# PIDS Top Abstracts in Infectious Diseases

**Thursday, August 6  4:30-6:00 pm EDT**

**Moderators**
Kristina Bryant  
Ann Chahroudi

<table>
<thead>
<tr>
<th>EDT</th>
<th>Abstract</th>
<th>Title</th>
<th>Presenting Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:30 pm</td>
<td></td>
<td>Introduction &amp; General Information</td>
<td></td>
</tr>
<tr>
<td>4:35 pm</td>
<td>3367288</td>
<td>Prolonged antibiotic exposure after discontinuing antibiotics in premature neonates receiving empiric treatment for early-onset sepsis</td>
<td>Kelly Wade</td>
</tr>
<tr>
<td>4:45 pm</td>
<td>3379747</td>
<td>Commensal bacteria directed postnatal development of neutrophils is essential for the protection of the newborn host against bacterial sepsis.</td>
<td>Natsumon Udomkittivorakul</td>
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<tr>
<td>4:55 pm</td>
<td>3377318</td>
<td>Natural acquisition of antibodies against respiratory syncytial virus in at-risk infants</td>
<td>Christina Michalski</td>
</tr>
<tr>
<td>5:05 pm</td>
<td>3374379</td>
<td>RSV infections among children in the PREVAIL birth cohort</td>
<td>Elizabeth Schlaudecker</td>
</tr>
<tr>
<td>5:15 pm</td>
<td>3370061</td>
<td>Substantially Enhanced Sensitivity of Dried Blood Spot (DBS) PCR for Diagnosis of Congenital Cytomegalovirus (cCMV) Infection in a Minnesota Study: It’s Time to Reconsider Using DBS for Universal cCMV Screening!</td>
<td>Mark Schleiss</td>
</tr>
<tr>
<td>5:25 pm</td>
<td>3382384</td>
<td>A Novel Approach to Bacterial Vaccines: Haemophilus influenzae as a Paradigm</td>
<td>Terrence Stull</td>
</tr>
<tr>
<td>5:35 pm</td>
<td>3370695</td>
<td>Rotavirus vaccine shedding is associated with maternal IgG, breastfeeding, and infant seroconversion</td>
<td>Rachel Burke</td>
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<tr>
<td>5:45 pm</td>
<td></td>
<td>Wrap Up</td>
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Note: Schedule subject to change based on presenter availability.
CONTROL ID: 3367288

TITLE: Prolonged antibiotic exposure after discontinuing antibiotics in premature neonates receiving empiric treatment for early-onset sepsis

PRESENTER: Kelly Wade

AUTHORS (LAST NAME, FIRST NAME): Le, Jennifer¹; Greenberg, Rachel G.²; Yoo, YoungJun¹; Clark, Reese H.³; Benjamin, Daniel⁴; Zimmerman, Kanecia⁴; Cohen-Wolkowiez, Michael⁴; Wade, Kelly⁵

AUTHORS/INSTITUTIONS: J. Le, Y. Yoo, University of California, San Diego Skaggs School of Pharmacy and Pharmaceutical Science, La Jolla, California, UNITED STATES; R.G. Greenberg, Pediatrics, Duke University, Durham, North Carolina, UNITED STATES; R.H. Clark, CREOS, MEDNAX, Sunrise, Florida, UNITED STATES; D. Benjamin, K. Zimmerman, M. Cohen-Wolkowiez, Duke Clinical Research Institute, Duke University, Durham, North Carolina, UNITED STATES; K. Wade, Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, UNITED STATES;

CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal Infectious Diseases/Immunology

KEYWORDS: Early onset sepsis, antimicrobial stewardship, ampicillin.

SESSION TITLE: PIDS Top Abstracts in Infectious Diseases | PIDS Top Abstracts in Infectious Diseases

SESSION TYPE: Platform|Webinar

ABSTRACT BODY:

Background: Antimicrobial stewardship programs support short duration of empiric therapy in premature neonates with suspected early-onset sepsis (EOS). Yet, the duration of therapeutic exposures after discontinuation of antibiotics has not been well characterized.

Objective: To evaluate therapeutic exposure of ampicillin and gentamicin both during and after (post-discontinuation antibiotic exposure [PDAE]) empiric therapy for EOS.

