with undetectable HI titers at 6 months of age may have resulted from assuming their undetectable HI titers to be 2.

On the basis of the cross-sectional analysis, the mean (95% CI) biologic half-life of maternal hPIV3 HI antibody was 50 (43–60) days in the 38 infants, 51 (45–59) days in the 28 infants with undetectable HI titers at 6 months of age, and 48 (38–66) days in the 10 infants with detectable HI titers at 6 months of age (table 1).

Cumulative proportion of hPIV3 infection. Figure 1B shows that the seroprevalence of hPIV3 HI antibody decreased from 97% (59/61) at 2 months of age to 36% (18/50) at 6 months of age and 29% (16/55) at 7 months of age and then increased to 48% (22/46) at 12–15 months of age and 51% (24/47) at 13–16 months of age. After adjustment for the biologic half-life of hPIV3 maternal antibody as 51 days, the cumulative proportions of hPIV3 infection were estimated to be 11% (5/45), 18% (9/50), 47% (20/43), and 50% (22/44) at 6, 7, 12–15, and 13–16 months of age, respectively (figure 1B).

To explore the correlation between maternal hPIV3 HI antibody titers and hPIV3 infection, we categorized hPIV3 HI antibody titers at 2 months of age into 3 groups (≤4, 8–16, and ≥32). The proportions of hPIV3 infection at 7 months of age in these 3 groups were 33% (2/6), 20% (7/35), and 0% (0/9), respectively (P = .09, χ² test for trend). The trend disappeared when the infants reached 12–15 months of age (P = .62, χ² test for trend) and 13–16 months of age (P = .60, χ² test for trend; data not shown).

Discussion

To our knowledge, no study estimating the biologic half-life of hPIV3 maternal antibody has been published. The biologic half-lives of pathogen-specific maternal antibody reported in published articles varied from 26 to 64 days for measles, from 25 to 55 days for poliovirus, and from 23 to 38 days for human immunodeficiency virus type 1 (M.-S.L., unpublished review). Of interest, Sato et al. [3] estimated the biologic half-lives of maternal neutralizing antibody against measles, mumps, and rubella in 30 infants to be 35–40 days. Therefore, the varied biologic half-lives for different pathogens may result from the differences in research methods rather than from the biologic properties of different pathogens. Our study estimated the biologic half-life of hPIV3 maternal antibody to be 51 days, which is similar to that of other pathogens.

Several methodology issues, including undetectable antibody titers, data analysis, and assay variation, need to be scrutinized. In regard to undetectable antibody titers, this study showed that the 28 infants with undetectable HI titers at 6 months of age had a slightly longer mean biologic half-life for maternal antibody than did the 10 infants with detectable HI titers, on the basis of longitudinal (59 vs. 51 days) or cross-sectional (51 vs. 48 days) analysis. It appears more reasonable to estimate the half-life on the basis of the infants with detectable antibody titers, since the precise antibody titers in the infants with undetectable titers remain unknown, and assigning antibody titers at one-half the level of the detectable limit may overestimate the half-life.

Regarding the data analysis, most published studies used a cross-sectional analysis to estimate the half-life of maternal antibody [2–8]. Some studies collected only cross-sectional data (i.e., no paired serum samples), so a longitudinal analysis could not be done. Overall, the estimates determined on the basis of longitudinal and cross-sectional analyses in our study did not vary much (51 vs. 48 days), which further supports our results. In our study, paired serum samples were obtained and their antibody titers were measured together, to avoid interassay variation. In addition, our study has the advantage of excluding the infected individuals on the basis of antibody titers in paired serum samples, a step that cannot be achieved in a cross-sectional study. Moreover, cross-sectional analysis must assume that the antibody titers are distributed normally after logarithmic transformation, which is not always true, as shown in our study (figure 1A). Overall, it is better to collect longitudinal data starting from birth (i.e., cord blood) and to use a longitudinal analysis for estimating the half-life of maternal antibody, especially with small sample sizes.

Pathogen-specific maternal antibodies measured by use of different assays may have different half-lives. One study showed that maternal HI antibody to measles had a longer biologic half-life than did maternal neutralizing antibody to measles (42 vs. 33 days) [4]. In addition, a study of pertussis antibodies found that the biologic half-lives of maternal antibody to lymphocytosis-promoting factor, filamentous hemagglutinin, and pertussis agglutinin were 36, 40, and 55 days, respectively, although the differences were not statistically significant [5]. The traditional HI and neutralizing assays are only semiquantitative. Therefore, the varied half-lives may result from the assay

Table 1. Biologic half-life of maternal human parainfluenza virus type 3 (hPIV3) hemagglutination inhibition (HI) antibody, as determined by longitudinal and cross-sectional analysis.

<table>
<thead>
<tr>
<th>HI titers at 6 mo of age</th>
<th>GMT at 2 mo (95% CI)</th>
<th>GMT at 6 mo (95% CI)</th>
<th>Longitudinal half-life, a (mean (95% CI))</th>
<th>Cross-sectional half-life, b (mean (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable</td>
<td>10</td>
<td>29.9 (21–43)</td>
<td>5.3</td>
<td>51 (42–60)</td>
</tr>
<tr>
<td>Undetectable</td>
<td>28</td>
<td>10.2 (8–13)</td>
<td>2.0</td>
<td>59 (49–70)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>13.6 (11–17)</td>
<td>2.6</td>
<td>57 (50–65)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; GMT, geometric mean titer.

* Calculated on the basis of paired antibody titers in each individual. For purposes of comparison, half-life was reported in days, assuming that 1 month is equal to 30 days.

* Calculated on the basis of the GMT at 2 and 6 months of age.
variation, which would be clarified with standardized and quantitative assays [2, 4, 14].

Assuming the biologic half-life of hPIV3 maternal antibody to be 51 days, we estimated that the cumulative proportions of hPIV3 infection in our study population increased gradually from 11% at 6 months of age to 47% at 12–15 months of age and to 50% at 13–16 months of age. These results are similar to those in a longitudinal study based on virus isolation and neutralization titers in paired serum samples (62% by 12 months of age and 92% by 24 months of age) [11]. In addition, Chanock et al. [15] reported that hPIV3 neutralizing antibody seroprevalences were 50% at 6–12 months of age and 56% at 13–24 months of age, and Reed et al. [12] reported that hPIV3 HI antibody seroprevalences were 48% at 6–12 months of age and >50% at >1 year of age, which are also similar to the findings in our study (48% at 12–15 months of age and 51% at 13–16 months of age).

Overall, our study may underestimate the cumulative proportions of hPIV3 infection, since hPIV3 infection in early infancy may not induce an increase in antibody levels [11]. On the other hand, our study may overestimate the cumulative proportions, since cross-reactions of HI antibody between hPIV3 and other paramyxoviruses, such as mumps virus, are possible [9]. However, the cross-reactions may not confound our study, since hPIV3 infection is more frequent in young infants [9, 15]. Because most hPIV3 primary infection–related illnesses occur within the first 6 months of life, PIV3 vaccination must be administered in early infancy [9–11]. Thus, the antibody responses to vaccination and natural infection, coupled with maternal antibody, will make interpretation challenging.

Acknowledgments

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References