An Integrative Literature Review: Two-Month Vaccines for Infants in the Neonatal Intensive Care Unit

Catherine C. Wilson, MSN, NNP-BC, FNP-BC

 Greenville Hospital System

 Greenville, SC

504 Reedy Fork Rd.

Piedmont, SC 29673

 Barbara Graves, PhD, RN

 The University of Alabama

 Tuscaloosa, AL

Abstract

Background: Published studies report a variance in adverse side effects for premature infants post-vaccination. The American Academy of Pediatrics (APA) guideline for premature infants recommends giving two-month vaccines based on chronological age. Purpose: To examine current literature to determine how evidence informs practice regarding the administration of the two-month vaccines to premature infants in the neonatal intensive care unit (NICU). Design: An Integrative literature review (ILR) was performed of studies done between 2003 and 2014, involving two-month vaccines administered in the NICU. PRISMA, reporting tool was used. Results: Ten articles met criteria for inclusion. Apnea and bradycardia were found potential adverse reactions after vaccines especially for certain populations. Discussion: This ILR suggests that two-month vaccines in the NICU for some of the smallest sickest baby may have less apnea and bradycardia if the DTaP and Prevar are separated by 48 hours and infants should be monitored 48 hours after vaccines.

An Integrative Literature Review: Two-Month Vaccines for Infants in the Neonatal Intensive Care Unit

**Background**

Infancy is an important time for vaccinations. Vaccinations are especially important for the premature infant. Infants acquire the vast majority of passive immunity in the form of immunoglobulin G (IgG) in the last trimester of pregnancy.1,2 Maternally acquired passive immunity has been shown to decline in infants during the first year of life. The premature infant is at a disadvantage due to limited passive immunity acquisition and because existing passive immunity declines faster in the preterm infant as compared to the full term infant.1,2 Therefore, premature infants are at increased risk for vaccine preventable illnesses. For example, more than 50% of pertussis occurs in infants with the preterm infants at greatest risk.3 The preterm infant is also at greater risk for pneumococcal infections that account for 11% of all neonatal sepsis (Bonhoeffer et al., 2005).1 Despite the need for vaccines, parents and some health care providers are reluctant to vaccinate premature infants based solely on chronological age without regard to the child’s size, chronic illnesses, or fear of adverse effects. Therefore, the prematurely born infant may be behind on vaccines at two years of age as compared to full term infants.4

**Present Guidelines and Problems**

The Centers for Disease Control (CDC) has developed guidelines for vaccination of infants at two, four, and six months of age, allowing the infant to develop active immunity during the time period when passive immunity naturally falls.5,6 At two months of age, many premature infants are still in the neonatal intensive care units (NICU). In 2003, the American Academy of Pediatrics (AAP) developed vaccination guidelines for infants cared for in an NICU.7 The guideline state that vaccines should be given to infants in the NICU based on chronological age and not adjusted age. The guidelines were written at a time when the evidence showed that mild vaccine-attributable adverse events were similar for full-term and preterm infants also reports of apnea after administration of acellular pertussis containing vaccines to extremely low weight infants (ELBW [<1000 g]) were not apparent.7 Apnea in the neonatal population is defined as pauses in breathing that last for at least 20 seconds or > 10 seconds if associated with bradycardia (<80 heart beats per minute) or oxygen desaturation (oxygen saturation <80-85%).8  Since the APA guidelines were published, some research continues to support the position that premature infants are at no increased risk from vaccines as compared to term infants. 9,10 Conversely, other studies have described apnea and bradycardia in premature infants after vaccines.11,12 Also, since the guidelines were published in 2003 vaccines have been added, changed, and/or combined. The current recommendation for rotavirus vaccine was added in 2006.13 The pneumococcal vaccine was changed from 7-valent to 13-valent in 2010.14 The APA guidelines automatically expire after five years unless updated or renewed.15 The guidelines published in 2003 have not been updated or renewed but remain the current standard of care.16.

**Significance**

The number of infants born prematurely and needing vaccines while still in the NCIU is significant. According to the World Health Organization in 2013 over 500,000 infants are born prematurely each year in the United States (US), and of these approximately 12.5% are 32 weeks gestation or less.17, 18 Using current recommendations, premature infants receive vaccines when they are due based on their chronological age.5 For babies born from 23 to 30 weeks gestation the average length of stay in the NICU is between 50-143 days the more preterm the infant the longer the stay.19  Therefore, the majority of these babies will be eligible for two-month vaccines in the hospital. Also, the number of premature infants who will receive their two-month vaccines in the NICU in the future will likely increase since premature births have increased by 36% in the US since the 1980s.20

**Current Vaccines**

The recommended vaccines for infants at two-months of age are rotavirus (RV), hepatitis B (HBV), inactivated poliovirus (IPV), diphtheria, tetanus, acellular pertussis (DTaP), pneumococcal 13-valent (PVC13), and haemophilus influenza type b (Hib).21 The HBV is slightly different from the other vaccines given at two months of age. The HBV is given at birth for infants above 2000 grams and should be given at 30 days of age for those under 2000 grams at birth.21 Rotavirus, a live vaccine, was approved for use and added to vaccine schedule in 2006.13 Since rotavirus is a live vaccine, it cannot be given in the NICU.5,13 As with any medical therapy or medication, all vaccines have the potential for side effects. The common adverse effects related to the Hepatitis B vaccine are injection site soreness, found in 1 out of 4 administrations and fever of 37.7°C, seen in 1 out of 15 people. 22 In general, vaccines are safe. Only 1 in 1.1 million doses result in major reactions.22 These statistics are typical for the other vaccines recommended at two months of age. However, this may not be the case with premature infants. The prevalence of adverse reactions due to vaccinations in premature infants ranged from 0 to 47%.10,11 For a list of all vaccines currently licensed in the US see Table 1.