Design/Methods: Using the Pediatrix Medical Group Clinical Data Warehouse, we created a virtual population of neonates born weighing <1500g at 22-27 weeks gestation (N=34,772). Using published population pharmacokinetic models and Monte Carlo simulations (NONMEM 7.3), we predicted exposures for ampicillin following doses of 50-100 mg/kg every 8–12 hours for 2 to 6 doses (24 to 48 hr empiric coverage) and one dose of gentamicin 5 mg/kg. Therapeutic exposure targets were defined for ampicillin as time above susceptible minimum inhibitory concentrations (MIC) 0.25 mcg/mL (GBS) to 8 mcg/mL (E. coli) and for gentamicin as area-under-curve (AUC) of 100 mcg-hr/L (E. coli). Post-discontinuation antibiotic exposure (PDAE) was defined as time between the last dose and time when the antibiotic concentration fell below therapeutic exposure target.

Results: Infants' median [range] GA and weight at birth were 26 [22–27] weeks and 790 [400–1497] grams, respectively. All evaluated ampicillin dosing regimens achieved therapeutic exposure during therapy in both 22-24 and 25-27 week GA infants. The mean [95% confidence interval] duration of PDAE for ampicillin after 2 to 6 doses ranged from 46 to 144 hours [29–162], with longer PDAE in the youngest GA group(Table 1). Ampicillin dosing of 50 mg/kg every 12 hrs x 2 doses resulted in therapeutic PDAE for an additional 2 to 4 days for E. coli and GBS, respectively. Ampicillin 100 mg/kg every 8 hrs x 6 doses resulted in PDAE of 4 to 7 days for E. coli and GBS, respectively. Single-dose gentamicin provided PDAE above the AUC target for 89% of infants within the first 24 hrs.

Conclusion(s): Premature neonates receiving a 48 hours course of ampicillin after birth, continue to have therapeutic exposure for EOS pathogens for 2-7 days after discontinuation. Ampicillin dosing 50 mg/kg Q12 hrs for 2 doses provides >48 hrs therapeutic exposure and limits post discontinuation antibiotic exposure. Exposure-driven dosing may enhance stewardship and potentially limit morbidities associated with prolonged antibiotic exposure in premature infants.
Table 1. Ampicillin post-discontinuation empiric antibiotics exposure among 22-27 week GA infants

IMAGE CAPTION:
Table 1. Ampicillin post-discontinuation empiric antibiotics exposure among 22-27 week GA infants

CONTROL ID: 3379747
TITLE: Commensal bacteria directed postnatal development of neutrophils is essential for the protection of the newborn host against bacterial sepsis.
PRESENTER: Natsumon Udomkittivorakul
AUTHORS (LAST NAME, FIRST NAME): Udomkittivorakul, Natsumon1; Nadeem, Amraha1; Gray, Jerilyn1; Bonfield, Madeline1; Deshmukh, Hitesh1
AUTHORS/INSTITUTIONS: N. Udomkittivorakul, A. Nadeem, J. Gray, M. Bonfield, H. Deshmukh, Neonatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, UNITED STATES;
CURRENT CATEGORY: Neonatology
CURRENT SUBCATEGORY: Neonatal Infectious Diseases/Immunology
KEYWORDS: Neutrophil, Antibiotic exposure, Bacterial sepsis.
SESSION TITLE: PIDS Top Abstracts in Infectious Diseases |PIDS Top Abstracts in Infectious Diseases
SESSION TYPE: Platform|Webinar
ABSTRACT BODY:
Background: Neutrophils are a critical role in host defense against bacteria in the newborns. We previously demonstrated that exposure to commensal bacteria directs the postnatal ontogeny of neutrophils. Early-life antibiotic exposure interrupted the postnatal increase in neutrophil numbers, and rendered neonatal mice susceptible to bacterial sepsis. Nevertheless, the underlying mechanism remains unclear.

Objective: To understand how early life antibiotic use disrupts the postnatal development of neutrophils and contributes to increased susceptibility to infections.

Design/Methods: We treated pregnant mice (B6) with drinking water containing Ampicillin, Gentamicin and Vancomycin starting at embryonic day 15 until the experimental age. Neutrophils isolated from blood, bone marrow (BM) and spleen of neonatal (postnatal day 3 [P3] and P7) and adult (P28) mice were incubated with antibodies to identify neutrophil, multipotent hematopoietic stem cell (LSK), common myeloid progenitor (CMP), and granulocyte monocyte progenitor (GMP) populations. Flow cytometry data were collected with Fortessa I and analyzed with FlowJo using the gating strategies in Figure 1. We quantified neutrophil development ex vivo using a low-density BM culture, wherein the cells were supplemented with SCF, FLIT3, and GCSF. We inoculated neonatal mice with S. pneumoniae via intraperitoneal route for mortality study.

