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Vaccination of preterm infants against pertussis and pneumococci

Immunogenicity, effectiveness and safety

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Abbreviations

aP	Acellular pertussis
CPS	Pneumococcal cell wall
DT	Diphtheria toxoid
ECDC	European Centre for Disease Prevention and Control
EL.U	ELISA units
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and drug administration
FHA	Filamentous Haemagglutinin
Fim 2& 3	Fimbriae types 2 and 3
GA	Gestational age
GMC	Geometric Mean Concentration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IPD	Invasive pneumococcal disease
MSIS	Meldingssystem for smittsomme sykdommer (Norwegian Surveillance System for Communicable Diseases)
NICU	Neonatal Intensive Care Unit
NIP	National Immunization Program
NIPH	Norwegian Institute of Public Health
OPA	Opsonophagocytic assay
PCV	Pneumococcal conjugate vaccine
PHAS	Public Health Agency of Sweden
PICO	Population, intervention, control and outcome
Prn	Pertactin
PT	Pertussis toxin
SPC	Summary of Product Characteristics
SYSVAK	Nasjonalt vaksinasjonsregister SYSVAK (Norwegian Immunisation Registry SYSVAK)
TT	Tetanus toxoid
WHO	World Health Organization
wP	whole cell pertussis

Glossary

Apnea	Transient cessation of breathing.
ABD event	Apnea, bradycardia and desaturation event. Usually an event where the infant reacts to an unpleasant stimulus with cessation of breathing, reduced pulse rate and decreased oxygen saturation.
Booster immunization	Dose given at a time interval after priming doses in order to enhance immunity and protection against disease.
Bradycardia	Slower heartrate than normal.
Full-term	Infants born after the completion of 37 weeks of pregnancy.
Gestational age	The time elapsed since the beginning of the woman's last menstrual period; it is usually counted in weeks and days.
GRADE	Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A methodology to assess the reliability of studies and to rank them according to level of evidence.
Immunogenicity	The ability of a substance, such as an antigen, to induce an immune response
Incidence	The number of new cases of a particular disease occurring during a defined period of time. Usually written as the number of cases per 100 000 population and year.
NIP	Government program of immunization charged with preventing disease, disability and death from vaccine-preventable diseases.
PICO	Framework to define and specify research questions. Questions always include a population, an intervention, a control group and outcome to meet the aim of the study.
Preterm	Infants born alive before completion of 37 weeks of pregnancy. Preterm infants are divided into 1) *Extremely preterm* infants born after less than 28 weeks of pregnancy; 2) *very preterm* infants born after completion of 28 weeks or before 32 weeks of pregnancy and 3) *moderate to late preterm* infants born after completion of 32 weeks or before 37 weeks pregnancy.

Seroepidemiological studies	Studies of immunity among a sample of the population. Studies are conducted by measuring the levels of serum antibodies against specific antigens.
Vaccine efficacy	Percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal conditions
Vaccine effectiveness	Ability of a vaccine to prevent outcomes of interest in a real life setting, usually outside of a randomized clinical trial. Measure most commonly used to evaluate the impact of a vaccination program at the population level.
2+1 schedule	Basic immunization schedule for vaccines used in NIPs with two primary doses and a booster dose during the second year of life.
3+1 schedule	Basic immunization schedule for vaccines used in NIPs with three primary doses and a booster dose during the second year of life.
3+0 schedule	Basic immunization schedule for vaccines used in NIPs with three primary doses and no booster dose during the second year of life.

Key messages

- Preterm infants are more vulnerable to certain infectious diseases such as whooping cough (pertussis) and invasive pneumococcal disease than full-term infants.
- Preterm infants show similar immunological responses after immunization against pertussis and pneumococcal disease compared to full-term infants.
- Effectiveness or efficacy of vaccination against hospitalization due to whooping cough and invasive pneumococcal disease seem to be comparable between preterm infants and full-term infants.
- Vaccination starting at approximately 8 weeks of chronological age may provide preterm infants with important, early protection and decrease their risk of severe disease especially with regards to pertussis.
- Post-vaccination apnea/ABD events are described in children born prematurely. With higher GA at birth there is a clear tendency of lower incidence of apnea/ABD events in the 48-72 hours post-vaccination period.
- There is no correlation between the chronologic age of the infants at first vaccination and the rate of occurrence of apnea/ABD events.
- Preterm infants, who have had sepsis and those with lung disease have an increased risk of apnea/ABD events post-vaccination compared with preterm infants without these co-morbidities.
- A causal relationship between vaccination and death has not been found in any study.
- Infants born before 30+0 weeks of gestation, preterm infants with significant lung disease, those who have previously experienced septicaemia and preterm infants that are cardiorespiratory unstable at the time of vaccination, need cardiorespiratory monitoring for at least 48 hours post-vaccination.

Executive summary

Introduction

Preterm infants are more vulnerable than full-term infants to certain infectious diseases, including vaccine preventable diseases like whooping cough and invasive pneumococcal disease. The aim of this literature review was to provide data on the effect and safety of vaccinating preterm infants against these two diseases as a knowledge base for a recommendation on immunization of preterm infants in Norway and Sweden.

Methods

We conducted a rapid, systematic literature review of studies on immunogenicity, effectiveness and safety of vaccines against whooping cough and invasive pneumococcal disease in premature infants. Articles published between 1986 and June 2017 were included.

Results

Antibody levels against pertussis toxin and pertactin achieved in premature infants were similar to that of full-term infants both with the use of different aP-containing combination vaccines and various vaccination schedules. Pneumococcal conjugate vaccines used with various vaccination schedules are immunogenic in preterm infants, and most preterm infants develop levels above putatively protective level for the majority of serotypes included in the vaccines.

The vaccine effectiveness against whooping cough in preterm infants was found to be 45-71 % after the first dose and 89-90 % after the third dose recommended at 12 months of age in the two studies included. The vaccine efficacy of PCV7 against invasive pneumococcal disease with vaccine serotypes was found to be 100 % in preterm infants.

Apnea/ABD events in the 48-72 h post-vaccination period was described in 8 included studies for 0-23% of children born prematurely. There was a clear tendency of lower incidence of apnea/ABD events with higher GA at birth. There was no correlation between the chronologic age of the infants at first vaccination and the incidence of post-vaccination apnea/ABD events. Preterm infants, who have had sepsis and those with lung disease, had an increased risk for apnea/ABD events post-vaccination compared with preterm infants without these co-morbidities. A causal relationship between vaccination and death was not found in any study. There may be a risk for recurrent apnea after the second dose if the infants had serious apnea after the first dose. Prospective studies are needed to make any conclusions if there is an increased risk of apnea/ABD events when multiple vaccines, especially conjugated vaccines, are given concurrently.

Conclusion

As the benefit of vaccination is high in preterm infants, vaccination should not be withheld or delayed. The first dose should be given starting at approximately 8 weeks of chronological age, especially with regards to protection against whooping cough. Infants born before 30+0 weeks of gestation and infants with significant comorbidity should be monitored during the first vaccination for at least 48 h, and should preferably be vaccinated before discharge from the hospital.

Preface

Preterm infants are especially vulnerable to infectious diseases. In spite of that, vaccination of preterm infants has been a matter for discussion. Thirty years ago these infants were left unvaccinated for a longer period than term infants, and often given reduced doses of vaccine. Even though times have changed, there is still some hesitation regarding vaccination of vulnerable infants and for some preterm infants vaccinations are withheld or delayed.

This literature review was conducted as a joint project between the Norwegian Institute of Public Health and the Public Health Agency of Sweden, and sums up what is known about safety and effect of vaccines against whooping cough and pneumococci in preterm infants. Hopefully the results and conclusions will add further knowledge for those caring for these infants, and make it possible to protect the preterm infants even better than we do today.

Oslo, March 2018

Ingeborg S. Aaberge

Introduction

In high-income countries such as Norway and Sweden, whooping cough and pneumococcal disease account for the highest burden of vaccine preventable diseases in infants. The risk of infection with pertussis and pneumococci is higher in preterm than in full-term children (1-3). Early protection induced by vaccination is highly advantageous in preterm children.

Previously, premature infants were considered to have an immature immune system that would not be able to evoke an optimal immune response. Consequently vaccination was often postponed based on their gestational age as opposed to chronological age.

After studies determined that post-natal maturation of the immune system is dependent on antigen exposure and not solely on degree of prematurity, preterm infants were recommended vaccination at the same chronological age as full-term infants (4). However, inclusion of several new vaccines in the national immunization program (NIP) and the use of combination vaccines with five or six different components has again raised questions whether or not current immunization practices regarding preterm infants are safe and efficacious.

Today, preterm infants are in many countries recommended vaccination with the same schedule and at the same chronological age as full-term infants. Pneumococcal and pertussis-containing vaccines are usually given in a 2+1, 3+0 or 3+1 schedule. The first vaccine dose is usually recommended at 2 months of age (5-7). However, clinical experience indicates that vaccines are often delayed for preterm infants due to the fear of adverse events.

Adverse events following immunisation (AEFI), including cardiorespiratory deterioration, are of concern and can sometimes be difficult to distinguish from adverse effects due to prematurity itself. Preterm infants with a previous history of cardiorespiratory instability or with significant comorbidities are usually recommended to have the first vaccine dose before discharge from hospital.

In the Norwegian and Swedish immunization programs, a six-valent combination vaccine (diphtheria, tetanus, pertussis, polio, Hib and hepatitis B) and 13-valent pneumococcal vaccine are commonly used for both preterm and full-term infants at 3, 5 and 12 months of age. There are no national recommendations for special vaccination programs for preterm infants in Sweden, but regional routine recommendations exist in some areas in Sweden, where an extra dose of pneumococcal and hexavalent DTaP-containing vaccines at 8 weeks of age is also recommended (8-11).

Many countries, including Sweden, have recently seen a rise in pertussis incidence among infants and experienced infant deaths due to pertussis. This has led to recommendations of maternal vaccination against pertussis in many high-income countries, including the USA, UK, Australia and Belgium. Norway and Sweden have both considered the necessity, effectiveness and safety regarding maternal vaccination against pertussis, and have concluded that a recommendation is not warranted for the time being (12-14).

The aim of this literature review was to collect data on safety, immunogenicity and effectiveness of pneumococcal and pertussis vaccination in premature infants, in order to guide updated recommendations regarding immunization of these infants in the Norwegian and Swedish NIPs.

Aims

Collect and present data retrieved from a literary review on preterm infants' response after vaccination against pertussis and pneumococcal disease, compared to the response in full-term infants.

The report aims to present data in three categories;

Immunogenicity

- Are the immune responses towards pneumococcal and pertussis vaccines in preterm infants similar to that in full-term infants?
- Are there any significant differences in immunogenicity against pneumococcal and pertussis vaccines according to degree of prematurity?

Effectiveness

- Are pneumococcal and pertussis vaccines effective in preventing invasive pneumococcal disease and whooping cough in preterm infants?

Safety

- Does vaccination during the first months of life of preterm infants increase the risk of apnea? If so,
    - Is the increased risk correlated to gestational age?
    - Is the increased risk correlated to concomitant vaccination with multiple vaccines?
    - What other factors are correlated with clinical deterioration after vaccination?
    - How long after vaccination does the increased risk persist?
- For children with apnea after the first vaccination, is there an increased risk of apnea also after the second vaccination?
- Does vaccination of preterm infants during the first months of life increase the risk of death?