**Problem Statement**

Conflicting research findings can leave health care providers confused about when, if, and how to give vaccines to premature infants. Evidence of the confusion is found in professional blogs. Some providers are giving all vaccines except the rotavirus on the same day, while others are giving one vaccine every day and still others are waiting until after discharge to administer vaccines. The only constant consensus towards the current guidelines is that vaccination is necessary.23,24 However, the health care provider in the NICU is given no clear directions on how to give the vaccines in the safest manner. Therefore, the purpose of this integrative literature review (ILR) is to examine the current literature to determine how evidence currently informs practice regarding the administration of the two-month vaccines to premature infants in the NICU.

**Apnea and Bradycardia**

Apnea in the neonatal population is defined as pauses in breathing that last for at least 20 seconds or >10 seconds if associated with bradycardia (<80 heart beats per minute) or oxygen desaturation (oxygen saturation <80-85%).8 Due to the risk of apnea and bradycardia infants in the NICU setting are monitored. The treatment for apnea and bradycardia depends on the degree or cause of the problem. A frequent medication used to treat apnea is caffeine.25 Interventional treatments for apnea and bradycardia are continuous positive air pressure (CPAP), high flow nasal cannula, or mechanical ventilation. Research has found that apnea and bradycardia is clinically correlated to developmental delays; therefore, it is the goal of health care providers to eliminate or decrease the number of apneic events (Cheung, Barrington, Finer, & Robertson, 1999; Greene et al., 2014; Janvier et al., 2004).26-28

**Method**

The methodology for this study is an ILR of the literature published from 2003 to 2014 that describes the administration of two-month vaccines to premature infants in the NICU. An ILR allows for critique and synthesis of the current literatures therefore allowing an understanding of current knowledge.29 PRISMA, the preferred reporting tool for systematic reviews and meta-analyses methodology, was used to prepare this review.30 The overall process includes a twenty-seven-point checklist that ensures a systematic process for developing the problem, searching the literature, and reporting the results. This review addresses the question of whether there is sufficient evidence to change or modify the present practice guideline of giving all the two-month vaccines to all premature infants when they are due based on chronological age on the same day. The retrieved literature was critiqued for method of giving vaccines and side effects of giving the vaccines.

**Literature Search and Selection Strategy**

The search strategy was a comprehensive literature search for English language studies published between the January 2003 and January 2014. All studies published in peer-reviewed journals with a study population of prematurely born infants who received two-months vaccines while in the NICU were considered. All suggested protocols for giving vaccines were included. The search was conducted using the following electronic databases: PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) using exploded medical subject heading (MeSH) terms: “premature infant,” “neonate”, “vaccines,” “care, neonatal intensive,” “adverse,” “apnea,” and “bradycardia” to yield the maximum number to results. The references of articles found were also searched for possible contributing studies. Studies not related to two-month vaccines or solely dealing with HBV or RV were excluded. Search terms and exclusions and inclusion criteria are outlined in Table 2.

Data from the included studies was extracted according to recommendation by the PRISMA method to produce a systematic article analysis including citation, purpose, design/method, sample/setting, major variables studied and their definition, measurement, data analysis, findings, level and quality of evidence, and funding. Level and quality of evidence (or rigor) was measured using a modified GRADE system (National Quality Form, 2011).31 This system was developed primarily to rate the strength of scientific research of randomized controlled trials (RCT). Since this study only contained one RCT the GRADE system was modified. The studies were ranked on type of study, sample size, bias, and consistency with other known work. Each study was given an A, B, C, or D rating for type of study, sample size, bias, and consistency with other studies. Bias was possible if the funding source was a vaccines manufacture or bias was reported in other studies when discussing the study in question (see Table 3). The principle measurement within the studies was the percentage of apnea and bradycardia and or cardiorespiratory events (CRE). The studies reviewed contained a variety of methodologies therefore each study was reviewed individually. The studies were reviewed in a consistent and prescribed manner and were used to answer the following research question: How does evidence currently inform practice regarding the administration of the two-month vaccines to premature infants in the NICU?

**Ethics**

The internal review board (IRB) of the University of Alabama reviewed this study protocol number 5237 and found it exempt from review since the study is a systematic review of published literature and did not include any human subjects.

**Results**

The total number of results from the databases searches was 9,955. There were 8,329 articles after screening for duplicates. The process of duplicate limitation is difficult and, therefore, some duplicates may exist in the total of studies reviewed.32 The majority of these articles dealt with only the HBV given soon after birth, influenza vaccine, rotavirus, or the long-term immune response to vaccines in premature infants. Once the parameters were set to eliminate these variables the actual number of reviewed abstracts was 1,449. As determined by relevance to the topic the number of full articles reviewed was 20. The final number of studies reviewed after eligibility criteria were considered was 10 including the original guideline article (see Diagram 1). The eliminated articles used out of date vaccines and had outdated data sets (3), were primarily review articles (3), were primarily concerned about reoccurrences of apnea after the second round of vaccines or four-month vaccines (2), included discharged infants (1), or were not in English (2) (Dutch, Spanish).