Results: BM neutrophil numbers increased in neonatal mice, peaking at P3, and decreased to adult level by P14. BM cells from neonatal mice had significantly decreased LSK/CMP/GMP and neutrophil expansion from bone marrow culture compared with adult mice. Expansion ability was more impaired in antibiotic-exposed group. Antibiotic-exposed neonatal mice demonstrated significantly decreased frequencies of neutrophils in blood, BM, and spleen, and BM LSK/CMP/GMP (Figure 2) and marked susceptibility to S. pneumoniae as compared to controls.

Conclusion(s): Neutrophil progenitors from BM of neonatal mice had diminished capacity to expand and generate mature neutrophils compared to adult mice. Antibiotic exposure further diminished the capacity of BM neutrophils to expand and generate mature neutrophils. Consequently, the antibiotic-exposed neonatal mice had significantly decreased numbers of storage (BM and spleen) and circulating (blood) neutrophils. Decreased numbers of these neutrophils directly
contributed to increased susceptibility of antibiotic-exposed neonatal mice to bacterial sepsis.

Figure 1: Gating strategy for identification of A) LSK (Lineage-Scal+CD117+), CMP (Lineage-Scal-CD117+FcrloCD34lo), GMP (Lineage-Scal-CD117+Fcr+CD34+), and B) neutrophil (CD45+CD11b+Ly6G+) in bone marrow of 7 day-old neonatal mice.

Figure 2: Frequency of neutrophils, LSK, CMP and GMP in bone marrow, spleen and blood of 7 and 28 day-old neonatal mice with no antibiotics (blue) and exposed to antibiotics (red).

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Figure 2: Frequency of neutrophils, LSK, CMP and GMP in bone marrow, spleen and blood of 7 and 28 day-old neonatal mice with no antibiotics (blue) and exposed to antibiotics (red).

CONTROL ID: 3377318

TITLE: Natural acquisition of antibodies against respiratory syncytial virus in at-risk infants

PRESENTER: Christina Michalski

AUTHORS (LAST NAME, FIRST NAME): Michalski, Christina¹; Boudreau, Carolyn M.⁴; Sharma, Ashish A.²; Chacko, Anil⁶; Christopherson, cheryl J.⁷; Burke, John S.⁴; Ramesh, Kuppuchipalayam K.⁸; Lai, Queenie⁸; Cieslak, Zenon⁹; Solimano, Alfonso¹⁰; Haddad, Elias K.³; Sekaly, Rafick P.²; Alter, Galit⁴; Lavoie, Pascal³

AUTHORS/INSTITUTIONS: C. Michalski, BC Children's Hospital, Vancouver, British Columbia, CANADA; A.A. Sharma, R.P. Sekaly, Case Western Reserve University, Cleveland, Ohio, UNITED STATES; P. Lavoie, Pediatrics, University of British Columbia, Vancouver, British Columbia, CANADA; C.M. Boudreau, J.S. Burke, G. Alter, Ragon Institute of MGH, MIT and Harvard, Cambridge, Massachusetts, UNITED STATES; E.K. Haddad, Drexel University College of Medicine, Philadelphia, Pennsylvania, UNITED STATES; A. Chacko, Surrey Memorial Hospital, Surrey, British Columbia, CANADA; C.J. Christopherson, RSV, C&W Hospital, Vancouver, British Columbia, CANADA; K.K. Ramesh, Q. Lai, Division of Neonatology, Royal Columbia Hospital, New Westminster, British Columbia, CANADA;
Background: Antibodies against respiratory syncytial virus (RSV) can be passively transferred from mothers to infants during pregnancy, however little is known about anti-RSV antibodies actively acquired after birth in infants through natural immunization.

Objective: We used systems serology to study the natural acquisition of RSV-specific humoral immunity in young infants over their first winter season.