Method

This report was based on a rapid, systematic literature review of studies published between 1986 - June 2017. We limited the vaccines of interest to acellular pertussis (aP)-containing vaccines and pneumococcal conjugate vaccines (7, 10 or 13-valent). A literature search was performed on the 2nd of June 2017 and articles were retrieved from PubMed, Cochrane Library and Scopus. The search strategy combined controlled vocabulary and free text terms and included words such as: preterm, newborn, low birth weight, immunogenicity, vaccine. The complete search strategy is listed in Appendix 1. Only articles in English, Dutch, French, German, Spanish and Italian were included.

As a first selection, titles and abstracts were reviewed. The search results were divided among eight researchers. A ninth researcher reviewed all of the titles and abstracts of included articles. At least two persons read each abstract. The research team was divided in three sub-teams assessing articles in full text for immunogenicity, effectiveness and safety respectively. At least two team members assessed each full text article. Disagreements were resolved through discussions among the researchers.

Articles were included according to the criteria listed in Figure 1.

Figure 1 PICO formulation

P	(Population)	=	A) Preterm (GA 23 to 36 weeks 6 days) B) Low birth weight (≤ 2499g)
I	(Intervention)	=	A) Pneumococcal vaccine (PCV7, PCV10, PCV13) B) Acellular pertussis vaccine C) Vaccination schedule 2+1 and 3+1 and 3+0
C	(Comparison)	=	A) Full-term (GA ≥37 weeks) B) Normal birth weight (≥ 2500g) C) Historical controls
O	(Outcome)	=	A) Immunogenicity in serum - Pneumococcal IgG antibodies - Pertussis IgG antibodies B) Vaccine effectiveness (VE) up to 5 years age C) Safety: Apnea or death

Articles from the literature search were excluded if they solely contained data from:

- Animal studies
- Mathematical modelling
- Case reports
- Maternal vaccination
- Cost benefit analyses

Where relevant, the results on immunogenicity, effectiveness and safety were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) terminology. Judgement about the quality of evidence with GRADE was based on

the terminology described by the GRADE Working Group (15). GRADE evaluations are primarily based on study design, where the studies evaluated are given a number of points on a scale from one to four plus (⊕). Randomized studies typically start with ⊕ ⊕ ⊕ ⊕ and the GRADE is reduced if there are problems with study quality, inconsistencies, imprecision or high probability of reporting bias. Typically such problems will reduce the number of points with one ⊕ for each of the above elements.

Overall quality of evidence was defined using the following terms:

- High (⊕⊕⊕⊕) = Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate (⊕⊕⊕) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low (⊕⊕) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low (⊕) = Any estimate of effect is very uncertain.

The regular GRADE methodology as a rule calls for an important final step where studies with high or moderate quality of evidence are presented together in a table according to a specific format. From this table an overall evaluation of the body of evidence is presented. In GRADE handbooks it is often stated that articles with low or very low quality of evidence are to be presented in another, separate list, and this approach was chosen for the current review (16). We did not find any studies with high or moderate quality of evidence for effectiveness or safety using the predefined criteria mentioned above.

Data on immunogenicity were assessed using geometric mean concentration (GMC) of pertussis and pneumococcal IgG antibodies in serum. Proportions of infants with pneumococcal antibody levels over a common consensus cut-off of 0.35 µg/ml were also reviewed. For pertussis, no correlate of protection has been determined and proportions over a hypothetical protective cut-off were therefore not included. Methods and assays used to analyze immunogenicity were evaluated in an attempt to optimize comparability of results from different laboratories.

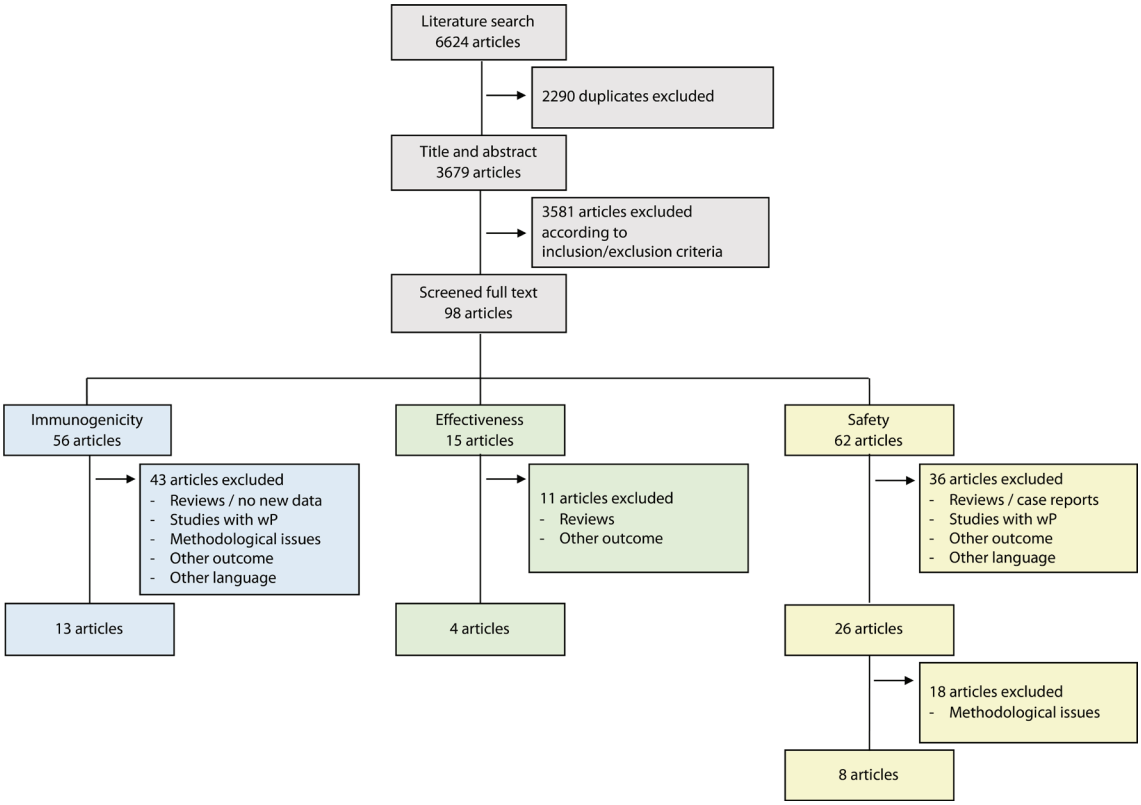
Vaccine effectiveness was assessed with invasive pneumococcal disease and whooping cough as endpoints.

Safety was reviewed mainly based on apnea as an endpoint. Definitions of apnea were assessed for comparability between different studies. In the safety assessment, studies using wP vaccines were excluded since these vaccines are not used in Norwegian and Swedish immunization programs any more. Also, the safety profile of wP vaccines is known to be different than aP vaccines and comparison between studies with wP and aP are difficult.

Results

The results of the literature review are shown in Figure 2. From the literature search, 3679 articles were retrieved after exclusion of duplicates. Following screening of titles and abstracts, 98 articles remained. After further screening for full text and excluding those not fulfilling PICO or those with methodological issues, 25 articles were included; 13 articles assessing immunogenicity, 4 articles assessing effectiveness and 8 articles assessing safety. During the process, reference lists of included articles were scrutinized for possible additional articles.

Figure 2 Selection of articles



Immunogenicity

Comparability of laboratory methods used to evaluate immunogenicity

The evaluation of vaccine responses against pertussis and pneumococcal antigens in this report is mainly based on IgG ELISA results from different laboratories. The ELISA methodology is well known, widely used, well characterized, relatively cheap and suited for dealing with large number of samples in a limited amount of time.

Pertussis ELISA

The ELISA methods used for pertussis, including types of antigen and reference material, were standardized in preparation for large aP vaccine trials performed during the 1990s. Subsequently, the methods were further developed for seroepidemiological studies and for diagnostic purposes in various laboratories (17). The aP vaccines were originally licensed based on non-inferiority antibody responses against some selected putative protective antigens in licensed wP vaccines (PT, Prn, FHA and Fim 2/3 (fimbriae 2 and 3)).

Various studies have attempted to find a serological correlate of protection after vaccination with aP vaccines. It has been suggested that low or undetectable levels of anti-PT correlate with risk of infection and also that anti-PT, anti-Prn and anti-Fim antibodies may be protective (18-21). It was concluded that no correlates of protection are generalizable to all aP vaccines. Probably, no single correlate of protection exists and antibodies to many antigens in addition to cell-mediated immunity, provide protection against symptomatic infection and reinfection (22).

Pneumococcal ELISA

The ELISA methods for pneumococci, including types of antigen, reference material and analytical computer programs were standardized somewhat later than the methodology for pertussis, and have been improved so far in three different major steps (23).

The first generation of pneumococcal ELISAs showed poor correlation of antibody concentration with the vaccine efficacy estimates against invasive disease obtained in clinical trials. This was primarily because the assay also measured unspecific antibodies to the pneumococcal cell wall (CPS) in addition to specific antibodies against capsular polysaccharides.

Hence, a second generation pneumococcal ELISA was developed where test sera were preadsorbed either with highly specific CPS from Statens Serum Institut, or with a crude cell wall preparation chosen by Wyeth (later Pfizer) laboratories. The correlation between antibody concentrations and vaccine efficacy estimates were improved by those measures, but was still far from perfect, with significant residual unspecificity.

It was found that the specificity could be further improved by preadsorption with an "irrelevant" pneumococcal polysaccharide, not used in the conjugate vaccines, in addition to CPS. Serotype 22F was chosen for this purpose. The third generation assay format was adopted at a WHO meeting in Geneva in 2000, and a detailed guidance protocol was later developed (23). Today´s WHO recommendations for pneumococcal conjugate vaccine production and control were established in 2003 and are published, with later revisions, in the WHO Technical Report Series (24). The standardized reference ELISA assays are described in a WHO Training Manual (25). Two WHO reference laboratories were established; one at the Institute of Child Health in London, UK and one at the University of Alabama in Birmingham, USA (26).

A common cut-off of 0.35 μg/ml for a number of diverse pneumococcal serotypes was chosen by consensus among experts. This threshold was originally based on analyses of immune responses (as measured by the second generation ELISA without 22F adsorption) to PCV7 in infants and young children in pre-license efficacy studies during the 1990s. Both the vaccine producers and the regulatory agencies stressed that this threshold did not necessarily predict protection on an individual level, and that the use of a common cut-off for all serotypes was an oversimplification.

Before the adoption of standard 3rd generation ELISAs, WHO arranged an international meeting in Canada. The consensus after the meeting was that a conservative, robust threshold was still needed for the foreseeable future, and that both ELISA and opsonophagocytic assay (OPA) should be performed in immunogenicity studies (26). The threshold of 0.35 μg/ml was retained.

