Mother-Infant Transfer of Anti-Human Papillomavirus (HPV) Antibodies following Vaccination with the Quadrivalent HPV (Type 6/11/16/18) Virus-Like Particle Vaccine

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The exploratory immunogenicity objective of this analysis was to characterize the titer of vaccine human papillomavirus (HPV)-type immunoglobulins in both peripartum maternal blood and the cord blood of infants born to women who received blinded therapy. Data were derived from a randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study (protocol 019; NCT00090220). This study enrolled 3,819 women between the ages of 24 and 45 years from 38 international study sites between 18 June 2004 and 30 April 2005. Data in the current analysis are from subjects enrolled in Philippines and Thailand. For each of HPV types 6, 11, 16, and 18, maternal anti-HPV was found in cord blood samples. Furthermore, HPV titers in cord blood samples were highly positively correlated with maternal HPV titers. Additionally, there were instances when anti-HPV antibodies were no longer detectable in maternal serum samples and yet were detected in matched cord blood samples. These results demonstrate that quadrivalent HPV (qHPV) vaccine-induced antibodies cross the placenta and could potentially provide some benefit against vaccine-type HPV infection and related diseases such as recurrent respiratory papillomatosis.

Human papillomaviruses (HPVs) are double-stranded DNA viruses that infect the cutaneous and mucosal epithelium of humans. HPV infection can lead to benign genital warts or papillomas and low- or high-grade intraepithelial neoplasia, including cervical cancer. In addition, HPV type 6 (HPV-6) and HPV-11 can infect the squamous epithelium of the oral cavity, oropharynx, larynx, and hypopharynx and cause recurrent respiratory papillomatosis (RRP) (19, 31). RRP is a rare disease (roughly 4 cases per 100,000 children [10]) characterized by benign squamous papillomas, noncancerous tumors, or warts that grow in the larynx and within the respiratory tract.

The quadrivalent HPV (qHPV) (types 6/11/16/18) virus-like particle (VLP) vaccine was approved in 2006 for the prevention of genital warts caused by HPV types 6 and 11 as well as vaginal, vulvar, and cervical cancer caused by HPV types 16 and 18 (12, 13). The vaccine has since been studied in both adult women (2) and men (15).

Vaccination with qHPV has been shown to elicit a strong neutralizing antibody response and to engender immune memory (anamnestic response) upon reexposure to HPV vaccine (26). In addition, few data exist on the transfer of anti-HPV antibodies from mothers to newborns (18). To establish whether antibodies induced by natural infection or following vaccination with qHPV can cross the placenta, we evaluated whether a type 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) and a total IgG Luminex immunoassay (LIA) could measure IgG neutralizing antibodies in matched maternal serum and fetal cord blood samples.

MATERIALS AND METHODS

Objective and study data. The exploratory immunogenicity objective of this analysis was to characterize the titer of vaccine HPV-type immunoglobulins both in peripartum maternal blood and in the cord blood of infants born to women who received blinded therapy. These data were derived from a randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study (protocol 019; NCT00090220). This study enrolled 3,819 women between the ages of 24 and 45 years from 38 international study sites between 18 June 2004 and 30 April 2005. Subjects were enrolled from community health centers, academic health centers, and primary health care providers in Colombia, France, Germany, Philippines, Spain, Thailand, and the United States, although the data for the current analysis come from subjects enrolled from either Philippines or Thailand.

Subjects. Women were eligible to participate in the vaccine study from which these data were taken if they were not pregnant and if they had not undergone hysterectomy. Subjects were asked to use effective contraception through month 7 of the study. Women with a history of genital warts or current/past cervical disease were not eligible for enrollment. Those with prior cervical definitive therapy and those having undergone a cervical biopsy within the past 5 years were also excluded. Additionally, those subjects infected with human immunodeficiency virus (HIV) and those who were otherwise immunocompromised were not eligible for enrollment. Further information on enrollment criteria and subject characteristics has been published previously (2, 25).