The evidence grid presents the details of the literature search (see Table 4). The grid presents the author, purpose, variables, study design, sample statistics, statistical tests done, years of data collection, ranking of rigor, and a summary of recommendations. The ten articles reviewed include the article published in 2003 by Saari presenting the original guidelines. The articles are from countries around the world, including the US (4), Australia (2), Switzerland (2), Italy (1), and Germany (1). The vaccines given in each study differ, but all included some use of DTaP. The time of data collection ranges from 1997 to 2008. During this time there were several changes in the two-month vaccines; diphtheria, tetanus, whole cell pertussis (DTPw) was changed to DTaP in 1998, PCV was added in 2000, and different combination vaccines were developed (Table 1).33,34

**Synopsis of Reviewed Studies**

Pfister et al.11 found that 47% of infants with a history of apnea, bradycardia, and/or desaturations events experienced ≥50% more events after vaccines. For infants not having events prior to vaccines 13% had apnea, bradycardia, or desaturation after vaccines. Further, bag-mask ventilation, CPAP, or mechanical ventilation was required in 6% of infants after vaccines. They found that ongoing apnea, bradycardia, and oxygen desaturations were associated with an increase risk of adverse reactions. However, neither gestational age nor birth weight alone predicted adverse outcomes. This study was funded in part by a manufacturer of vaccine, Glaxo Smith Kline (GSK). The study advocated immunizing infant between 50 and 60 days if discharge is planned within the next 10 to 20 days, the infant is clinically stable and free from severe cardiorespiratory episodes.

In a study of infants with stable respiratory status Schulzke, Heininger, Lucking-Famira, & Fahnenstich35 found vaccine related apnea and bradycardia in 13% of the sample. They defined a vaccine related apnea as ≥50% above baseline apnea and bradycardia or recurrences of apnea and bradycardia in infants not currently having any. Beyond apnea bradycardia five of the infants needed repeated tactile stimulation, three needed supplemental oxygen, and one needed bag mask ventilation. The infants in this sample were considered low risk they were not's receiving any respiratory support or supplemental oxygen at the time of vaccination. For the infants with vaccine related apnea bradycardia most episodes resolved within 48 hours. From this study researchers recommended monitoring infants for 48 hours after vaccines.

In a study by Ellison, Davis, & Doyle9, in 2005, researchers sought to determine the adverse reaction rate to the newer available vaccines in premature infants. They found the apnea rates to be the same as pre-vaccination rate. Interestingly, they found a 27% increase in apnea in infants given three vaccines at once compared to 9% in infants given only two vaccines at once; however, this result did not demonstrate statistical significance. Fever (defined as temperature >37 degrees Celsius) appeared in 33% of infants. The fever along with the apnea did lead to sepsis evaluations in 8% in their infants, but sepsis was not proven. There were no serious events requiring assisted ventilation. They recommended monitoring post vaccinations.

Faldella, Galletti, Corvaglia, Ancora, & Alessandroni36 examined the safety of a combined DTaP/IPV/Hib/HBV vaccine in infants less than 31 week gestation. They designed a prospective observational study to assess apnea, bradycardia, and oxygen desaturation while also assessing cerebral blood flow and electrocardiogram changes associated with vaccine administration. The study showed no change in cerebral blood flow or electrocardiogram changes after vaccination. It did find an overall cardiorespiratory event (CRE) rate that required medical support in 11% of the premature infants and 21.7% among chronically ill premature infant. The present state of illness was the most predictive factor for adverse events following vaccines. These results strongly support a recommendation to immunizing and monitoring infants before hospital discharge.

Pourcyrous, Korones, Arheart, & Bada37 studied, for the first time, the effect of vaccines on C-reactive protein (CRP) levels and CRE rates when vaccines were given one at a time compared to multiple vaccines given at the same time. They conducted a prospective observational study of 239 infants. The actual number of subjects tested with each single vaccine was low, but provides area basis for further research. Among the single vaccines DTaP (22%) had the highest incidence of CRE followed by PCV7 (12%) and Hib (11%). HVB had no reported incidences and IPV only had a 3% incidence rate of CRE. Over all immunization-associated CRE were four times more likely (32%) in the infants given multiple vaccines at the same time.

 The purpose of a study by Klein et al.38 was to identify predictors of apnea in infants who had not been apneic prior to vaccination. They reviewed charts (N=497) of immunized infants from 1997 to 2003. In this study 73 infants were only given HBV and 41 infants were 31 weeks gestation or over. They did not breakdown the number in each of these two groups who only received the HBV. Infants in their study were given the vaccine over 1 to 4 days. At the start of the study infants were given a DTPw vaccine later changed to DTaP. The rate of apnea post-vaccination for the DTPw was 11.9% and 13.5% for DTaP. Two infant required intubation. The results did not address if apnea was more common amongst the infants given vaccines simultaneously or divided. They concluded that infants less than 2000 grams at vaccination and those less than 67 days old were at the highest risk for apnea post-immunization and that pre-immunization apnea was the best predictor of post-immunization apnea.