Pertussis immunogenicity-studies in preterm infants

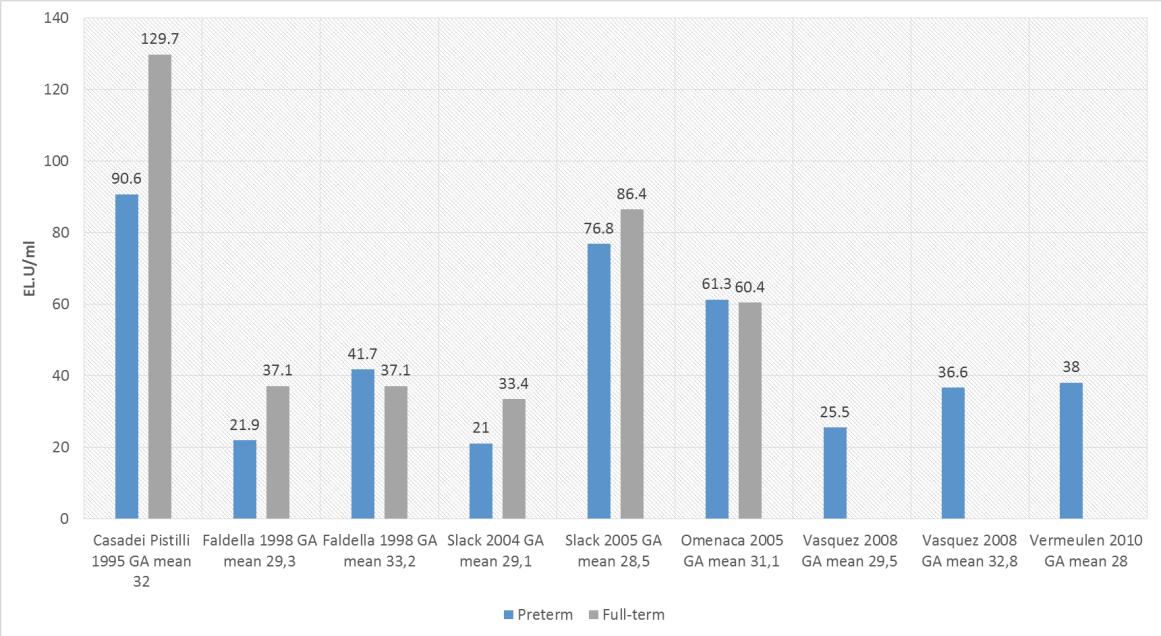
For the purpose of this review, we will in this text focus on studies where ELISA IgG results have been obtained with standardized methodology and where results have been expressed in ELISA Units per ml (EL.U/ml) calibrated against FDA standards. We have chosen to limit the data presented to two antigens (pertussis toxin (PT) and pertactin (Prn)) with documented relation to protection against pertussis, acknowledging that a proper serological correlate of protection has not been defined (27).

Eight studies included data on pertussis immunogenicity in concordance with PICO (Table 1) (28-35). Anti-PT and anti-Prn GMCs after the primary series from these studies are shown in Figure 3 and 4. The studies will be mentioned in detail below. Further details regarding results on pertussis immunogenicity can be found in Table A1 and A2 in the appendix.

Table 1 Pertussis studies included in immunogenicity assessment

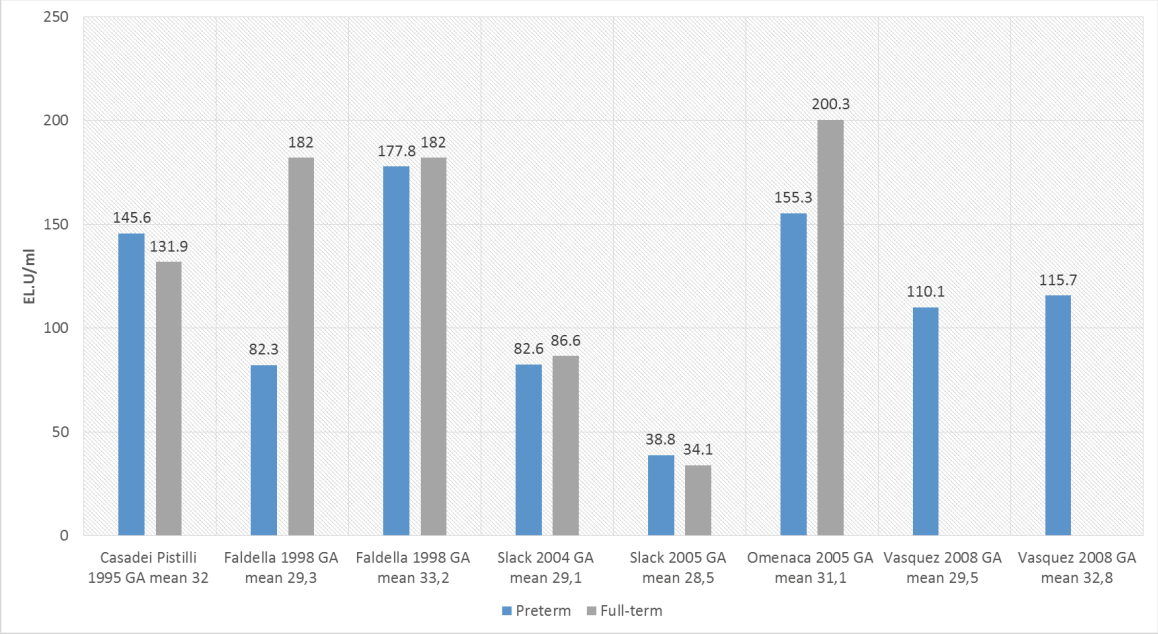
Reference	Study design	GA in weeks (mean)	N	Vaccine	Schedule
Casadei Pistilli 1995 (28)	Open prospective controlled	26-37 (32)	87	aP (Acelluvax®)	Primary 2 + 4 + 6 / 3 + 5 + 7 / 4 + 6 + 8 months
		Above 37	83		
Faldella 1998 (29)	Open prospective controlled	Below 30+6 (29.3)	10	GSK DTaP-HBV (Produced by GSK)	Primary 3 + 5 months Booster 11 months
		31-35 (33.2)	24		
		38 - 42	28		
Slack 2004 (31)	Prospective controlled	Below 32 (29.1)	130	DTaP-Hib (Infanrix-Hib®)	Primary 2 + 3 + 4 months
		Above 36+6	54		
Slack 2005 (30)	Prospective controlled	Below 32 (28.5)	50	DTaP-IPV-Hib (Pediacel®)	Primary 2 + 3 + 4 months
		Above 36+6	60		
Omenaca 2005 (32) Omenaca 2007 (35)	Prospective controlled	24-36 (31.1)	93	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 16-18 months
		37-42	89		
Vasquez 2008 (33)	Prospective observational	24-35 (29.5)	79	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 18-24 months
		30-36 (32.8)	82		
Vermeulen 2010 (34)	Prospective observational	25-30 (28)	18	DTaP-IPV (Tetravac®)	Primary 2 + 3 + 4 months

Figure 3 Anti-PT GMC levels in preterm and full-term infants one month after primary series



Note: Faldella and Vazques both contain 2 datapoints due to inclusion of two separate groups in each of these studies.

Figure 4 Anti-Prn GMC levels in preterm and full-term infants one month after primary series



Note: Faldella and Vazques both contain 2 datapoints due to inclusion of two separate groups in each of these studies.

In an Italian study by **Casadei Pistilli et al**, 87 preterm infants born between 26 and 37 (mean 32) weeks gestation were compared with 83 full-term infants (28). The infants received three doses of Acelluvax®, a genetically inactivated stand-alone pertussis vaccine starting at 2-4 months chronological age and with 8 week intervals. This vaccine-candidate is no longer produced or marketed. Immunogenicity was assessed at Laboratori Biocine S.p.A, Siena, Italy. After the primary series, anti-PT and anti-Prn levels were significantly lower in preterm than full-term infants with anti-PT and anti-Prn GMCs of 90.6 and 145.6 EL.U/ml for preterm, and 129.7 and 131.9 EL.U/ml for full-term infants

respectively after the primary series and the booster dose. As shown in Figure 3 and 4, this vaccine produced robust responses and PT responses seem to be higher than those seen after other aP vaccine studies in preterm infants.

Faldella et al conducted an open label Italian study in the 1990s using a 2+1 schedule with a DTaP-HepB vaccine (produced by GSK) that is no longer marketed (29). Thirty four preterm infants were included and compared with 28 full-term infants. Vaccines were given at 3, 5 and 11 months of age. At first dose, the minimum preterm infant weight was 1980 g, and all children were reported to be in good medical condition. After the primary series, preterm infants with GA 32-35 weeks had anti-PT and anti-Prn GMCs of 41.7 and 177.8 EL.U/ml, which was similar to that of full-term infants (37.1 and 182.0 EL.U/ml). Values were also similar between these two groups after the booster dose. For infants with GA below 32 weeks, anti-PT and anti-Prn GMCs were significantly lower (anti-PT 21.9 and anti-Prn 82.3 El.U/ml) compared to full-term infants as well as preterms with higher GA, both after the primary series and booster.

Slack et al have published two different studies on post primary responses in preterm UK infants vaccinated at 2, 3 and 4 months age (30, 31). In both studies, infants below 32 weeks GA were compared to full-term infants, and immunogenicity was assessed at Centre for Applied Microbiology and Research (CAMR), at Porton Down in UK one month after the third dose. In the first study, the vaccine used was Infanrix-Hib®, whereas Pediacel® was used in the second study. In both studies, anti-PT and anti-Prn GMCs were similar in preterm infants compared to full-term. After the third dose, anti-PT was 21.0 and 76.8 EL.U/ml in the preterm and 33.4 and 86.4 EL.U/ml in the full-term groups. Anti-Prn levels were 38.8 and 82.6 EL.U/ml in the preterm and 34.1 and 86.6 EL.U/ml in full-term groups. Anti-PT levels for Infanrix-Hib and anti-Prn levels for Pediacel were lower for both preterm and full-term infants than seen in similar studies. The authors stated that a booster dose later in life would be necessary.

Omenaca et al conducted a comparative study in 2000-2001, recruiting 93 healthy preterm (mean GA 31.1 weeks) and 89 full-term infants in Spain (32, 35). Infants were vaccinated at 2, 4 and 6 months of age, with Infanrix hexa®. A booster was given at 16-18 months of age. Immunogenicity was assessed at GSK Biologicals. After the primary series, GMCs for anti-PT and anti-Prn were 61.3 and 155.3 EL.U/ml in the preterm and 60.4 and 200.3 EL.U/ml in the full-term infants. The differences between the two groups were not statistically significant, neither after the primary series nor the booster dose.

Vazquez et al conducted an open study in Argentina recruiting 161 healthy preterm infants, half of them with a birth weight between 1500 grams (g) and 2000 g (low birth weight (LBW)) with mean GA 32.8 weeks, and the other half with a birth weight less than 1.5 kg (very low birth weight (VLBW)) with mean GA 29.5 weeks (33). No control group was included. Infants were vaccinated with Infanrix hexa® at 2, 4 and 6 months, in addition to a booster at 18-24 months of age. Immunogenicity was assessed at GSK Biologicals. Anti-PT and anti-Prn GMCs were slightly lower in the VLBW group compared to the LBW group after the primary series with anti-PT of 25.5 EL.U/ml and anti-Prn of 110.1 EL.U/ml in VLBW infants and anti-PT of 36.6 EL.U/ml and anti-Prn of 115.7 EL.U/ml in the LBW infants. After the booster dose, GMCs were again lower in VLBW infants compared to LBW infants. However, both anti-PT and anti-Prn GMCs were in the same range as seen in similar studies.