Vaccine. Subjects were randomized and received either quadrivalent HPV (types 6, 11, 16, and 18) L1 VLP vaccine (Gardasil/Silgard; Merck &
TABLE 1 Summary of serostatus of mother-infant pairs (all mother-infant pairs with serology data) 

<table>
<thead>
<tr>
<th>HPV type</th>
<th>cLIA Mother’s serostatus</th>
<th>cLIA Infant’s serostatus</th>
<th>IgG assay Mother’s serostatus</th>
<th>IgG assay Infant’s serostatus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Positive m (%)</td>
<td>Negative m (%)</td>
<td>Positive m (%)</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>16 (66.7)</td>
<td>4 (16.7)</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>20 (83.3)</td>
<td>0 (0.0)</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>24</td>
<td>22 (91.7)</td>
<td>1 (4.2)</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>23</td>
<td>9 (39.1)</td>
<td>1 (4.3)</td>
<td>13</td>
</tr>
</tbody>
</table>

*Abbreviations: n, number of mother-infant pairs contributing to the analysis; m, number of mother-infant pairs with the indicated serostatus; cLIA, competitive Luminex immunoassay.

Serostatus positive (negative) for HPV-6, -11, -16, and -18 is defined as HPV IgG values of ≥ (<) 20, 16, 20, and 24 mMU/ml, respectively.

Serostatus positive (negative) for HPV-6, -11, -16, and -18 is defined as HPV IgG values of ≥ (<) 15, 15, 9, and 14 mMU/ml, respectively.

Percent is calculated as 100 × (m/n).

RESULTS

There were a total of 44 subjects (qHPV, 24; placebo, 20) with available mother-infant pair serology data whose data were considered for the antibody analysis. In general, the serum samples obtained at the time of infant delivery from mothers given placebo were seronegative for vaccine-type anti-HPV. There were only 4 mothers who received placebo whose serum samples obtained at the time of infant delivery were seropositive for HPV-6.

Among the subjects whose mother-infant pairs were used in the correlation analysis, the median time after vaccine dose 3 when the maternal serum and cord blood samples were obtained was 28 months (range, 14 to 43 months; interquartile range, 19 to 35 months). Relative to day 1, the median time after vaccine dose 1
when the maternal serum and cord blood samples were obtained was 34 months (range, 19 to 48 months; interquartile range, 24 to 40 months).

As seen in Table 1, the majority of infants whose mothers received qHPV vaccine and were seropositive for a vaccine HPV type were also seropositive for that HPV type. Overall, 67%, 83%, 92%, and 39% of infants were seropositive via the cLIA assay to HPV types 6, 11, 16, and 18, respectively, when their mothers were also seropositive at the time of birth. When all HPV-specific IgG molecules are considered, 84%, 65%, 100%, and 62% of infants were seropositive for HPV-6, -11, -16, and -18, respectively, when their mothers were also seropositive at the time of birth.

Figure 1 shows the scatter plot on the 2-dimensional xy plane of the HPV cLIA data points (x = cord blood anti-HPV result, y = maternal serum anti-HPV result) for each of HPV types 6, 11, 16, and 18. The data indicate that HPV titers in maternal serum samples are positively correlated with anti-HPV titers from infant cord blood samples. Pearson correlation coefficients of 0.94, 0.83, 0.80, and >0.99 were calculated for HPV-6, -11, -16, and -18, respectively.
A plot of the distribution of the ratios of infant to mother cLIA anti-HPV results for each of the 4 vaccine HPV types is shown in Fig. 2. The distribution of the ratio of anti-HPV results centered on 1.0 further illustrates the highly concordant mother and infant anti-HPV antibody titers.

**DISCUSSION**

For each of HPV types 6, 11, 16, and 18, maternal anti-HPV was found in infant cord blood samples. Furthermore, HPV titers in cord blood samples were highly positively correlated with maternal HPV titers. Moreover, there were instances when titers against vaccine HPV types that were no longer detectable in maternal serum samples were detected in cord blood samples, although the clinical relevance of this finding is unclear.

Newborn infants have immature immune systems, especially when the infant is born prematurely. This immature immune system is not fully capable of actively protecting against vaccine-preventable infections such as diphtheria, HPV infection, tetanus, and pertussis (9, 20, 30). Maternal immunoglobulins are transported across placental membranes during pregnancy by an active, receptor-mediated process. These antibodies are capable of protecting against infections until the infants’ immune system has time to mature (24).

Transplacental transport of vaccine-induced antibodies has been shown to various degrees for a variety of vaccines, including vaccines against measles (16), varicella-zoster (23), rubella (22), and hepatitis A (21), among others. In the case of HPV, antibodies generated through qHPV vaccination and transported to the fetus across the placenta could potentially be capable of preventing infection.

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