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

Christiana Smith[1], Yanling Huo[2], Kunjal Patel[2], Kirk Fetters[1], Russell Van Dyke[3], Adriana Weinberg[1], and the IMPAACT P1025 and PHACS SMARTT study teams

[1]University of Colorado, [2]Harvard T.H. Chan School of Public Health, [3]Tulane University School of Medicine

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 and 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

Objectives

- 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 (IMPAACT) Protocol 1025 study in the United States between 2002-2013. Some of the infants were co-enrolled in the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring for ART Toxicities (PHACS SMARTT) study
- Infants were included if they had plasma/serum collected at ≥3 time points (2, 6, 16, 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
- Univariable and multivariable 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

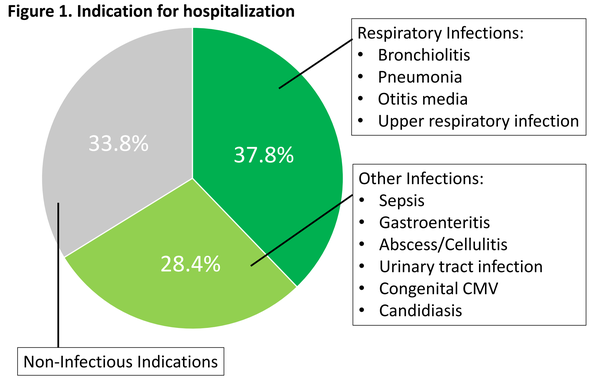
Results

- 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)

Table 1. Participant demographic characteristics

			Hospitalization by 12mo	
		Total (N=556)	No (N=493)	Yes (N=63)
Male sex	Yes	300 (54%)	266 (54%)	34 (54%)
Race	White/Other	209 (38%)	181 (37%)	28 (44%)
	Black	306 (55%)	275 (56%)	31 (49%)
	Unknown	41 (7%)	37 (8%)	4 (6%)
Hispanic	Yes	227 (41%)	191 (39%)	36 (57%)
Gestational age (weeks)	Median (Q1, Q3)	38 (37, 39)	38 (37, 39)	38 (36, 38)
Preterm birth (<37 weeks)	Yes	94 (17%)	76 (15%)	18 (29%)
Birth Weight (grams)	Median (Q1, Q3)	3000 (2640- 3305)	3005 (2667- 3310)	2900 (2590- 3195)
Low birth weight (<2500g)	Yes	74 (13%)	63 (13%)	11 (17%)
Cesarean section	Yes	326 (59%)	284 (58%)	42 (67%)
Breastfeeding status	Not breastfed	553 (99%)	491 (100%)	62 (98%)
Last maternal CD4 at/prior to delivery (cells/mm³)	<200	63 (11%)	55 (11%)	8 (13%)
	200 - <350	75 (13%)	68 (14%)	7 (11%)
	≥350	405 (73%)	359 (73%)	46 (73%)
	Unknown	13 (2%)	11 (2%)	2 (3%)
Last maternal HIV RNA at/prior to delivery (copies/mL)	>1000	63 (11%)	56 (11%)	7 (11%)
	400 - 1000	17 (3%)	13 (3%)	4 (6%)
	<400	465 (84%)	415 (84%)	50 (79%)
	Unknown	11 (2%)	9 (2%)	2 (3%)

Figure 1. Indication for hospitalization



Results

- The incidence rate of seroconversion to each virus is shown in Figure 2
- Seroconversion to at least 1 virus occurred in 45.9% of infants (Figure 3)
- 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 hospitalized for a respiratory infection than infants who seroconverted to 1 virus

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

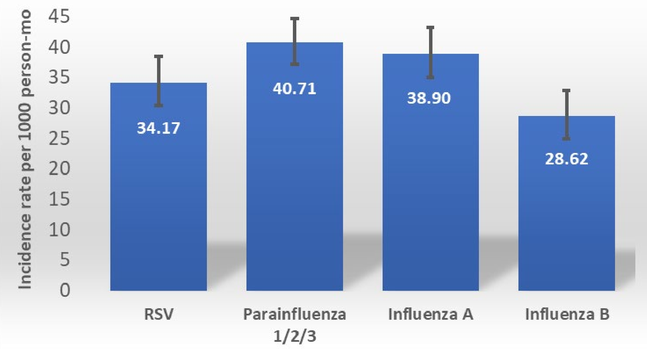


Figure 3. Number and proportion of infants who seroconverted to one or more virus

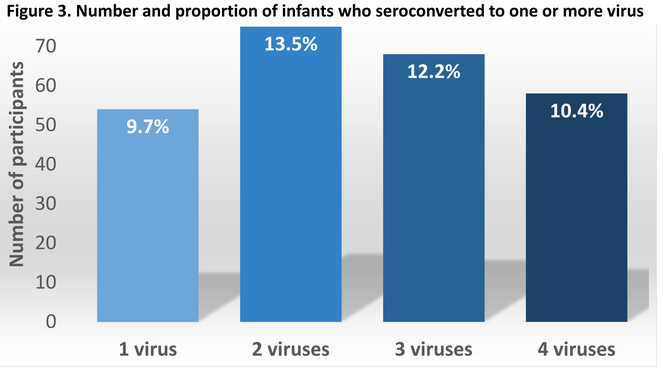
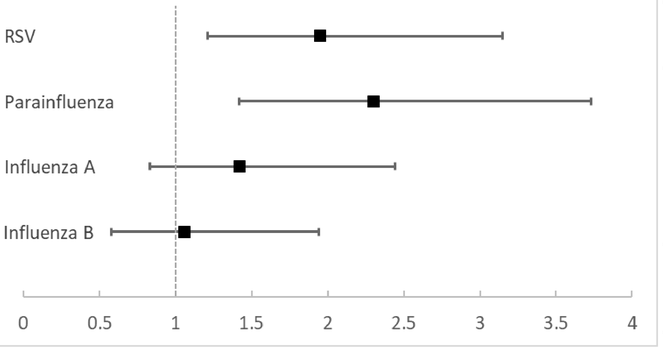


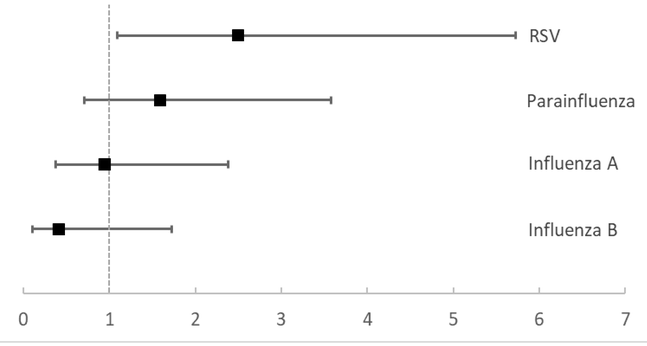
Figure 4. Relative risk of all-cause hospitalization (95% CI) in infants who seroconverted to each virus*



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

Results

Figure 5. Relative risk of hospitalization for a respiratory infection (95% CI) in infants who seroconverted to each virus*



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

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
  - > one-third 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 either higher 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.

Acknowledgements

- This study was funded by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) Early Career Investigator Mentored Research Award
- Overall support for IMPAACT was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH
- Funded by the National Institutes of Health, under cooperative agreements HD052104 (PHACS Coordinating Center, Tulane University School of Medicine) and HD052102 (PHACS Data and Operations Center, Harvard T. H. Chan School of Public Health)
- We thank the study participants, clinical sites, PHACS CAB, Frontier Science & Technology Research Foundation, and Westat