Vermeulen et al published immunogenicity results after vaccinating preterm infants (mean GA 28 weeks) from France and Belgium with Tetravac® at 2, 3 and 4 months of age

(34). The report principally concentrates on cellular immune responses. Immunogenicity was assessed one month after the third dose. Anti-PT was 38.0 EL.U/ml, which is comparable to levels reported in studies mentioned above.

In addition to the eight studies already mentioned, five other studies were found that fulfilled the search criteria for pertussis (35-39). However, these studies either evaluated immunogenicity using different methodology or studied longterm immunogenicity in older children born prematurely, making it difficult to compare the results. Overall, they did not provide any valuable additional information related to the aims of this review. Two of the additional studies are briefly mentioned below.

Esposito et al and **Omenaca et al** published longterm data for preterm and full-term children at the age of 5-6 and 3-4 years, respectively (35, 36). In **Esposito et al**, preterm infants below 31 weeks GA had lower GMCs for anti-FHA and anti-Prn than full-term infants. There was no difference for the older preterm infants with GA 32-37. Both **Esposito et al** and **Omenaca et al** showed no difference in anti-PT GMCs comparing children born preterm and full-term.

In summary, preterm infants have a good immune response following vaccination with different aP-containing combination vaccines in various immunization schedules, both after the primary series as well as after booster dose. Antibody titers are usually comparable to that full-term infants.

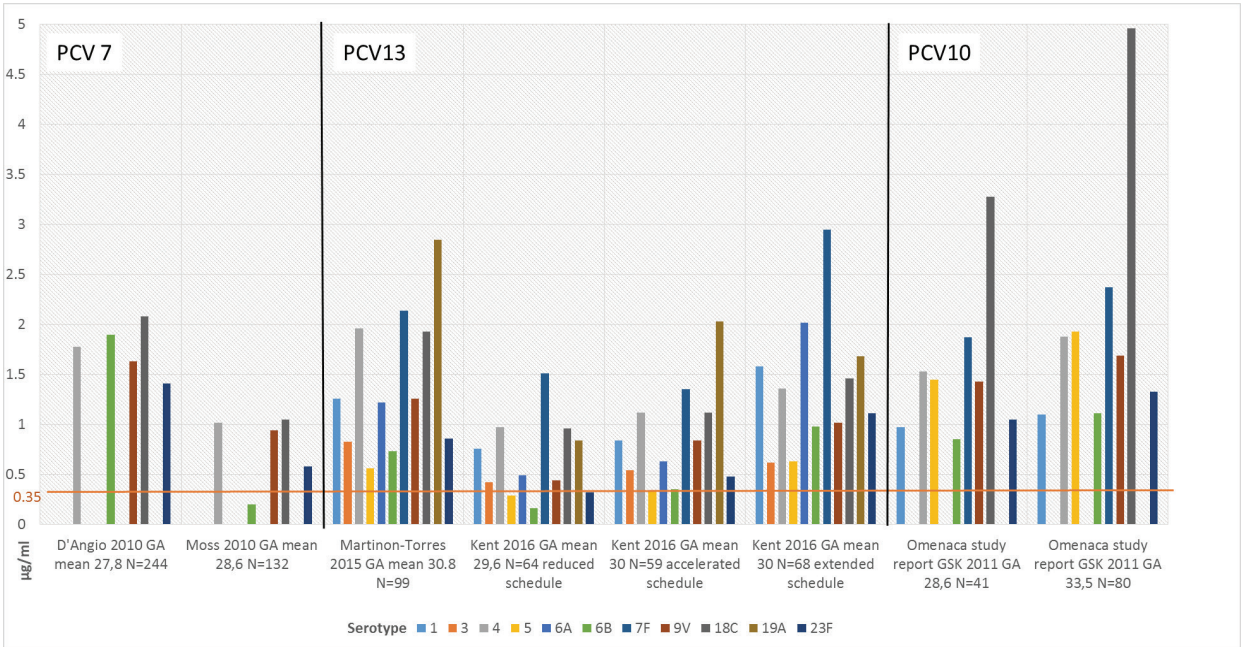
Pneumococcal immunogenicity-studies in preterm infants

For comparison of immunogenicity between different studies, only studies using standardized third generation ELISA for the measurement of pneumococcal antigens were selected in order to allow comparability between laboratories and over time (23). In total, we found five studies that fulfilled our criteria (40-44) with supplementary information given in two study reports (45, 46) (Table 2). The studies will be mentioned in detail below. Anti-pneumococcal GMCs after the primary series and after booster dose from these studies are shown in Figure 5 and 6, where serotypes 14 and 19F are omitted due to very high values. Proportions of infants with values above 0.35 µg/ml after the primary series are shown in Figure 7. Further details regarding results on pneumococcal immunogenicity can be found in the appendix Table A3-A6.

Table 2 Pneumococcal studies included in immunogenicity assessment

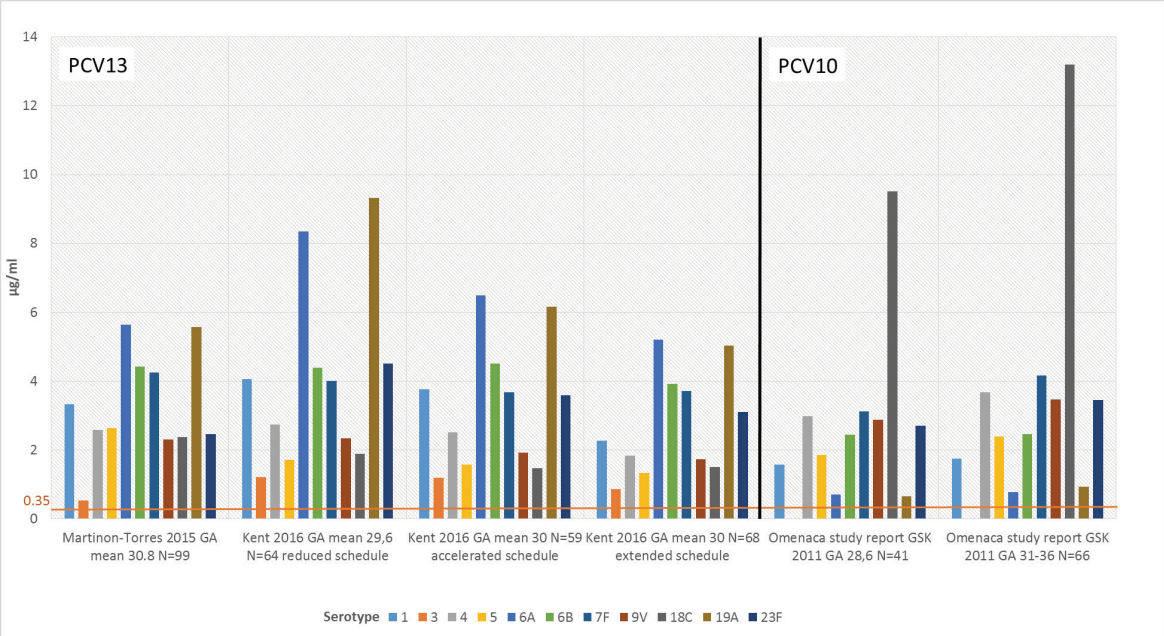
Reference	Study design	GA in weeks (mean)	N	Vaccine	Schedule
D'Angio 2010 (41)	Prospective observational	23-32 (27.8)	244	PCV7 (Prevenar®)	Primary 2 + 4 + 6 months
Moss 2010 (44)	Prospective controlled	23-35 (28.6)	132	PCV7 (Prevenar®)	Primary 2 + 3 + 4 months
		36-42 (39.7)	53		
Martinon-Torres 2015 (43)	Prospective controlled	Below 37 (30.8)	99	PCV13 (Prevenar13®)	Primary 2 + 3 + 4 months Booster 12 months
		Above 36+6 (39.5)	97		
Kent 2016 (42)	Randomized controlled	24-34 (29.6)	64	PCV13 (Prevenar13®)	Primary 2 + 4 months Booster 12 months
		23-34 (30)	59		Primary 2 + 3 + 4 months Booster 12 months
		23-34 (30)	68		Primary 2 + 4 + 6 months Booster 12 months
Omenaca 2011 (40) and GSK technical reports (45, 46)	Prospective controlled	27-30	41	PCV10 (Synflorix®)	Primary 2 + 4 + 6 months Booster 16-18 months
		31-36	80		
		≥ 37	129		

Figure 5 Anti-pneumococcal GMCs in preterm infants one month after primary series (ST 14 and 19F omitted due to very high values)



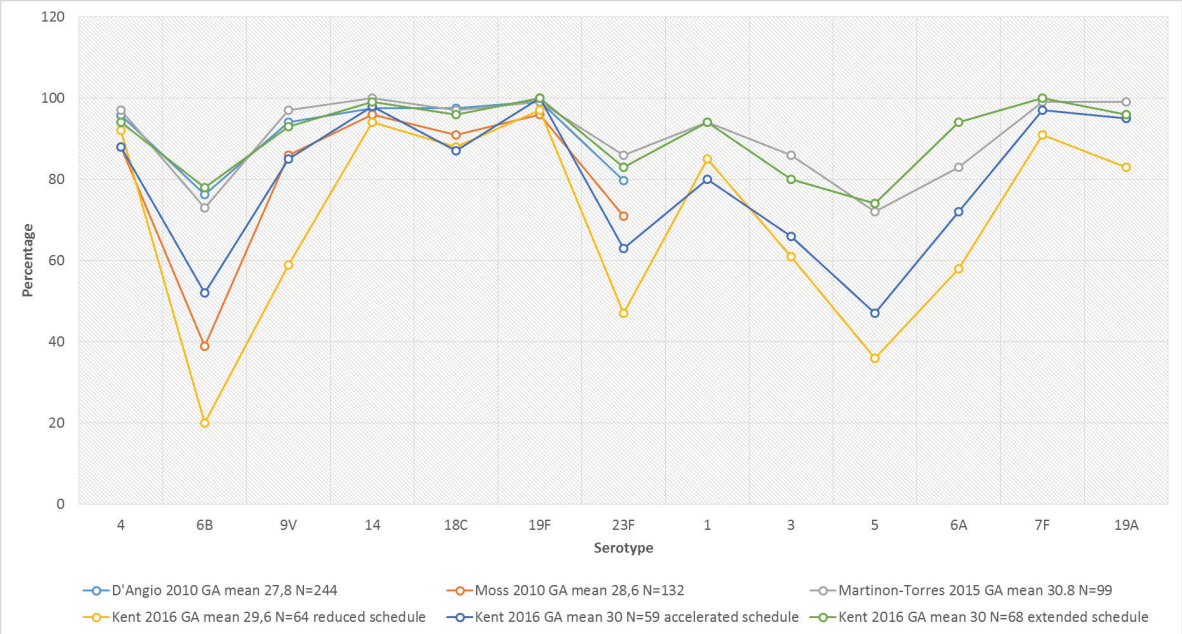
For explanations of reduced, accelerated and extended schedules, please see text below for Kent 2016.