Design/Methods: Pre- and post-viral fusion antibody isotypes/subclasses against RSV serotype A and B, Fc receptor binding and antibody-dependent phagocytosis were measured from 39 infants at high-risk of RSV infection, either born premature, with chronic lung or congenital heart diseases or other co-morbidities at 2 time points: pre- (after birth, before discharge home) and post-season (after March 31, 2019). Since all infants also received palivizumab, detection of this anti-RSV antibody in assays was effectively blocked exogenously. RSV-related hospitalizations (including viral testing) and respiratory infections medical attention were tracked for all infants.

Results: RSV-specific IgG1 and IgG4 decreased across the winter season, consistent with a waning of maternal antibodies (Figure 1), whereas IgA and IgG2 & 3 subclasses were variable or remained stably low (Figure 2). Concomitantly, RSV-specific IgM, Fc gamma receptor binding and antibody-dependent phagocytosis by THP-1 monocytic cells and primary syngeneic neutrophils increased during the same period (Figure 3). Correlations between RSV-specific Ig levels and Fc receptor binding were high pre-season, and increased in heterogeneity across the season, consistent with antigen-driven functional maturation of antibody structures; in contrast, similar correlations remained more homogenous for season-matched influenza strains (Figure 4). Eight infants developed in-season respiratory symptoms requiring healthcare assistance and five required hospitalization, but none tested positive for RSV.

Conclusion(s): Overall these data suggest that the natural acquisition of antibody immunity against RSV is common in young infants and likely related to a subclinical exposure to the virus. In contrast, this may not be the case for other respiratory viruses like influenza. Future studies are required to understand the impact of this natural in-season immunization on clinical outcomes, but results may have implications for prevention and vaccination programs against these common respiratory infections.
Background:
Respiratory syncytial virus (RSV) infection is a major cause of morbidity and mortality in young children.
Objective: PREVAIL, a prospective birth cohort study underway in Cincinnati, OH, has tested infants over two RSV seasons (2017-18 and 2018-19) to understand the natural history of RSV in the United States.

Design/Methods: After enrollment in pregnancy, healthy mother-infant pairs were followed up to 2 years postnatally. Mothers were trained to collect mid-turbinate nasal swabs weekly. Cases of acute respiratory infection (ARI) were documented by weekly cell phone questionnaires and medical records. ARI was defined by cough or fever (≥38.0°C, rectal) at any time in the previous week. Laboratory testing was conducted using a molecular respiratory viral panel. We analyzed all weekly nasal swabs that were collected from infants under follow-up in the PREVAIL cohort during typical RSV seasons (defined as October through April each year).

Results: The 245 children ranged in age from 2 weeks to 2 years during the study period and contributed 4684 nasal swabs for testing. A total of 83 infections were detected: 39 (47%) were RSV A and 44 (53%) were RSV B. RSV incidence was 56.7 infections per 100 RSV seasons. Median age at onset of RSV infection was 8.6 months (range 2 weeks to 22 months), with no difference at age of RSV onset by A or B subtype. There were no differences in subtype by season, and no infants had both subtypes. The 83 RSV infections occurred in 78 children, of whom 5 had a repeat infection. Of the 78 first infections, 12 (15%) were asymptomatic, 12 (15%) were symptomatic but not medically attended, and 56 (69%) were medically attended. Of the medically attended, 36 (64%) were seen only in outpatient settings, 16 (29%) in the emergency department (ED), and 4 (7%) were hospitalized. Analysis of first RSV infections by logistic regression found that severe disease (ED or hospital visit) was associated with lack of any breastfeeding (adjusted odds ratio [aOR]=9.3, p=0.002) and age under 6 months (aOR=8.6, p=0.003); co-infection, RSV subtype, and season were not significant.

Conclusion(s): We found a high incidence of infection and medically attended RSV in infants enrolled in the PREVAIL cohort over two respiratory seasons. RSV A and B occurred with similar frequency over both seasons. Severe RSV occurred most often in infants <6 months of age and was independently associated with lack of breastfeeding. Understanding the timing, type and severity of RSV will contribute to current development of immunotherapy and vaccines.

Funded by the CDC
DBS for PCR-based cCMV diagnosis could be readily integrated into state health department screening programs, but previous studies reported unacceptably low DBS analytic sensitivity.

Objective: Objectives included: 1) developing an infrastructure to incorporate universal cCMV screening into the Minnesota Department of Health (MDH) newborn screening program; 2) comparing the analytic sensitivity of saliva-based and DBS PCR assays for cCMV screening; 3) describing clinical outcomes associated with cCMV in a universal screening cohort.