The relationship between DTaP and CRE in stable premature infant in the NICU was reexamined by Carbone et al.10 This study was conducted over four years in 10 NICU units in the US (N=191). Babies in the study group were monitored 24 hours before and 48 hours after receiving only the DTaP vaccine. Infants in the control group were monitored for 72 hours. The neonatologists in the different units selected infants stable enough for the study. The study found no difference in the rate of CRE between the two groups. This study did not find apnea to be related to vaccines. Bias is possible because they included only infant at very low risk for post-vaccine apnea.39 Also, while they recommended giving vaccines per AAP recommendations they did not study this since they only gave the DTaP and not the four vaccines recommendation at two months of age.

A prospective observational study by Furch, Richter, & Kattner40 examined adverse events of vaccines in the very low birth weight infants. The study was conducted over eight years from 1998 to 2006. During this time the vaccine combination changed; therefore they divided their study into three groups. Groups A and B were combined for statistical purposes since they included the same vaccines in different combinations. Group A was DTaP/Hib/IPV and a separate HBV. Group B were given DTaP/Hib/IPV/HBV combination vaccine (this vaccine is not licensed in the US, see Table 1). In group C, the same combinations of vaccine were used along with PVC7. The study concluded extreme prematurity and birth weight less than 999 grams was a significant risk factor for apnea and bradycardia. They found that more “severe adverse events” occurred in 10.8% of infants overall and was significantly higher (14.2%) in group C. They concluded that vaccination is safe for the smallest infants, but CRE adverse reactions can occur.

In a retrospective study Hacking, Davis, Wong, Wheeler, & McVernon 39 examined the frequency of respiratory deterioration after vaccines in the NICU. Up front the researchers acknowledged that apnea and bradycardia existed after vaccines for some infants. The purpose of the study was to identify the portion of infants who would need the most extreme intervention after the vaccines. They found that a small number of extremely low birth weight infants especially those with significant lung disease and previous septicemia were at risk for respiratory deterioration. Twenty-two (5.35%) of the 411infants weighting <1000 grams who received vaccines in the NICU needed intermittent positive pressure ventilation or continuous positive airway pressure. This number is consistent with the six percent of infants who have major CRE found by Pfister et al.11. Hacking et al. recommend administering the vaccines in the hospital where ventilation support is available.

**Limitations**

One limitation of this ILR is the lack of RCT reporting on adverse reactions to vaccines. Since approximately 36,000 babies a year are vaccinated in the NICU with a possible adverse reaction rate of at least 10% these types of studies are needed. Another limitation is the studies reviewed cover a long time period and involves several different combinations of vaccines. Only three studies involved the PCV7 and none involved the PCV13 now recommended.

**Conclusions**

 Caregivers in the NICU want to promote the best and safest care possible; therefore, they want to vaccinate all infant according to current recommendation while limiting or eliminating the frequency of apnea and bradycardia experienced by the infants. Vaccines given in the two-month period put some infants at greater risk for CRE. The dilemma is how to vaccinate infants in the NICU with the least amount of risk. Vaccinating infants in the NICU is the best way to prevent vaccine related illness, however, all but one study found apnea and bradycardia to be a critical risk for infants vaccinated in the NICU when current age-based recommendations are used. Research shows the risk of adverse side effects ranges from 9 to 47% for general apnea and bradycardia and 6% risk for severe apnea and bradycardia requiring intervention.11,39 Current evidence also shows the risk of apnea, bradycardia, and oxygen desaturation increased with the administration of multiple vaccines.9,37,40 The two vaccines that appear to have the highest risk for apnea and bradycardia are the DTaP and PCV.37,40 The risk of apnea and bradycardia is highest after the first 48 to 72 hours with the first 48 being the time of greatest risk (Klein et al., 2008; Pourcyrous et al., 2007; Schulzke et al., 2005). Lastly, evidence supports that the smallest and clinically unstable babies are at a greater risk for CRE.36,38,39,40 Using these findings, updated recommendations are possible to decrease the rate of apnea and bradycardia after vaccines.

**Recommendations**

 Based on the current evidence infants with birth weights of 1,000 grams or less, especially those with apnea and bradycardia or who have had a more complicated clinical course, should have the DTaP containing vaccine and the PCV vaccine separated by 48 hours and the infants should remain in the hospital for 48 hours after vaccines for cardiorespiratory and saturation monitoring before discharge. Furthermore, it is beneficial for infants at risk for apnea and bradycardia to receive the recommended two-month vaccines in the hospital setting. Therefore, if vaccines are due within 10 days of discharge they should be given in the NICU.

From this ILR it is evident that more research is needed. There is a clear need for well-designed prospective RCT studies and further development of clinical practice guidelines for vaccinating infants in the NICU.

**Funding**

The authors declare no conflict of interest or any funding.

**Acknowledgement**

We are thankful for Reece Hunter Clark, MD’s support and suggestions.