Figure 6 Anti-pneumococcal GMCs in preterm infants one month after booster (ST 14 and 19F omitted due to very high values)



For explanations of reduced, accelerated and extended schedules, please see text below for Kent 2016.

Figure 7 Proportion of premature infants with anti-pneumococcal IgG GMC ≥0.35 µg/ml 1 month after primary series



The study by Omenaca et al 2011 is not shown in Figure 7 since cut-off for anti-pneumococcal IgG was set to 0.20 µg/ml.

D'Angio et al evaluated immunogenicity of PCV7 in an observational study in 2004-2006 in the USA of preterm infants below 32 weeks GA and with a birth weight between 401 and 1500 g (41). Infants were divided in two subgroups according to birthweight; 401-1000 g and 1001-1500 g. PCV7 was administered at 2, 4 and 6 months age. Immunogenicity was assessed by the WHO reference laboratory in Birmingham, Alabama, USA. One month after the primary series, anti-pneumococcal IgG GMCs were above 0.35

μg/ml for all 7 vaccine serotypes. Furthermore, over 90 % of infants had anti-pneumococcal IgG levels above 0.35 μg/ml for all vaccine serotypes, except for the group of infants with the lowest weights where this level was not achieved for serotype 6B and 23F for almost 20 % of infants.

Moss et al studied preterm infants under 36 weeks GA admitted to a neonatal ward and requiring respiratory support during the neonatal period (44). Full-term infants without comorbidities were used as controls. Infants were recruited in 2004-2006. PCV7 was administered at 2, 3 and 4 months of age. Anti-pneumococcal IgG ELISAs were analyzed with an in-house third generation ELISA at Newcastle University. One month after the primary series, both preterm and full-term infants had anti-pneumococcal IgG GMCs above 0.35 μg/ml for all serotypes except 6B. Over 90 % of preterm and full-term infants obtained results over the putative protective level of ≥ 0.35 μg/ml against 3 of the 7 and 6 of the 7 serotypes respectively. The authors comment that the preterm infants recruited in this study had lower GA and more comorbidities than in similar previous studies. The 6B ELISA results for full-term infants are also markedly lower than in other comparable studies, indicating that there might be methodological problems with the method used. These two factors make it difficult to compare the results from this study with results from other similar studies.

Healthy infants in Poland and Spain were included in an open-label, phase IV study by **Martinon-Torres et al** (43). Two hundred infants were recruited in 2010-2011 and divided in two equally sized groups according to GA at birth; preterm < 37 weeks and full-term ≥ 37 weeks. Mean GA and weight at birth were 30.8 weeks and 1500 g for the preterm infants. All infants received PCV13 at 2, 3, 4 and 12 months age. Immunogenicity was assessed at Pfizer's laboratory one month after primary series and booster dose respectively. After both the primary series and booster dose, anti-pneumococcal IgG GMCs for both groups were above 0.35 μg/ml for all 13 vaccine serotypes. Even though GMCs were above the cut-off, the proportion of preterm infants reaching levels of anti-pneumococcal IgG > 0.35 μg/ml after the primary series was lower than for full-term infants. In particular, proportions were lower than full-term and below 90% for serotypes 3, 5, 6A, 6B and 23F. After the booster dose, > 98 % of all infants reached GMCs above 0.35 μg/ml for all vaccine serotypes, except serotype 3, without significant differences between groups.

In an open-label, randomized controlled trial conducted in 2012-2013 in UK, **Kent et al** randomly assigned preterm infants < 35 weeks GA to receive PCV13 at three different schedules; 1) vaccine at 2, 4 and 12 months (Reduced schedule), 2) vaccines at 2, 3, 4 and 12 months (Accelerated schedule) or 3) vaccines at 2, 4, 6, and 12 months (Extended schedule) (42). Mean GA and weight at birth were around 30 weeks and 1400 g in all groups. Immunogenicity was assessed by the WHO reference laboratory in London, UK. After the primary series, infants in the extended group generally had higher GMCs than infants in the reduced and accelerated groups. In the extended group, anti-pneumococcal IgG GMCs were above 0.35 μg/ml for all vaccine serotypes. In the accelerated and reduced groups GMCs were above 0.35 μg/ml for 12 of the 13 and 10 of the 13 serotypes respectively. IgG GMCs were lowest for serotypes 3, 5 and 6B across all groups after the primary series. The proportion of infants achieving GMCs above 0.35 μg/ml after the primary series was above 90% for 9 of the 13 serotypes in the extended group, compared to 4 of the 13 in the reduced and accelerated groups. The serotypes that did not reach the cut-off level of 90% in the extended group were 3, 5, 6B and 23F.

Immunogenicity evaluated before the booster dose showed waning of immunity as expected. After the booster dose at 12 months, values were significantly lower for the extended group, but all groups had GMCs well above 0.35 μg/ml for all vaccine serotypes.

In a study by **Omenaca et al** infants recruited in 2006-2009 were immunized with PCV10 at 2, 4, 6 and 16-18 months of age (40). Infants were divided in three groups according to GA; 1) ≤ 30 weeks, 2) 31-36 weeks and 3) over 37 weeks. Immunogenicity was assessed by GSK's laboratory. The cut-off used in this study to calculate proportions was set to 0.2 μg/ml instead of 0.35 μg/ml. Even though GMCs were lower for some serotypes in the preterm groups, the proportion of infants with anti-pneumococcal IgG GMCs above 0.2 μg/ml was above 90 % for all vaccine serotypes, without differences between the groups.

GMCs from the same study were not published in the same paper, but were available in two clinical study reports (45, 46). Anti-pneumococcal GMCs were somewhat lower in the infants with GA below 30 weeks, but all three vaccinated groups had anti-pneumococcal IgG GMCs above 0.35 μg/ml for all vaccine serotypes both one month after the primary series as well as after the booster dose.

Only three of the studies presented immunogenicity data based on OPA results, but complete data were not presented from any of the studies, and a meaningful comparison between preterm and full-term infants based on OPA results was not possible (40, 41, 43).

In addition to the five studies mentioned above, eight further studies fulfilled the search criteria for pneumococcal immunogenicity (47-54). These studies did not use third generation ELISA methods and were therefore not directly comparable to the already mentioned studies.

In a PCV7 efficacy trial (Kaiser Permanente study), almost 40 000 infants were randomized to receive either PCV7 or meningococcal vaccine in a double blind fashion (55). Children with low birth weight or preterm birth were included in the trial and the immunogenicity data for this subgroup was reported in a separate article by **Shinefield et al** (53). The immunogenicity was evaluated by the vaccine manufacturers laboratory, now Pfizer´s laboratory, Rochester USA, using second generation ELISA methods. The authors concluded that PCV7 was as immunogenic in LBW and preterm infants as in normal birth weight and full-term infants.

In summary, anti-pneumococcal GMCs were above 0.35 μg/ml for the majority of vaccine serotypes after both primary and booster doses. Over 90% of preterm infants achieved GMCs above 0.35 μg/ml for the majority of vaccine serotypes after the primary series, but the rate reaching this level was lower for the infants with the lowest GA. In general, the response rate against serotypes 3, 5, 6A, 6B and 23F were somewhat lower after the primary series. After the booster dose almost all preterm infants had GMCs above 0.35 μg/ml for all vaccine-serotypes.

Effectiveness

Effectiveness against pertussis

A Danish cohort study by **Hviid et al** included almost 880 000 infants with GA 20-41 hospitalized with pertussis in the period 1990-2004 (56). In 1990-1996 wP vaccine was given at 5 and 9 weeks and a booster at 10 months. From 1997 mono-component aP vaccine replaced the wP vaccine in a 3, 5 and 12 month schedule. Preterm infants were vaccinated later than full-term infants, especially those receiving wP vaccine. Effectiveness of the wP vaccine in preterm infants for the 1st, 2nd and 3rd dose was calculated to -23%, 47% and 95% respectively. Compared to full-term infants a reduced response was observed after the 1st dose, but not after the 2nd and 3rd dose. Effectiveness of the aP vaccine in preterm infants for the 1st, 2nd and 3rd dose were 45%, 77% and 90% respectively, and statistically similar to full-term infants.

In a Norwegian cohort study by **Riise et al**, 713 000 infants were studied between 1998 and 2010 (1). Irrespective of GA, aP-combination vaccine was recommended at age 3, 5 and 12 months according to Norwegian recommendations. Age at vaccination was not reported, however the analysis controlled for different chronological age at vaccination between preterm and full-term children. The vaccine effectiveness for reported pertussis among children born preterm for the 1st, 2nd and 3rd dose was 73.0% 80.1% and 93.0%, while the effectiveness for reported pertussis hospitalization for the 1st, 2nd and 3rd dose was 71.2%, 93.8% and 88.7%, respectively, statistically similar to children born full-term.

Effectiveness and efficacy against pneumococcal disease

We did not identify any studies on effectiveness post-licensure against invasive pneumococcal disease (IPD) for preterm children.

The efficacy of PCV7 in 4340 preterm children ≤38 weeks GA was assessed in the pivotal Kaiser Permanente randomized double blind study (RCT) mentioned earlier on page 24 (55). Infants received either PCV7 or meningococcal C conjugate vaccine (MCV) concomitantly with routine childhood vaccines at ages 2, 4, 6 and 12-15 months. For the main efficacy analysis, the disease had to be caused by vaccine serotypes and with disease onset more than 14 days after the 3rd dose in addition to occurring in a subject vaccinated according to protocol. Children at least 16 months of age were considered fully vaccinated after receipt of the 4th dose. **Black et al** reports nine children with IPD in the control group and zero in the PCV7 group giving a vaccine efficacy of 100% (57).

Further details from studies on effectiveness against pertussis and efficacy against pneumococci are found in Table A7 in the appendix.

In summary, aP vaccine induced effectiveness against whooping cough was similar among preterm and full-term children in a national recommended 3, 5 and 12 month schedule. The efficacy of PCV7 when administered at 2, 4, 6 and 12-15 months in preterm infants, was 100% against invasive pneumococcal disease caused by vaccine-serotypes. Specific data on efficacy or effectiveness after the first dose given at 2 months to preterm infants were not identified neither for aP nor PCV vaccine.

Safety

The main objective of the safety part of this literature review was to evaluate the incidence of apnea or death after the first dose of aP and/or pneumococcal conjugate vaccine. Of the 26 studies included in the safety assessment (Figure 2), many of the studies demonstrated selection bias. Specifically, a number of the studies preferentially included children that were hospitalized for a prolonged period (tending to inflate number of events, over-estimate risk), or oppositely included only stable, well children (tending to reduce number of events, underestimate risk). Using GRADE terminology, only 8 studies were found with some (⊕ or ⊕⊕) quality of evidence to answer the main objectives of this review.

Definitions of apnea used in different safety studies

Apnea was defined as cessation of breathing for 20 seconds (s) or longer in most studies. In some studies cessation of breathing for more than 15 s accompanied by bradycardia or desaturation was classified as apnea. In other studies, apnea was not presented separately, but together with bradycardia or bradycardia and desaturation (ABD) episodes. It was decided to include those studies because very few studies reported the outcome apnea alone and because apnea in neonates is often associated with, or difficult to contrast from, episodes of bradycardia due to desaturation.