Design/Methods: Newborn screening for cCMV was undertaken at five Twin Cities nurseries in collaboration with the CDC. Real-time PCR was performed on dried saliva swabs, using a UL83 primer/probe set. DBS PCR was also performed independently by the UMN and CDC labs. Primary care providers were notified about positive screens by MDH genetic counselors, and additional consultation/referral provided. Infants with positive screens underwent urine CMV PCR testing and, upon confirmation of cCMV, laboratory, ophthalmologic, audiologic, and neuroimaging evaluation.

Results: Through late 2019, 12,475 newborns have been screened for cCMV. The parental consent rate at participating sites was 70%. A total of 56 cCMV cases have been identified (overall prevalence of 0.45%). The saliva detection rate has been 52/56 (93%). Notably, the analytic sensitivity of DBS cCMV detection has been 48/56 (86%). The positive predictive value for saliva-based screening has been 87%, and for DBS 98%. Using the International Congenital CMV Recommendations Group criteria [DOI: 10.1016/S1473-3099(17)30143-3], 75% (42/56) of infants cCMV have been classified as asymptomatic (Table 1). Varying degrees of hearing loss have been noted in 9% of infants (Table 2).

Conclusion(s): In this study - the only active universal cCMV screening program in the US - we observed a prevalence of cCMV of 0.45%. More significantly, we find that improved extraction methodologies substantially enhanced the analytic sensitivity of DBS PCR for cCMV diagnosis. Based on logistic feasibility, cost-effectiveness, and enhanced sensitivity, DBS PCR should be re-considered as a feasible approach for universal cCMV screening.

| Table 1. Study Population Characteristics Analyzed by cCMV Disease Sub-Category [Using Criteria Described at DOI: 10.1016/S1473-3099(17)30143-3].
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<td>Characteristic</td>
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<td>Infant Sex</td>
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<td>Girl</td>
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<td>Asymptomatic with isolated SNHL</td>
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<td>Asymptomatic without SNHL</td>
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<tr>
<td>Mildly Symptomatic</td>
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<td>Vision/Thrombocytopenia</td>
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<td>Neuropenia</td>
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<td>LFT Abnormalities</td>
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<td>Asymptomatic</td>
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<td>Moderately-to-Severely Symptomatic</td>
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<td>SNHL</td>
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| Table 2. Overall Summary of Characteristics for Minnesota Infants with cCMV Infection, Combined Disease Categories.
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<thead>
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<tbody>
<tr>
<td>Characteristic</td>
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IMAGE CAPTION:
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Table 2. Overall Summary of Characteristics for Minnesota Infants with cCMV Infection, Combined Disease Categories.

CONTROL ID: 3382384
TITLE: A Novel Approach to Bacterial Vaccines: Haemophilus influenzae as a Paradigm
PRESENTER: Terrence Stull

AUTHORS (LAST NAME, FIRST NAME): Whitby, Paul4; Morton, Daniel3; Mussa, Huda J.1; Mirea, Lucia2; Stull, Terrence4
AUTHORS/INSTITUTIONS: H.J. Mussa, Phoenix Children's Hospital, Phoenix, Arizona, UNITED STATES; L. Mirea, Clinical Research, Phoenix Children's Hospital, Phoenix, Arizona, UNITED STATES; D. Morton, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, UNITED STATES; P. Whitby, T. Stull, University of Arizona COM-P, Phoenix, Arizona, UNITED STATES;
CURRENT CATEGORY: Infectious Diseases
CURRENT SUBCATEGORY: None
KEYWORDS: Bacterial Vaccines, Haemophilus influenzae, Otits media.
SESSION TITLE: PIDS Top Abstracts in Infectious Diseases | PIDS Top Abstracts in Infectious Diseases
SESSION TYPE: Platform|Webinar

ABSTRACT BODY:
Background: The H. influenzae type b vaccines target the type b capsule and therefore have no impact on the nontypable (unencapsulated) H. influenzae (NTHi). With the effectiveness of the Pneumococcal conjugate vaccines, NTHi has become the most common cause of otitis media. Because NTHi it is the most common reason for prescribing antibiotics in very young children, it is an appropriate target for vaccine development.