References

1. Bonhoeffer J, Siegrist C-A, Heat PT. Immunization of premature infants. *Arch Dis Child.* 2006;91:929-935. doi.org/10.1136/adc.2005.086306
2. Whitlow P, Forsythe PL. Update on immunizations commonly used in the NICU. *Adv Neonatal Care*. 2011; 3(3): 173-179.
3. Murray E L, Nieves D, Bradley JS, et al. Characteristics of severe Bordetella pertussis infection among infants ≤90 days of age admitted to pediatric intensive care units – Southern California, September 2009–June 2011. *J pediatric Infect Dis Soc*, 2013;2(1):1-6. doi:[10.1093/jpids/pis105](http://dx.doi.org/10.1093/jpids/pis105%22%20%5Ct%20%22_blank)
4. [Tozzi AE](http://www.ncbi.nlm.nih.gov/pubmed?term=Tozzi%20AE%5BAuthor%5D&cauthor=true&cauthor_uid=24397902), [Piga S](http://www.ncbi.nlm.nih.gov/pubmed?term=Piga%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24397902), [Corchia C](http://www.ncbi.nlm.nih.gov/pubmed?term=Corchia%20C%5BAuthor%5D&cauthor=true&cauthor_uid=24397902). Timeliness of routine immunization in a population- based Italian cohort of very preterm infants: results of the ACTION follow-up project. *Vaccine*, 2014;32(7):793-799. doi: 10.1016/j.vaccine.2013.12.044
5. Centers for Disease Control and Prevention (CDC). General recommendations on immunization—Advisory Committee on Immunization Practices (ACIP), 2011. *MMER Morb Mortal Wkly Rep*. 2011; 60(RR02):1-60.
6. Waaijenborg S, Hahne SJ, Mollema L, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. *J Infect Dis*. 2013;208(1):10-16. doi:10.1093/infdis/jit143
7. Saari TN, American Academy of Pediatrics Committee on Infectious Disease. Immunization of preterm and low birth weight infants. *Pediatr*. 2003;112: 193-198.
8. Finer NN, Higgins R, Kettwinkel J, Martin R J Summary proceedings from the apnea-of-prematurity group. *Pediatr*. 2006;117, S47-S51. doi:10.1542/peds.2005-0620H
9. Ellison VJ, Davis PG, Doyle LW. Adverse reactions to immunization with newer vaccines in the very preterm infant. *J Paediatr Child Health*. 2005;*41*:441-443.
10. Carbone T, McEntire B, Kissin D, Kelly D, Steinschneider A, Violaris K, Karamchandani N. Absence of an increase in cardiorespiratory events after diphtheria-tetanus-acellular pertussis immunization in preterm infants: a randomized multicenter study. *Pediatr*. 2008;*121*(5): E1085-1090. doi:10.1542/peds.2007-2059.
11. Pfister RE, Aeschbach V, Niksic-Stuber V, Martin BC, Siegrist C. Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: Frequent but mostly benign cardiorespiratory events. *J Pediatr*. 2004;145(1):58-66. doi:10.1016/j.jpeds.2004.04.006.
12. Meinus C, Schmalisch G, Hartenstein S, Proquitte H, Roehr CC. Adverse cardiorespiratory events following primary vaccination of very low birth weight infants. *J Pediatr (Rio J)*. 2012; 88(2):137-142. doi:10.2223/JPED.2182.
13. American Academy of Pediatrics (APA). Prevention of rotavirus disease: Updated guidelines for the use of rotavirus vaccine. *Pediatr*. 2009;123(5):1412-1420. doi:10.1542/peds.2009-0466
14. Centers for Disease Control and Prevention (CDC). Licensure of a 13-valent pneumococcal conjugate vaccine and recommendations for the use among children--Advisory committee of immunization practices, 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5909a2.htm
15. American Academy of Pediatrics (APA). 2014 Recommendations for Pediatric Preventive Health Care. *Pediatr*. 2014;133(3):568-570. doi:10.1542/peds.2013-4096
16. Tozzi AE, Piga S, Corchia C, et al. Timeliness of routine immunization in a population-based Italian cohort of very preterm infants: Results of the ACTION follow-up project. *Vaccine*. 2014;*32*;793-799. doi:10.1016/j.vaccine.2013.12.044.
17. World Health Organization (WHO). Preterm birth. http://www.who.int/mediacentre/factsheets/fs363/en/. Accessed June 19, 2014
18. National Perinatal Information Center (NPIC). Special care nursery admissions. http://www.npic.org/MOD/Special\_Care\_Nursery\_Admissions.pdf. Accessed June 19, 2014.
19. Miracle Baby Foundation. How long will be in the hospital. http://www.miraclebabies.org.au/premature-sick-babies/how-long-will-my-baby-be-in-hospital/. Accessed June 19, 2014
20. March of Dimes. Prematurity Campaign. http://www.marchofdimes.com/mission/prematurity-campaign.aspx. Accessed June 19, 2014.
21. Centers for Disease Control and Prevention (CDC). Recommended immunization schedule for persons age 0 through 18 years. http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. Accessed June 19, 2014.
22. Centers for Disease Control and Prevention (CDC). Possible side-effects from vaccines. http://www.cdc.gov/vaccines/vac-gen/side-effects.htm. Accessed December 28, 2013.
23. Allnurses. Vaccinations in the NICU [Blog comment]. 2012. http://allnurses.com/nicu-nursing-neonatal/vaccinations-in-nicu-763804. Accessed June 19, 2014.
24. Demirjian A, Levy O. Safety and efficacy of neonatal vaccination. *Eur J Immunol*. 2009; 39(1):36-46. doi:10.1002/eji.200838620.
25. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment of apnoea in preterm infants. *Cochrane Database Syst Rev*. 2010;8(12): CD000140. doi: 10.1002/14651858.CD000140.pub2.
26. Cheung PY, Barrington KJ, Finer NN, Robertson CM. Early childhood neurodevelopment in very low birth weight infants with predischarge apnea. *Pediatr Pumonol*. 1999*;27*(1):14-20.
27. Greene MM, Patra K, Khan S, Karst JS, Nelson MN, Silvestri JM. Cardiorespiratory events in extremely low birth weight infants: neurodevelopmental outcome at 1 and 2 years. *J Perinatol* 2014. doi:10.1038/jp.2014.44.
28. Janvier A, Khariy M, Kokkotic A, Cormier C, Messmer S, Barrington K.J. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *J Perinotol*, 2004; 24(12):763-768.
29. Burns N, Grove SK. *The practice of nursing research: Appraisal, synthesis, and generation of evidence*. St Louis, MO: Saunders Elsevier; 2009.
30. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339. doi:10.1136/bmj.b2700.
31. National Quality Form. *Guidance for Evaluating the evidence related to the focus of quality measurement and importance to measure and report*. National Quality Forum. 2011: http://www.qualityforum.org/docs/measure\_evaluation\_criteria.aspx.
32. Xingshun Q, Yang M, Ren W, Wang J, Han G, Fan D. Find duplicates among the PubMed, EMBASE, and Cochrane library databases in systematic review. *PLOS one*. 2013;8(8):1-12. doi:10.1371/journal.pone.0071838
33. Centers for Disease Control and Prevention (CDC). Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. *MMWR Morb Mortal Wkly Rep.* 1997;46(7):1-32. U.S. Government Printing Office: 1997-532-228/47066 Region IV
34. American Academy of Pediatrics(APA). Policy statement: Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatr*. 2000; 106(2), 362-266. http://pediatrics.aappublications.org/content/106/2/362.full.
35. Schulzke S, Heininger U, Lucking-Famira M, Fahnenstich H. Apnoea and bradycardia in preterm infants following immunisation with pentavalent or hexavalent vaccines. *Eur J Pediatr*.2005;164:432-435. doi.org/10.1007/s00431-005-1674-3.
36. Faldella G, Galletti S, Corvaglia L, Ancora G, Alessandroni R. Safety of DTaP-IPV-HIb-HBV hexavalent vaccine in very premature infants. *Vaccine*. 2007; *25*;1036-1042. www.sciencedirect.com.libdata.lib.ua.edu/science/article/pii/S0264410X06010693
37. Pourcyrous M, Korones SB, Arheart KL, Bada HS. Primary immunization of premature infants with gestational age <35 weeks: Cardiorespiratory complications and C-Reactive Protein responses associated with administration of single and multiple separate vaccines simultaneously. *J Pediatr*. 2007;151*(*2):167-172.
38. Klein NP, Massolo ML, Greene J, Dekker CL, Black S, Escobar GJ. Risk factors for developing apnea after immunization in the neonatal intensive care unit. *Pediatr.* 2008; 121(3):463-469. http://dx.doi.org/10.1542/peds.2007-1462.
39. Hacking DF, Davis PG, Wong E, Wheeler K, McVernon, J. Frequency of respiratory deterioration after immunisation in preterm infants. *J Paediatr Child Health*. 2010;46:742-748. doi:10.111/j/1440-1754.2010.01832.x.
40. Furch AK, Richter JW, Kattner E. Very low birth weight infants have only few adverse events after timely immunization. *J Perinatol*. 2010;30:118-121. doi:10.1038/jp.2009.112
41. U.S. Food and Drug Administration (USFDA). Complete list of vaccines licensed for immunization and distribution in the US. 2013: http://www.fda.gov/biologicsblood vaccines/vaccines/approvedproducts/ucm093833.htm. Accessed March 16, 2014.