Definitions of bradycardia varied in the studies included, with heart rate limits varying from < 80 beats per minute (bpm) to < 100 bpm, and duration varying from 10 to 20 s. Definitions of desaturation varied from oxygen saturation < 85 % to < 88 %. In most studies, desaturation was reported without a time limit, but in one there was a time limit of 15 s in the definition.

Does vaccination during the first months of life of preterm infants increase the risk of apnea/ABD events (mean GA at birth < 28 weeks)?

There were 13 studies including infants with mean GA 28 weeks or younger studying apnea/ABD events after the first dose of vaccine that fulfilled the criteria in the literature search. Only six of these studies fulfilled all the quality assessment criteria in this review (58-63) (Table 3). The six studies are described in detail below.

Table 3. Studies included in the safety assessment of apnea/ABD events after first vaccination in infants with mean GA at birth 28 weeks or younger

Reference	Study design	GA in weeks (mean)	N	Observational time post-vaccination (hours)	Vaccine
Ellison 2005 (58)	Prospective observational	26.4	48	48	DTaP (Infanrix®)
Schulzke 2005 (59)	Retrospective observational	28	53	72	DTaP-IPV-Hib / DTaP-IPV-Hib-HepB (Infanrix-IPV+Hib® / Infanrix hexa®)
Carbone 2008 (60)	Randomized controlled	26.9	93	48	DTaP (Infanrix® / Pediatrix®)
Furck 2010 (61)	Prospective observational	27.6	260 group C	48	DTaP-IPV-Hib-HepB (Infanrix hexa®) PCV7 (Prevenar®)
Anderson 2013 (62)	Retrospective observational	26.3	203	24	DTaP-HepB / DTaP-IPV-Hib-HepB / Hib-MenB Conj
Wilinska 2016 (a) (63)	Prospective observational	27	73	72	DTaP-IPV-Hib (Infanrix-IPV+Hib®) PCV7 (Prevenar®)

In an Australian study by **Ellison et al** 48 very preterm infants were studied 48 h before and after their first immunization with Infanrix® in the NICU, during a period from 1999 to 2003 (58). Mean GA at birth was 26.4 weeks and mean postnatal age at immunization was 76 days. All infants were monitored electronically pre- and post-immunization. Endpoints included apnea and bradycardia requiring stimulation, defined as apnea responding to tactile stimulation and/or low flow oxygen administration and/or responding to positive pressure by means of a face mask. The incidence of apnea requiring stimulation was increased post-vaccination (23 %) in the 48 h post-vaccination compared to pre-vaccination period (15 %), but the difference was not statistically significantly.

Schulzke et al retrospectively analysed medical records of 53 Swiss preterm infants with mean GA of 28 weeks, hospitalized for at least eight weeks after birth and who had received their first vaccination with Infanrix-IPV+Hib® or Infanrix-hexa® between 2000 and 2003 in the NICU (59). All infants had a previous history of typical apnea or bradycardia of prematurity. At the time of immunization, all infants were medically stable and did not require any ventilatory support or oxygen supplementation. Infants were continuously monitored electronically. Seven infants (13 %) in this study of clinically stable infants, showed a transient recurrence of or increase in episodes of apnea or bradycardia episodes 8-24 h following immunization. Five of these seven infants required intervention ranging from tactile stimulation to bag and mask ventilation. All episodes settled within 48 h.

An RCT conducted by **Carbone et al** in 10 NICUs in the US between 2000 and 2004 enrolled 191 infants who were born at mean GA 26.9 weeks and who at the time of the study entry were 56-60 days in chronological age (60). Infants were randomly assigned to receive immunization with either Infanrix® or Pediatrix® immunization (n =93) or no vaccine (n =98). Infants were included only if clinically stable. Recording monitors were used continuously during 48 h post-vaccination to document prolonged apnea and prolonged bradycardia. In this study of clinically stable infants, 16.1 % of infants in the vaccinated group experienced at least one episode of prolonged apnea, compared with

20.4 % of control infants. The frequency of episodes was not significantly different between groups. Infants in both the immunization group and the control group each had an average of 0.5 episodes of prolonged apnea.

Between 1998 and 2006, **Furck et al** enrolled 473 German preterm infants with a birth weight under 1500 g in a prospective observational study (61). All infants received their first vaccination during their primary hospitalization in the neonatal ward. Mean GA at birth was 27.6 weeks and all were immunized and observed for up to 48 h post-vaccination. In infants already suffering from single apnea/bradycardia events before immunization, only an increase in frequency was used as an adverse event. Three different vaccinee combinations were used and 260 infants received Infanrix-hexa® and Prevenar® (group C). In this group 15 % of the infants had apnea in the 48 h post-immunization period. Infants with apnea were born on an average 1.4 weeks earlier than those without apnea (26.3±1.8 versus 27.7±2.1 weeks). The incidence of apnea decreased with increasing gestational week at birth.

Anderson et al conducted a retrospective audit between 2001 and 2011 in the tertiary neonatal centers of South Australia (62). A database was searched for records of suspected vaccine reactions in extremely preterm babies. The 203 babies identified had mean GA of 26.3 weeks and received their first immunization at mean age of 71 days while still admitted to the NICU. All babies were immunized in accordance with national guidelines but the vaccines used varied slightly over the 10-year period due to changes in the Australian Immunization Schedule and were either 1) Infanrix-hepB® and Pedvax®, 2) Infanrix-hepB®, Pedvax® and Prevenar® or 3) Infanrix-hexa® and Prevenar®. Cardiorespiratory monitoring at the time of first immunization was routine clinical practice. A likely apneic reaction was defined as occurring within 24 h and resolving within 48 h, as a clinically important increase in apnea and that there was an absence of confounding factors. Once babies with potential vaccine reactions were identified from the database, medical records were independently reviewed by each author. Apneic reactions were then reclassified into likely, possible or unlikely using predefined criteria. After independent classification, a consensus decision on final classification was derived. Following medical record review, 12 were classified with a likely apneic reaction, five with a possible apneic reaction and one with an unlikely reaction possibly caused by first vaccination. In all cases prior to immunization there was no clinically significant apnea, and no respiratory support was required. The incidence of likely or possible apnea following first immunization was 8.4 % within 24 h post-vaccination.

Wilinska et al studied 73 infants born at GA 28 weeks or younger (mean GA 27 weeks) admitted to the NICU and vaccinated at a mean age of 49 days with Infanrix-IPV+Hib® and Prevenar® (63). The infants´ cardiac and respiratory functions were monitored over 72 h after vaccination and followed up according to standardized protocol.

Apnea within 72 h after vaccination occurred in five infants (7 %).

The other seven studies on infants with mean GA 28 weeks or younger were assessed but not further described because they did not fulfilled all the criteria for the quality assessment. These studies were assessed as having reporting-, observation-, and/or selection-bias and did not contribute any further information regarding the PICO of this review (64-70). Even so, **Hacking et al** (68) is a large study that adds important information on risk factors for severe events post-immunization in preterm infants, and will therefore be further described in the section below on page 32 regarding risk factors associated with the risk of apnea/ABD events and in the discussion.

Does vaccination during the first months of life of preterm infants increase the risk of apnea/ABD events (mean GA at birth > 28 - < 30 weeks)?

There were six studies including infants with mean GA > 28 - ≤ 30 weeks studying apnea/ABD events that fulfilled all the criteria in the literature search. Two of these studies also fulfilled the quality assessment and will be mentioned in detail below (Table 4) (63, 71).

Table 4. Studies included in the safety assessment of apnea/ABD events after first vaccination in infants with mean GA at birth > 28 - < 30 weeks

Reference	Study design	GA in weeks (mean)	N	Observational time post-vaccination (hours)	Vaccine
Faldella 2007 (71)	Prospective observational	28.4	81	72	DTaP-IPV-Hib-HepB (Infanrix hexa®)
Wilinska 2016 (b) (63)	Prospective observational	30	65	72	DTaP-IPV-Hib (Infanrix-IPV+Hib®) PCV7 (Prevenar®)

Faldella et al assessed the safety of hexavalent vaccine (DTaP–IPV+Hib+HBV, vaccine type not specified) in very premature infants born at less than 31 weeks gestation (71). All babies were continuously monitored for three days before and after vaccination to record episodes of ABD-episodes and related interventions. ABD-episodes were considered moderate when responding to tactile stimulation and/or low-flow O_2 administration, and severe when sustained respiratory support (O_2 delivered through CPAP or mechanical ventilation) was required. Eighty-one preterm newborns were included with a mean GA 28.4 weeks and mean age at vaccination 73 days. Forty-five infants were vaccinated while admitted to NICU; 19 infants were discharged before vaccination; 17 infants were vaccinated at primary level hospital. Among the 45 babies immunized in the NICU, 22 received the vaccine between age 60 and 90 days. For 17 infants, immunization was given before they were 60 days old (49–59 days) to allow immunization under medical monitoring before hospital discharge. Finally, in six cases immunization was postponed beyond 90 days of life because of some kind of clinical problem. ABD-episodes related to vaccination was recorded in five infants (6.2 %), all in the group of newborns with chronic disease.

Wilinska et al conducted a study on 65 infants admitted to NICU and born at 29-36 gestational weeks (63). Infants were vaccinated at a mean age of 44 days with Infanrix-IPV+Hib® and Prevenar®. The infants´ cardiac and respiratory functions, as well as body temperature was monitored over 72 h after vaccination and followed up according to standardized protocol. Apnea occurred in 1 infant (2 %) after vaccination.

The other four studies including infants with mean GA > 28 - ≤ 30 weeks were assessed but not further described because they did not fulfil all the criteria for the quality assessment. These studies were evaluated to have reporting-, observation-, and/or selection-bias and did not contribute any further information to this review (40, 49, 72, 73).

Does vaccination during the first months of life of preterm infants increase the risk of apnea/ABD events (mean GA > 30 - < 32 weeks)?

There were three studies included from the literature search on infants with mean GA > 30 - ≤ 32 weeks (37, 54, 74). Only one fulfilled the quality criteria and is mentioned below (Table 5) (74).

Table 5. Studies included in the safety assessment of apnea/ABD events after first vaccination in infants with mean GA at birth > 30 - < 32 weeks

Reference	Study design	GA in weeks (mean)	N	Observational time post-vaccination (hours)	Vaccine
Buijs 2012 (74)	Prospective observational	30.8	41	48	DTaP-IPV-Hib / DTaP-IPV-Hib-HepB (Infanrix-IPV+Hib® / Infanrix hexa®) PCV7 (Prevenar®)

Buijs et al conducted a prospective observational cohort study in the Netherlands from 2009 until 2010 (74). The 41 babies with mean GA 30.8 weeks received their first immunization at mean age of 9.2 weeks and were vaccinated at the NICU or after being discharged. Infants vaccinated at the NICU were observed 48 h post-vaccination. Vaccines used was Pediacel®, Infanrix-hexa® and Prevenar®. No apneic events were reported in the post-vaccination period.

Two studies were assessed but not further described due to problems with study quality. These studies were assessed as having reporting-, observation-, and/or selection-bias and thereby no adding value (37, 54).