Objective: We used the methods of genomics, structural biology, and immune protection models, to identify specific peptide targets in the surface proteins, to develop a method for delivery of the targets, and to test the effectiveness in a relevant preclinical model.

Design/Methods: To characterize potential vaccine targets, the core outer proteins of NTHi present in the available sequenced genomes were identified through genomic bioinformatics. The structures of the outer proteins were analyzed through comparison with the publicly available structures of homologues characterized by X-ray crystallography. Sequenced conserved outer regions of these proteins were analyzed for their protective capacity in the infant rat model of H. influenzae infection.

Results: Nine peptides that were protective in the infant rat model were used in a novel vaccine to immunize chinchillas, the most established animal model of otitis media. Chinchillas (40 vaccinated and 41 controls) were infected with NTHi 86-028NP. The vaccinated group cleared infection more quickly than the control group as indicated by significantly decreased positive findings on video-otoscopy (p<0.0001) and tympanometry (p=0.0002) on day 7, and presence of middle ear fluid obtained by aspiration (p=0.0001) on day 10 post-infection.

Conclusion(s): These data demonstrate the effectiveness of this methodology in development of a vaccine against NTHi with protection in a relevant preclinical model of otitis media. The methods are applicable to other bacteria, and this approach to a vaccine against NTHi serves as a paradigm for development of similar vaccines to protect against other bacterial infections.

(No Image Selected)

CONTROL ID: 3370695
TITLE: Rotavirus vaccine shedding is associated with maternal IgG, breastfeeding, and infant seroconversion
PRESENTER: Rachel M Burke

AUTHORS (LAST NAME, FIRST NAME): Burke, Rachel M.1; Morrow, Ardythe L.2; Conrey, Shannon C.3; Cline, Allison R.4; Piasecki, Alexandra M.1; Parashar, Umesh1; Mijatovic-Rustempasic, Slavica1; Bowen, Michael1; White,
Background: In the US, live, oral rotavirus (RV) vaccines are given in a 2-dose (Rotarix) or 3-dose (RotaTeq) series at 2, 4, and 6 (RotaTeq only) months of age. Immune response to RV vaccines can be measured by changes in serum antibody levels (seroconversion) or by viral replication in the gut (shedding), and may be affected by levels of anti-RV IgG antibody (transferred placentally and persisting after birth), or by breast milk components.

Objective: We assessed the association between vaccine virus shedding and infant seroconversion, maternal IgG, maternal secretor status, and breastfeeding (BF).

Design/Methods: The Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal (PREVAIL) cohort enrolled pregnant mothers who delivered healthy singletons. Maternal serum was taken in the third trimester. Maternal saliva was genotyped for FUT2; breast milk from mothers who are homozygous positive or heterozygous for the FUT2 gene (“secretors”) contains oligosaccharides that may act as decoy receptors for human RV. Infant serum was taken before and after receipt of RV vaccine (6 weeks, 6 months), and infant stool was sampled weekly. Infant seroconversion was defined as a threefold rise in IgA between the two time points; shedding was defined as qRT-PCR detection of vaccine virus in a stool collected 4 – 21 days after a dose of RV vaccine. BF was defined as “any” vs. “none” at the age of vaccination. Infant seroconversion, maternal characteristics, and BF were tested for association with shedding 4 – 21 days after the first dose of RV vaccine, using generalized estimating equations (GEE) given within-child correlations.

Results: There were 370 analyzed stool samples taken 4 – 21 days after vaccination, from 97 unique infants. Most infants (76; 78%) shed vaccine virus in at least one post-vaccination sample. Shedding was highest after the first dose and within 4 – 7 days after vaccination (Table). Of 78 infants with paired serum samples, 55 (71%) seroconverted. Infant seroconversion was positively associated with shedding (Odds Ratio [OR] 3.8; 95% Confidence Interval [CI] 1.7 – 8.3). Maternal IgG was negatively associated with shedding (OR for a 100-unit increase: 0.95 [95% CI: 0.91, 0.98]). BF was negatively associated with shedding among the 71 children of secretor mothers (OR 0.4 [0.1 – 0.9]; p = 0.03).

Conclusion(s): Infants who shed after the first dose of RV vaccine were more likely to seroconvert. Maternal exposure to RV, and BF among secretor mothers, may inhibit infant shedding.

Table: Stool samples and percent shedding after each rotavirus vaccine dose, within the analysis population.

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