Table 1Two-Month Vaccines Currently Licensed in the US41

.

|  |  |  |
| --- | --- | --- |
| Product Name | Trade Name | Sponsor |
| [Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm101568.htm) (DTaP) | Infanrix | GlaxoSmithKline Biologicals |
| [Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm101572.htm) (DTaP) | DAPTACEL | Sanofi Pasteur, Ltd |
| [Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm136517.htm) (DTaP/HBV/IPV) | Pediarix | GlaxoSmithKline Biologicals |
| [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094027.htm) (DTaP/IPV) | KINRIX | GlaxoSmithKline Biologicals |
| [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094030.htm) (DTaP/IPV/Hib) | Pentacel | Sanofi Pasteur Limited |
| [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm253644.htm) (Hib) | PedvaxHIB | Merck & Co, Inc |
| [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094028.htm) (Hib) | ActHIB | Sanofi Pasteur, SA |
| [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm179527.htm) (Hib) | Hiberix | GlaxoSmithKline Biologicals, S.A. |
| [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) & Hepatitis B Vaccine (Recombinant)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094032.htm) (Hib/HBV) | Comvax | Merck & Co, Inc |
| [Hepatitis B Vaccine (Recombinant)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm110098.htm) (HBV) | Recombivax HB | Merck & Co, Inc |
| [Hepatitis B Vaccine (Recombinant)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm110102.htm) (HBV) | Engerix-B | GlaxoSmithKline Biologicals |
| [Pneumococcal 7-valent Conjugate Vaccine](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094057.htm)(Diphtheria CRM197 Protein) (PCV 7) | Prevnar | Wyeth Pharmaceuticals Inc |
| [Pneumococcal 13-valent Conjugate Vaccine](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm201665.htm)(Diphtheria CRM197 Protein) (PCV13) | Prevnar 13 | Wyeth Pharmaceuticals Inc |
| [Poliovirus Vaccine Inactivated (Monkey Kidney Cell)](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094058.htm) (IPV) | IPOL | Sanofi Pasteur, SA |