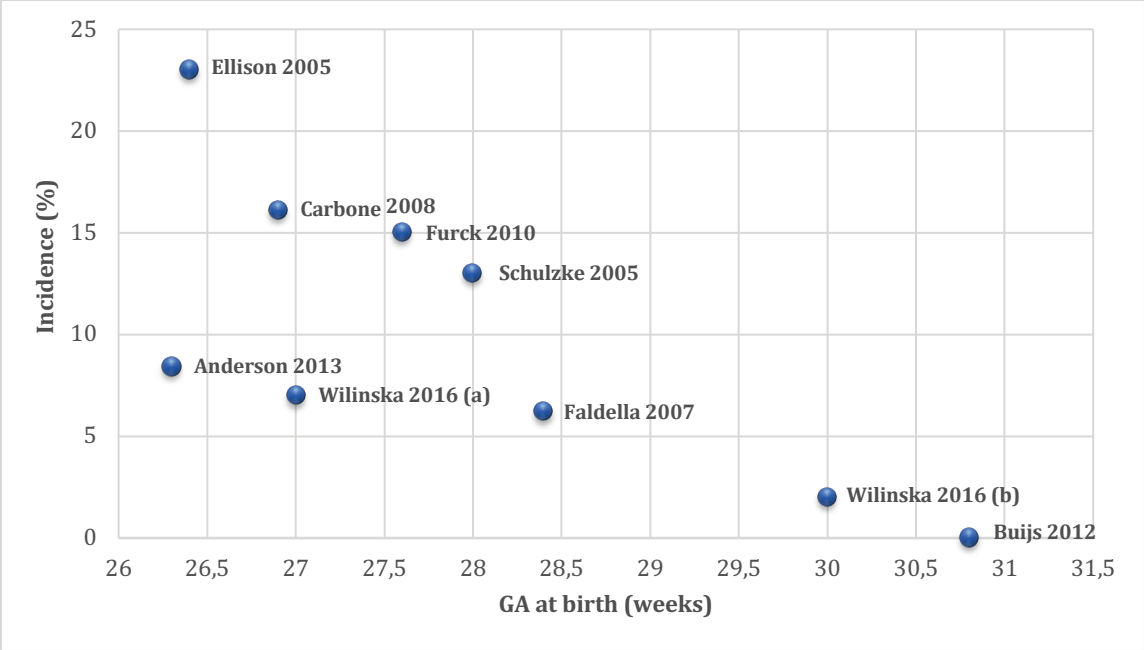
Does vaccination during the first months of life of preterm infants increase the risk of apnea/ABD events (mean GA > 32 - < 37 weeks)?

There were two studies included from the literature search in this group. One study included infants with mean GA > 32 - ≤ 37 weeks and the other study included infants with GA ranging between 32 to 36 weeks (40, 52). These studies were assessed as having reporting-, observation-, and/or selection-bias and thereby not further described.

Summary of apnea/ABD events after first vaccination in premature infants related to GA

The eight studies that fulfilled the criteria for the quality assessment described in the paragraphs above are included in Figure 8 (58-63, 71, 74). The study by Wilinska et al has two data points since the study included two different GA-groups; a) and b). In this figure incidence of apnea/ABD events within 48-72 h (except Anderson et al with 24 h observation) period after first vaccination is described as a function of GA at birth.

Figure 8 Incidence (%) of apnea/ABD-events in preterm infants 48-72 hours after first vaccination as function of mean GA at birth



There is a clear tendency of lower incidence of apnea/ABD events with higher GA at birth (Figure 8).

No correlation between the chronologic age of the infants at first vaccination and the rate of occurrence of apnea/ABD events was found in studies included in the review of apnea/ABD events described above (58-63, 71, 74, 75) .

Does vaccination during the first months of life of preterm infants increase the risk of apnea/ABD events after concomitant vaccination with multiple vaccines?

Three studies with data on the impact of concomitant vaccination with multiple vaccines are previously summarized in Table 3.

In **Furck et al** all premature infants with a birth weight below 1500 g who received their first vaccination during their primary hospitalization, between 1998 and 2006 were included prospectively. Infants received three different vaccine combinations according to time period when they were included into the study; in group A, 162 infants were included from January 1998 to November 2000 and received Infanrix-IPV-Hib®, and Gen H-B-Vax K pro infantibus® (DTaP-Hib and HepB vaccine); in group B, 51 infants were included from 2000 to 2001 and received Infanrix-hexa®; in group C, 260 infants were included from 2001 to 2006 and received Infanrix-hexa® and Prevenar®.

There was significantly more apnea and bradycardia in infants in group C, vaccinated with both Prevenar® and Infanrix®-combination compared to a group A and B, vaccinated with DTaP-containing vaccines alone. When correcting for age this difference was no longer significant between group B and C (61). As the groups in this study were not well balanced, there may be residual confounding and a firm conclusion cannot be drawn from this observational study.

In **Schulzke et al**, there was no difference in the incidence of apnea/bradycardia between infants if vaccinated with two different DTaP-containing vaccines within 72 h post-vaccination period (59).

In **Ellison et al**, 48 very preterm infants were immunized during the period; 37 infants with Comvax® (Hib and hepatitis-B), Infanrix® and inactivated poliomyelitis vaccine (vaccine type not specified), and 11 infants with Comvax® and Infanrix® only (58). There was no statistically significant difference in the incidence of apnea within the 48 h post-vaccination period when comparing the two groups.

What other factors are correlated with clinical deterioration after vaccination?

In a study by **DeMeo et al** described below on page 34, they did not look at apnea/ABD events as an outcome, but rather the need for increased respiratory support (76) and thereby did not fulfilled the criteria in the literature search. Due to high quality and large number of extremely preterm infants studied, this study is still of interest for this evaluation. Results showed an increase in respiratory support from 6.6/1,000 patient-days in the pre-vaccination period to 14.0/1,000 patient-days in the post-vaccination period. The incidence of need for increased respiratory support was 12.7/1,000 patient-days after DTaP-IPV-HiB, 16.4/1,000 after DTaP-IPV-HepB and 14.7/1,000 after PCV. Also, incidence of intubation was similar between those three vaccine groups, 3.5/1,000.

DeMeo et al observed a decrease in the incidence of respiratory support and intubation in the 30-day period before first immunization leading up to immunization day, especially in the several days before immunization. The investigators, as well as the editorial comment from Kuzniewicz and Klein in the same issue of JAMA pediatrics (77), highlight this observation as possibly indicating the well-known healthy vaccinee effect, by which physicians postpone immunization until children are clinically stable to immunize, thus reducing the observed incidence of pre-immunization adverse events and overestimating the rate ratio of adverse events post-immunization/adverse events pre-immunization.

Hacking et al, mentioned previously on page 28, sought to find risk factors associated with the requirement for intermittent positive pressure ventilation (IPPV) or CPAP following immunization (68). Of the 411 infants who were immunized in hospital at about 2 months of age, 368 received their immunization without any respiratory support whilst 43 were vaccinated on either IPPV or CPAP. The mean age at immunization was 73 days and the mean corrected GA was 37.5 weeks. Infants who required respiratory support following immunization had the same GA, birth weight, Apgar scores and weight at discharge as those infants whose immunization was not associated with respiratory deterioration. There was no difference between the two groups in the incidence of respiratory distress syndrome (RDS) or the requirement for IPPV and CPAP. However, the infants requiring respiratory support post-vaccination had an increased total accumulated time on CPAP as well as a higher incidence of septicemia prior to vaccination.

In **Wilinska et al** mentioned previously on pages 28 and 29, six out of 138 (4 %) infants had post-vaccination apnea (63). The occurrence of apnea after vaccination positively correlated with the time of non-invasive ventilation and the occurrence of late infection. Long-term non-invasive respiratory support and late infections were shown to be risk factors for apnea following vaccinations. Late infection was defined as clinical signs of infection after the third day of life in addition to abnormal laboratory markers of infection and/or by positive blood-, urine- or cerebrospinal fluid culture.

How long after vaccination does the increased risk of apnea/ABD event persist?

In Table 6 studies with information on time-point for last observed apnea/ABD event post-vaccination are listed. The overall time-point for observed apnea ranged from 3 to 48 h post-vaccination (59, 62).

Table 6 Studies with information on time-point for last observed apnea/ABD event post-vaccination

Reference	Study design	Observational time post-vaccination (first dose) (hours)	Time-point for last observed post-vaccination apnea/ABD events (hours)
Schulzke 2005 (59)	Retrospective observational	72	Apneas started 8-24 h after vaccination and settled within 48 h after vaccination
Anderson 2013 (62)	Retrospective observational	48	Apneas occurred 3-20 h after vaccination

Three studies did not fulfill all the requirements for providing valid answers to the PICO questions of this review, but they are listed underneath because they provide time point data for last observed apnea/ABD event post vaccination (72, 75, 78).

In a prospective observational study by Pourcyrous et al, 239 preterm infants at >2 months of age were immunized with the first dose of vaccine in the NICU (72). Cardiorespiratory manifestations were monitored for 72 h post-vaccination. Onset of new cardiorespiratory symptoms or worsening of cardiorespiratory status was noted 4 to 66 h after vaccination; 95 % occurred within 48 h of vaccination.

Pfister et al conducted an observational study of 78 very low birth weight premature infants (mean gestational age, 28 ± 2 weeks) given first dose DTaP-IPV-HiB vaccine before hospital discharge (75). Immunization was performed under continuous monitoring, 24 h preceding and 48 h after vaccination. Apnea/ABD events occurred in the first 48 h after vaccination and all infants returned to baseline within 48 to 72 h.

In a study performed by Clifford et al, seven preterm infants had recurrent apnea (both at first and at second vaccination) (78). Apnea after the second dose occurred 0–12 h post-vaccination in three infants, 24 h in three other infants and 30 h in the last infant.

For children with apnea after the first vaccination, is there an increased risk of apnea also after the second vaccination?

A study by **Anderson et al** mentioned previously on page 28, included 203 extremely preterm infants vaccinated during inpatient care (62). Apnea/ABD events were reported after the first vaccine dose for 17 (8%) of children. In twelve of these, apnea was assessed by the investigators as likely and five as possibly causally associated with immunization. All except one of the 17 infants were given a second dose and none of them suffered adverse events after this dose (Table 3).

In a sub analysis in **Furck et al**, mentioned previously on pages 28 and 31 forty-seven of the 473 infants initially included received a second vaccine dose while still in hospital (61). After the second vaccination, apnea and bradycardia occurred in two infants, neither of which had apnea or bradycardia after their first vaccination.

Clifford et al, mentioned previously on this page, included 38 Australian preterm infants (<37 weeks GA, median GA of 27 weeks) with reported apnea after first vaccination (78).

Seven (18 %) had recurrent apnea in timely connection with dose two at four months chronological age; two of the episodes were self-resolving and the other five responded to stimulation . None of the infants with a second apnea had recurrence of apnea after the third vaccine dose.

In **Flatz-Jequier et al**, not mentioned previously, preterm infants were studied after each of the first two vaccinations (73). Infants (mean GA at birth 26.6 weeks) that experienced apnea/ABD event after first vaccination were observed for apnea/ABD events after second vaccination, vaccinated with second dose at a mean age of 98.4 days. Among the 33 infants who had a significant apnea/ABD event after first vaccination, six (18 %) had a recurrent apnea/ABD event also after the second vaccination. Four of those six children were monitored again during the third vaccination, which was well tolerated by all. The only difference seen in this study between the infants with adverse reactions after the second vaccination compared with those without reaction was a previous reaction at the first vaccination. No reactions were seen in the group who did not react at the first vaccination.

