Hospitalization is Associated with Seroconversion to Parainfluenza and Respiratory Syncytial Virus in HIV-Exposed, Uninfected Infants

Born in the United States

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Background

- Perinatally HIV-exposed, uninfected (PHEU) infants around the globe experience higher rates of morbidity and mortality than HIV-unexposed, uninfected (HUU) infants with similar demographic characteristics
- Much of the burden of disease experienced by PHEU infants in the US is globally is attributed to lower respiratory tract infection (LRTI)
- Few publications describe the etiology of LRTI in PHEU infants, but those available list respiratory viruses such as respiratory syncytial virus (RSV), influenza, parainfluenza (PIV), adenovirus, and human metapneumovirus as significant contributors
- To our knowledge, no study has reported on the epidemiology of respiratory viral infections among PHEU infants born in the US

Objective

- Estimate the incidence rate of respiratory viral infections in the first year of life among U.S.-born PHEU infants
- Evaluate the association between respiratory virus seroconversion and hospitalization

Methods

Study population

- Participants included PHEU infants enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPACT) Protocol 1025 study in the United States between 2002-2013. Some of the infants were co-enrolled in the Pediatric HIV/AIDS Cohort Surveillance Monitoring for ART Toxics (PHACS SMARTT) study
- Infants were included if they had plasma/serum collected at ≥3 time points (2, 6, 12, 24, and 48 weeks of life), including at least one specimen at 2 or 6 weeks of life and at least one specimen at 24 or 48 weeks of life
- For infants co-enrolled in both P1025 and SMARTT, the 48-week sample collected under SMARTT was used if there was no sample collected under P1025
- There were no infant deaths during the follow-up period

Laboratory assays

- We measured IgG antibody titers to influenza A and B, RSV, and parainfluenza 1, 2, and 3, using quantitative ELISA
- Serum and plasma were used interchangeably in this study. Although serum may contain higher antibody concentrations than plasma, preliminary studies using plasma and serum obtained from the same healthy controls demonstrated that the conversion ratio for each ELISA assay used in this study was essentially 1:1

Statistical analysis

- Seroconversion to a respiratory virus was defined as either:
  - A 4-fold increase in Ab titer between at least one pair of time points, OR
  - A 48-week Ab titer greater than the upper confidence limit of the predicted mean titer at week 48, based on a mixed effect model built to assess the trajectory of natural log titers of maternally acquired antibodies, separately for each antibody titer, among infants who didn’t have a 2-fold increase in titers observed at ≥24 weeks of life
- Samples collected after administration of seasonal influenza vaccine were excluded from the analysis of seroconversion to influenza A or B
- We estimated the incidence rate and 95% confidence interval of seroconversion to each viral respiratory pathogen using the age at the time of sample collection to calculate person-months
- Irreversible and multivariate modified Poisson regression models were fit to evaluate the association of seroconversion to each viral respiratory pathogen with the risk of:
  - All-cause hospitalization in the first 12 months of life
  - Hospitalization with a respiratory infection diagnosis
- Among infants with seroconversion to the viral respiratory pathogens, we compared the level of each antibody titer at the time of seroconversion by hospitalization status

Results

- 556 participants were included (Table 1): 183 with 12-month samples collected in SMARTT
- Hospitalization occurred in 11.3% of infants
- Median age at hospitalization: 63 days (IQR 30-153 days)
- 66.2% of hospitalizations were for infectious indications (Figure 1)
- Hospitalization by 12mo

Table 1. Participant demographic characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th>Hospitalization by 12mo</th>
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<tbody>
<tr>
<td>(N=556)</td>
<td>(N=81)</td>
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<tr>
<td>Male sex</td>
<td>Yes</td>
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<tr>
<td>Race</td>
<td>White/Other</td>
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<tr>
<td></td>
<td>Black</td>
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<tr>
<td></td>
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<tr>
<td>Hispanic</td>
<td>Yes</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>Median (Q1, Q3)</td>
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<tr>
<td>Preterm birth (&lt;37 week)</td>
<td>Yes</td>
</tr>
<tr>
<td>Birth Weight (grams)</td>
<td>Median (Q1, Q3)</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500g)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>Yes</td>
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<tr>
<td>Maternal smoking status</td>
<td>Not breastfed</td>
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<tr>
<td></td>
<td>Seroconverted at (prior to delivery)</td>
</tr>
<tr>
<td></td>
<td>≥200 - &lt;350</td>
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<tr>
<td></td>
<td>≥350</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Maternal HIV RNA</td>
<td>(prior to delivery)</td>
</tr>
<tr>
<td></td>
<td>&lt;1000</td>
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</tbody>
</table>

Figure 1. Indication for hospitalization

- Respiratory Infections:
  - Bronchitis
  - Pneumonia
  - Otitis media
  - Upper respiratory infection
- Non-infectious Indications:
  - Asthma
  - Sepsis
  - Gastroenteritis
  - Appendicitis/Carcinoids
  - Urinary tract infection
  - Congenital DM
  - Candidiasis
- Other Infections:
  - Metapneumovirus
  - Human metapneumovirus

Figure 2. Incidence rate of hospitalization per 1000-person months (95% CI)

- Most seroconversions occurred between 6 and 12 months of age for all viruses
- Seroconversion to RSV and parainfluenza were significantly associated with hospitalization (Figure 4)
- Seroconversion to RSV was associated with hospitalization for a respiratory infection diagnosis (Figure 5)
- Among infants who seroconverted to RSV, the median antibody titer in the first sample after seroconversion was higher in infants who required hospitalization for a respiratory infection diagnosis than in those who did not (p<0.005)
- Infants who seroconverted to >1 virus were no more likely to be hospitalized or hospitalised for a respiratory infection than infants who seroconverted to 1 virus

Figure 3. Number and proportion of infants who seroconverted to one or more virus

- Seroconversion to at least 1 virus occurred in 45.9% of infants (Figure 3)
- The incidence rate of seroconversion to each virus is shown in Figure 2
- The relative risk of all-cause hospitalization (95% CI) in infants who seroconverted to each virus*

Summary

- >10% of HIV-exposed, uninfected infants born in a U.S. cohort required hospitalization in the first year of life
- > two-thirds of hospitalizations were for infections
- These results are consistent with previous studies of hospitalizations were for respiratory infections
- Seroconversion to RSV and parainfluenza were significantly associated with hospitalization, but only seroconversion to RSV was associated with hospitalization for a respiratory infection
- This may reflect decreased power to detect an association with hospitalization for a respiratory infection
- Anti-RSV antibody titers were higher after seroconversion in infants who required admission for a respiratory infection than in infants who did not
- This may reflect earlier antigenic stimulation (i.e., higher RSV viral load) or lower pre-exposure antibody titers (i.e., lower maternally derived anti-RSV antibodies) in infants who developed more severe disease

Limitations

- Infants may have been exposed to different respiratory viruses depending on their year of birth, and we were unable to control for year of birth in this cohort
- We were unable to measure antibody titers at birth

Conclusion

- Respiratory viruses, especially RSV, play an important role in infectious morbidity and contribute to a high rate of hospitalizations among HIV-exposed, uninfected infants born in the U.S.

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*Model adjusted for sex, race, ethnicity, preterm birth, low birth weight, mode of delivery, and maternal HIV viral load and CD4 count at delivery

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