Table 2.Search Criteria

|  |  |  |
| --- | --- | --- |
| Search Terms | Inclusion Criteria  | Exclusion Criteria  |
| Premature infantNeonateVaccinesCare, neonatal intensive AdverseApneaBradycardia | EnglishStudies that focused on any of the normal two month vaccine (DTaP/IPV/PCV/HBV/HiB) given in the NICU | Non-EnglishNon-systematic reviewsStudies focused on:Reoccurrence of  adverse reactions with 4 month dosing Involving older vaccines not currently used. Involving discharged infants |

Diagram 1. Selection Map

Identification

 9955 of records were identified

11 of full articles excluded with reason

 20 of full test articles assessed

1449 of records screened

 8329 of records after duplication removed

Screening

1,426 of records excluded

9 of studies included in review

Included

Eligibility

Table 3.Rigor Criteria

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | A | B  | C | D  |
| Design | Randomized control trial  | Prospective | Retrospective | Expert opinion |
| Sample Size  | 301 or greater | 201-300 | 101-200 | 0-100 |
| Consistency  | Consistent |  |  | Not consistent |
| Bias  | No appearance |  |  | Possible |

Table 4 Evidence Grid

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No** | **Author, Year****Country where study was conducted****Funding source**  | **Purpose**  | **Research design** **Sample size** **Sample statistics** **Data collection dates****Ranking of rigor** | **Independent and dependent variable****Intervention****Statistical tests** | **Recommendations**  |
| 1 | Saari et al. (2003) USAFunding; none stated | To provide information on safety of routinely recommended vaccines in preterm and low birth weigh infants. | Clinical report Rigor: D/na/na/na/na |  | Medically stable (see definition below) premature infants should receive all routinely recommended vaccines at the same chronologic age as full term infants. The guideline also recommends observing the infant for 72 hours after vaccines.  |
| 2 | Pfister et al. (2004)SwitzerlandFunding: GlaxoSmithKline | To evaluate the safety of DTaP-IPV-HIB combined vaccine in premature infants. | Observational n=78MGA= 28 weeksMBW= 1045 gmsMAV=69 days1/2000-12/2002Rigor: C/D/A/D | **IV**: DTaP-IPV-Hib**DV**: Temperature, apnea, bradycardia, desaturation, O2 requirement, feedings, medical interventionsObserved for 24 hours before and 48 hours after vaccines. Kruskal-Wallis test, *X*2 Fisher exact test, odds ratios, and multiple logistic regression  | Immunize infants at 50 to 60 days of age if discharge is imminent and the infant is not having severe cardiorespiratory events and is clinically stable. Then monitor for 48 hours after vaccines.  |
| 3 | Schulzke et al. (2005) Switzerland Funding: none stated | To study if infants not on respiratory support or oxygen infants have significant apnea or bradycardia after vaccination with DTaP/Hib/IPV with or without HBV.  | Retrospective chart review. n=53MGA= 27.9 weeksMBW=997 gmsMAV= 59 days in those who had CRE versus 68 days in the non-CRE 1/2000-6/2003Rigor: C/D/A/A | **IV**: DTaP/Hib/IVPWith or without combined HVB**DV**: apnea or bradycardiaReviewed chart 72 hours before and after vaccines Student *t*-test, Mann-Whitney test and Fisher’s exact test | Monitor even clinically stable preterm infants, for 48 hours after vaccines. |
| 4 | Ellison et al. (2005)AustraliaFunding: none stated  | To study the frequency and types of adverse reaction to vaccines currently available. | Retrospective n=4837 had 3 vaccines (Hib- HBV), DTaP, IPV 11 had 2 vaccines (Hib-HBV) and DTaP MGA= 26.4 weeks MBW=872 gmsMAV=76 days1999-2003 Rigor: C/D/A/A | **IV**: (Hib/HBV), DTaP, IPV (Hib/HBV) and DTaP only. **DV**: Fever >37.5 ApneaBradycardiaThen if the apnea and bradycardia required:Respiratory supportStimulationBag and mask ventilationSepsis workups Chart reviewed 48 hours before and after vaccine.*X*2 test or McNemar’s test, or by unpaired and paired *t*-test | Infants need monitoring after vaccines. Current vaccines need improvement to decrease adverse reactions.  |
| 5 | Faldella et al. (2007)ItalyFunding: none stated | To assess the clinical safety of DTaP-IPV-Hib-HBV in infants < 31 week gestation infants and to verify if the first administration requires monitoring after vaccination.  | Observational prospective study n= 45 MGA=27.3 weeksMBW= 901 gmsMAV=66 days11/2003-5/2005Rigor: B/D/A/A | **IV**: vaccine with DTaP-IPV-Hib-HBV**DV**: Heart rate; saturation; respiratory rate, resistance index at the anterior cerebral artery, and electrocardiogram corrected QT interval airway pressureMonitored 3 days before and 3 days after vaccinesTwo-tailed Fisher’s exact test and Student’s *t*-test | Infants at risk for apnea and bradycardia, mainly those with chronic disease, should be monitored for apnea, bradycardia, and desaturations after vaccines. Vaccines should be given in the hospital rather than delaying them so that the infant is not vaccinated without monitoring.   |
