ID: 363

**TITLE:** PROTECTIVE ANTIBODY LEVELS AND TIMELINESS OF PRIMARY IMMUNIZATIONS IN PRETERM INFANTS

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**CONTENT:**

The Dutch National Immunization program (NIP) currently includes a primary vaccination series at 2-3-4 months and a booster at 11 months of age. This scheme may however not provide optimal protection to premature infants given their immature immune system. The goal of this study is to measure vaccination responses in premature infants and by gestational age (GA) following the regular NIP-scheme and to examine the influence of a delayed start of immunizations in preterm infants. Therefore, we compared the timeliness of immunizations with the vaccine induced antibody levels after the primary series.

In this prospective observational study, preterm infants were recruited and stratified according to gestational age (GA) (<28, 28-32 and 32-36 weeks). Blood samples were collected at 6 weeks (pre-vaccination), one month after the primary series and one month after the booster vaccination. Immunization dates were collected from vaccination certificates and medical data from monthly parental questionnaires and patient records. Serum antibody levels were measured against all vaccine components with multiplex immunoassay using Luminex technology. Percentage of protection was determined using internationally standardized correlates of protection. For pertussis, an arbitrary level of 20 IU/ml was used.

In total, 296 preterm infants were enrolled (GA<28: n=87; GA 28-32: n=119; GA 32-36: n=90). Of all infants, 60.1% received their first immunization on time (6-9 weeks after birth). This proportion varied by GA group between 36.7%, 72.8% and 65.1%, respectively.

The proportion of preterm infants with protective antibody levels after the primary series was high for pertussis, diphtheria and tetanus in all GA groups and did not differ by immunization timeliness (Table). Insufficient protection (<80%) was observed for Hib and several pneumococcal serotypes (4, 6B, 18C and 23F) with the lowest levels for GA<28 weeks. Higher antibody levels, for most pneumococcal serotypes, were observed with delayed start of first immunization in infants <28 weeks, but not in older GA groups.

These findings indicate that premature infants are insufficiently protected for multiple, in particular conjugated, vaccine components. Overall, limited differences in protective antibody levels were observed between the three GA groups. The role of timing of immunizations in antibody responses needs further exploration.

**IMAGES:**

https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=b6a1ef1a3f6c5bb458f6bc1b513597f-MjAxOS0wNSM1Y2UyNyY2YzNiOTE5

Table 1.  
Geometric mean concentrations and percentages of protected antibody levels per antigen, per GA group and timeliness of vaccination.

**COI:** None declared
ID: 443
TITLE: CHORIOAMNIONITIS IS A RISK FACTOR FOR EARLY AND LATE ONSET SEPSIS IN PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS
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CONTENT:

Chorioamnionitis (CA) is considered a key risk factor for (very) preterm delivery and for adverse neonatal outcome. Sepsis is one of the major causes of morbidity and mortality in the newborn and is classically divided into early onset sepsis (EOS; 72 h of life; acquired after delivery and often nosocomial). Association between CA and EOS appears to be self-evident, but several studies suggest that CA might be protective against LOS. We aimed to conduct a systematic review of studies reporting on CA as risk factor for neonatal sepsis.

PubMed/MEDLINE and EMBASE databases were searched. Studies were included if they examined preterm infants and reported primary data that could be used to measure the association between exposure to CA and the presence of neonatal sepsis. A random-effects model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Sources of heterogeneity were determined by subgroup and meta-regression analyses. The following categories of sepsis were analyzed: EOS, LOS, undefined onset sepsis (UOS), culture-proven, and clinical sepsis. CA was subdivided into clinical and histological.

3,768 potentially relevant studies, 113 meeting inclusion criteria (387,899 infants; 44,832 cases of CA) were analyzed. Meta-analysis showed a significant association between any CA and any EOS (OR 4.34, CI 3.68 to 5.11), any LOS (OR 1.27, CI 1.10 to 1.47), and any UOS (OR 1.59, CI 1.34 to 1.89). CA was significantly associated with culture-proven EOS (OR 4.57, CI 3.83 to 5.44), clinical EOS (OR 3.74, CI 1.84 to 7.62), and culture-proven LOS (OR 1.31, CI 1.12 to 1.53), but not with clinical LOS (OR 1.48, CI 0.75 to 2.90) in subgroup analysis. CA-exposed infants had significantly lower gestational age (-1.11 weeks, CI -1.34 to -0.89), lower birth weight (-48.30g, CI -70.25 to -26.35), and higher mortality than the infants not exposed to CA in meta-analyses. Lower GA in the CA-exposed group was significantly associated with a higher risk of LOS, but not with EOS, in meta-regression.

We observed a strong positive association between CA and EOS and a moderate, but still significant, association between CA and either LOS and UOS. Meta-analysis confirmed that preterm infants exposed to CA are younger and sicker than those without exposure. This fact appears to confound the association between CA and nosocomial LOS, since CA-exposed preterm infants would require longer hospitalization and more days of invasive therapies.

COI: None
ID: 877

TITLE: MOLECULAR PROFILING OF NEONATAL DRIED BLOOD SPOTS REVEALS CHANGES IN INNATE AND ADAPTIVE IMMUNITY FOLLOWING FETAL INFLAMMATORY RESPONSE

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CONTENT:

The fetal inflammatory response (FIR) increases the risk of perinatal brain injury, particularly in extremely low gestational age newborns (ELGANs, < 28 weeks of gestation). One of the mechanisms contributing to such a risk is a postnatal intermittent or sustained systemic inflammation (ISSI) following FIR. The link between prenatal and postnatal systemic inflammation is supported by the presence of well-established inflammatory biomarkers in the umbilical cord and peripheral blood. However, the extent of molecular changes contributing to this association is unknown.

Using RNA sequencing and mass spectrometry proteomics, we have profiled the transcriptome and proteome of archived neonatal dried blood spot (DBS) specimens from 21 ELGANs (8 females and 13 males). Histological acute chorioamnionitis was diagnosed in 15 cases, where 10 of them were affected by FIR. Total RNA sequencing of the 21 archived DBSs produced more than 500 million paired-end reads, which we transformed into a table of 25,221 gene-level summarized count expression profiles. Nearly half of these genes (11,279) showed reliable levels of expression in at least 6 of the 21 samples. Mass-spectrometry proteomics on DBSs produced 650 quantified protein expression profiles, from which we selected 245 as being reliably expressed in at least 6 of the 21 samples.

Sample-level gene and protein expression changes, projected in two dimensions, show a clear separation between infants with and without FIR. Comparing FIR-affected and unaffected ELGANs, we identified 783 gene and 27 protein expression changes of at least 50% magnitude with an experiment-wide significance level below 5% false discovery rate. Our data show in detail the postnatal activation of the innate immune system, including NLRC4-inflammasome dependent mechanisms, and support the expansion of myeloid-derived suppressor cells, in FIR-affected ELGANs. We also observed in FIR-affected...
ELGANs that downregulated genes support the inhibition of adaptive immune responses, consistently with lower levels of T-cell receptor excision circles and of lymphocyte percentage over leukocytes during the first postnatal week.

We have generated the largest catalog to date of postnatal transcriptomic and proteomic changes associated with FIR in archived DBS, which confirm the postnatal activation of the innate immune system and reveal an impairment of the adaptive immunity in FIR-affected ELGANs. The altered pathways provide novel insights into the possible mechanisms that trigger a systemic inflammation after FIR and the onset of perinatal brain injury.

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