| 6 | Pourcyrous et al. (2007)USAFunding: none stated  | To determine the incidence of cardiorespiratory events and abnormal CRP level associated with administration of a single vaccine or multiple separate vaccines simultaneously. | Prospective observational study quasi-experimental Either single of multi vaccines were given N= 239 168= single vaccine group DTaP n=41 Hib n=27 PCV 7 n=26 IPV n=30 HBV n=44Multiple vaccine n=71 MBW=865 gms MGA= 28.4 weeksMAV=71 daysJuly 2001-July 2004Rigor: B/B/A/A | **IV:**Single group DTaP Hib PCV 7 IPV HBV Or all the vaccines above together. **DV:** ApneaBradycardia CRPCREMonitored 72 hours after vaccines *t*-test, analysis of variance, and *X2* test, multivariable logistic regression  | When following AAP guidelines the infants need close monitoring for 48 hours.  |
| 7 | Klein et al. (2008)USA Funding: Vaccine Safety Datalink in contract with America’s Health insurance Plans funded byCenter for Disease Control and Prevention through as America’s Health Insurance Plans Vaccine Safety Fellowship.Permanente medical Group and Kaiser Foundation of Hospitals | To study predictors for post-immunization apnea among NICU infants without pre-immunization apnea  | Retrospective chart reviewn= 497 342 had two-month vaccineson the same dayand 120 over 2 days34 over 3 days1 over 4 days73 of these infants were given only HBV in this vaccination period.MGA=27.3 weeks MBW = 995 gmsMAV=67 daysJanuary 1997 to December 2003 Rigor: C/A/A/A | **IV:**VaccinesHBV; IPV and oral poliovirus vaccine, DTPw; DTaP; Hib; PCV7 (the vaccines changed during the long study time)**DV**: Apnea, bradycardia, and desaturations Charts reviewed 24 hours before and 48 hours after the last set of immunizations*X*2 test, *t*-test, multivariate logistic regression analyses | Monitor infants for 48 hours post vaccination especially those with a history of apnea, severe illness at birth, younger age, and lower weight.  |
| 8 | Carbone et al. (2008)USA Funding:American SIDS institute | To reexamine the relationship between DTaP and CRE in stable nonventilated premature infants. | Randomized blinded controlled clinical trial. Study infants were given DTaP. The control group had no vaccine. n=197 Study=93 Control=98 MGA 27 weeks MBW=916 gmMVA=57 days9/2000- 9/2004Rigor: A/C/D/D | **IV:** DTaP only**DV:** Apnea and bradycardiaMonitored 24 hours before and 48 hours after vaccine in study group. Control group was monitored for 72 hours. *X*2 test and *t*-test | Vaccines should be given to according to AAP guidelines since there is no rationale for delay of the DTaP vaccine.  |
| 9 | Furck et al. (2010)GermanyFunding: none stated | To analyze adverse events associated with the immunization of very low birth weight infants. | Prospective Observational protocol n= 473 Group A= 162Group B= 51 Group C =260Median BW 910 gms Median GA 27.6 weeks MVA=11.7 weeks at beginning of study 8.6 weeks at end of study1/1998-12/2006Rigor: B/A/A/A | **IV:**Group A(DTaP Hib, IVP) & HBVGroup B(DT(a)P/ IPV/ HiB/ HBV)Group C(DT(a)P IPV Hib HBV) and Prevar**DV:** Apnea, bradycardia, anddesaturations Monitored 48 hours after vaccination. Mann-Whitney U test or Wilcoxon signed rank test, *X*2-test, two sided Fisher’s exact test or binomial logistic regression | It is safe to vaccinate infants according to the guidelines, but CRE can occur especially in the extremely low birth weight infants. |
| 10 | Hacking et al. (2010)AustraliaFunding: none stated  | To determine the relationship between the initiation of respiratory support and the first routine immunization of neonates at two- months of age during primary hospitalization | Retrospective chart reviewn= 411  MGA =27 weeks MBW =709 gmsMVA =73 days 2001 to 2008Rigor: C/A/A/A | **IV:** HBV/DTaP/Hib and OPV PCV7 added 1/2005 OPC changed to  IPV in 11/2005 Rotavirus added 7/2007**DV:** Initiation of respiratory support continuous positive airway pressure or mechanical ventilation within 7 days of two-month vaccines Charts reviewed for 7 days after vaccines.*t*-test, paired *t*-test, Mann-Whitney test.  | Since severe apnea after vaccines can require respiratory support immunize infants prior to discharge in a setting that can provide ventilator support especially the very low birth weight and those with significant respiratory disease or a history of septicaemia. |

BMV=bag mask ventilation

CRE=cardiorespiratory events;

CRP= C-reactive protein

DTaP=diphtheria tetanus acellular pertussis

DTPw=diphtheria tetanus pertussis whole cell

DV=dependent variable

Gm=grams

Hib= haemophilus influenza type b

HVB=hepatitis B vaccine

IPV= inactivated poliovirus vaccine

IV=Independent variable

MBW=mean birth weight

MGA=mean gestational age

MVA=mean vaccination age (in days)

n=sample size

O2=oxygen

OPV=oral polio vaccine

PCV=Prevar

Rigor Key:

 Design: A= RCT B=prospective C=retrospective D=Expert opinion

 Sample size: A=301=400 B=201= 300 C=100-200 D=<100

 Consistent results: Yes A No D

 Bias: Probable No appearance **A** Possible D

Medically stable: Preterm of low birth weigh infant without the need for significant ventilator support or debilitating infection, metabolic disease, renal, cardiovascular of respiratory instability with a pattern of recovery.