Does vaccination of premature infants during the first months of life increase the risk of death?

All 26 studies included in this review were assessed for the outcome of reported fatal cases post-vaccination. Three studies reported fatal events (40, 41, 76).

A multicenter observational study by **D'Angio et al** mentioned previously under immunogenicity on page 22, included 369 preterm infants with GA < 32 weeks and a birth weight of 401-1500 g in a pre-specified, according to a specific vaccinated within a time-line, cohort (41). Infants had received a primary series of three PCV7 doses, given at least four weeks apart, and completed the study within the time windows defined. Two infants, neither in the time-line cohort, died of sudden infant death syndrome within 4 months after vaccination.

Omenaca et al mentioned previously under immunogenicity on page 24, studied adverse events in 137 preterm infants vaccinated with 10-valent PCV (Synflorix®) at 2, 4, 6 and 16-18 months age (40). One infant death associated with choking after aspiration was reported. The event occurred 25 days after the third vaccine dose and was assessed by the investigator as not causally related to vaccination.

In a multicentre retrospective cohort study by **DeMeo et al**, mentioned previously on page 32, described above, 13926 extremely preterm infants born at 28 weeks' gestation or less receiving at least one vaccination between the ages of 53-110 days (DTaP-IPV-HiB, DTaP-IPV-HepB and PCV7) were included (76). Five deaths were reported post-vaccination. Three of the five infants died within three days after vaccination and had a diagnosis associated with death unrelated to vaccination (bowel perforation, necrotizing enterocolitis and presumed sepsis, pneumonia and respiratory failure, respectively). No further information about the two remaining infants was available in the study report.

In summary, 0-23 % of preterm infants had apnea/ABD events in the 48-72 h post-vaccination period. There was a clear tendency of lower incidence of apnea/ABD events with higher GA at birth. There was no correlation between the chronologic age at first vaccination and the incidence of apnea/ABD events. Some infants had increased risk, especially infants with previous sepsis or previous lung disease. A causal relationship between vaccination and death was not found in any study.

Discussion

Premature infants are more vulnerable than full-term infants in several aspects. Depending on the degree of prematurity, premature infants may have incomplete transfer of maternal antibodies before birth (79). In addition, they have immature immune systems. This increases the risk of vaccine-preventable diseases such as whooping cough and invasive pneumococcal disease (1, 2). The first dose of pertussis vaccine given in infancy is known to protect against death due to pertussis (12, 80). Pneumococcal conjugate vaccines have on their side provided a dramatic impact on the incidence of invasive pneumococcal disease in infants globally (81).

In Norway and Sweden, premature infants have historically been recommended the same vaccines and schedules as full-term infants. However, due to the vulnerability and comorbidities of preterm infants, as well as the fear of adverse events after vaccination, the uptake and timeliness of vaccination has not been as good for this group as that of full-term infants. The aim of this literature review was to gain knowledge around the immunogenicity, effectiveness and safety of vaccination of premature infants against whooping cough and invasive pneumococcal disease in order to inform future vaccination policy for this risk group.

Immunogenicity

The evaluation of vaccine responses against pertussis and pneumococcal antigens in this report is mainly dependent on IgG ELISA results from different laboratories. It was decided to limit the selection of immunogenicity studies to those using standardized methods. Immunogenicity data from different laboratories should nevertheless be compared with caution due to the possibility of residual differences in methodology.

The ELISA method used for pertussis was standardized for vaccine trials during the 1990s and has subsequently been developed for seroepidemiological studies and for diagnostic purposes. Since there is no established correlate of protection for pertussis, the clinical relevance of immunogenicity results may be difficult to determine with certainty. There is consensus among regulatory authorities that the achievement of similar post-vaccination antibody levels, as those obtained in earlier vaccine efficacy trials on aP vaccines, is necessary and sufficient for licensure of a new pertussis vaccine, indicating that such levels may infer protection (82, 83).

Eight studies retrieved in this literature review reported immunogenicity data after vaccinating premature infants with aP-containing combination vaccines. Antibody levels were similar to that obtained for full-term infants. Results were also fairly consistent across studies and indicated that preterm infants have a good immune response to pertussis vaccination both with the use of different aP-containing combination vaccines and various vaccine schedules (2+1, 3+0 and 3+1). Preterm infants with GA below 31 weeks reach somewhat lower GMCs post primary series than older preterm and full-term infants. However, there is reason to believe that these lower levels still induce protection against whooping cough since antibody levels were in the same range as those obtained in earlier pertussis vaccine efficacy studies (82, 83). Furthermore, all infants, including the smallest preterms, showed a good response to booster dose.

Todays WHO standard for assessing pneumococcal vaccine immunogenicity (third generation ELISA using both CPS and 22F preadsorption) was established in 2003. A

common cut-off of 0.35 µg/ml has been chosen by consensus among experts, but there is still disagreement whether this threshold is a good general proxy indicating clinical protection. Both IgG ELISA and opsonophagocytic assay (OPA) should be performed in future immunogenicity studies (26).

Of the five studies on pneumococcal immunogenicity reviewed in this report, most showed that pneumococcal conjugate vaccines are immunogenic in preterm infants, also with the first dose given as early as 2 months age. Anti-pneumococcal IgG GMCs after the primary series are somewhat lower than for full-term infants, but most preterm infants develop anti-pneumococcal IgG above 0.35 µg/ml for the majority of serotypes included in the vaccines. Serotypes 3, 5, 6A, 6B and 23F elicit the lowest immune responses in several studies, especially in the preterm infants with the lowest GA. A 3+1 schedule with at least one of the intervals in the primary series longer than one month seems superior for reaching the threshold of 0.35 µg/ml during the high-risk period in the first 6 months of life, even though the number of infants studied is limited. The ability to respond to pneumococcal vaccines seems to be correlated with gestational age at birth and not with chronological age at vaccination, implying that vaccination should not be delayed unnecessarily.

Effectiveness and efficacy

We found two studies (one Danish and one Norwegian) on pertussis hospitalization and vaccine effectiveness. The effectiveness of aP vaccine on pertussis hospitalization was comparable in preterm and full-term children (difference not statistically significant) (1, 56). Among preterm children the vaccine effectiveness after the 3rd dose was 89-90%, but with wide confidence intervals.

The Norwegian study also included reported pertussis as an outcome and found statistically similar vaccine effectiveness in preterm and full-term infants (89% and 91% respectively) after the 3rd dose (1).

The studies included on aP vaccine effectiveness followed a 3, 5 and 12 months schedule. Effectiveness after the 1st dose was between 45% and 71-73%, with wide confidence intervals. We did not identify data on vaccine effectiveness after a 1st dose administered as early as 2 months of age. It is therefore difficult to estimate the effect of aP vaccines on clinically significant pertussis disease in the first six months of life when the first dose is given as early as two months age.

The especially high risk of pertussis among children aged less than six months and the consequence of severe pertussis complications among young infants is nevertheless in favor of vaccination from 2 months of age as long as it is safe and immunogenic (1, 84).

Only one study on vaccine efficacy and IPD was included in this review. The RCT demonstrated 100% vaccine efficacy against vaccine serotypes (PCV7) for IPD in preterm children. The schedule was 2, 4, 6 and 12-15 months of age. Those who had received 3 or 4 doses of PCV7 were included in the efficacy analysis. The study had few IPD cases and did not report vaccine efficacy after the 1st dose at age 2 months (53, 57).

The evidence of vaccine efficacy after one dose at 2 months is unknown, and recommend-ations on a 1st dose at 2 months should be based on studies on immuneogenicity and safety as well as epidemiological studies on the burden of disease in the youngest infants.

Safety

Apnea/ABD events in the post-vaccination period in this review is described in 0 - 23 % of children born prematurely (Table A8 in the appendix). There is a clear tendency for lower incidence of apnea/ABD events within 48-72 h post-vaccination, with higher gestational age at birth (Figure 3).

Percentage of children with increased and/or recurrent apnea/ABD events vary between studies, largely due to differences in methodology and definitions. In the only randomised controlled study in this review, no difference was seen between the vaccinated group and the controls (60). However, a large American study showed an increased need for respiratory support in preterm infants post-vaccination (76). Also, historical data on wP vaccines and clinical experience in Sweden (personal communication Andreas Ohlin, paediatrician at Örebro University Hospital, Feb 2018, abstract and oral presentation at Sachs' Children and Youth Hospital, Stockholm, Nov. 2015 presented by Karin Bäck) has shown that vaccination of extremely preterm babies can lead to cardiorespiratory instability. Therefore monitoring of preterm infants after vaccination is important.

Preterm infants with underlying co-morbidities may be more at risk for severe events after immunization. Hacking and co-workers describe that severe apnea leading to the requirement of respiratory support appeared to be associated with immunization, particularly in ELBW infants with significant lung disease and those who have previously experienced septicemia (68). This is also found in a small study by Wilinska et al (63). It can be concluded that there are some risk groups, especially preterm infants with previous sepsis, previous clinical significant apneas or previous lung disease. Such infants in addition to infants born before GA 30+0 weeks and those who are cardiorespiratory unstable at the time of vaccination, may need prolonged observation after vaccination.

All 26 studies included in this review were assessed for the outcome of reported fatal cases post-vaccination. There were in total three studies that reported fatal cases (40, 41, 76). Eight fatal cases were reported in these three studies. Six of these cases are described in detail and a causal relationship between vaccination and death has not been found.

Only one study indicated that multiple vaccines given concurrently, relevant for the Swedish and Norwegian NIP (Infanrix® plus Prevenar®) may give more apnea and bradycardia than DTaP-containing vaccine alone (61). However the study design included low number of infants and had significant difference between the study groups and when correcting for age the difference was no longer significant between compared groups. Prospective studies are needed to make any conclusions if there is an increased risk of apnea/ABD events when multiple vaccines, especially conjugated vaccines, are given concurrently.

Most studies, have not shown increased risk of apnea at second vaccination for infants with apnea/ABD event after the first vaccination. However, some preterm infants with reported apnea after first vaccination also had apnea at the second vaccination at four month of age (73, 78). There may be a need for monitoring infants with a history of apnea post dose 1 also after dose 2, as best decided by the child's pediatrician.

Conclusion

The risk of pertussis and invasive pneumococcal disease is high in preterm infants. Acellular pertussis and pneumococcal conjugate vaccines are immunogenic and effective in preterm infants.

The benefit of vaccination clearly outweighs the risks, and vaccination should in general not be withheld or delayed. Vaccination starting at approximately 8 weeks chronological age decreases the risk of severe disease, especially with regards to pertussis. As there is waning of immunity, a booster in the second year of life is recommended.

While the infants' chronological age at vaccination does not seem to affect the risk of cardiorespiratory side effects, the GA at birth with lower risk in higher GA groups. Preterm infants with underlying co-morbidities may be more at risk for severe events after immunization. Infants born before 30+0 weeks of gestation, infants with significant lung disease, those who have previously experienced septicaemia and preterm infants that are cardiorespiratory unstable at the time of vaccination, need cardiorespiratory monitoring for at least 48 h post-vaccination.

A causal relationship between vaccination and death has not been found in any study.

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Appendix

Tables

Table A1 Anti-PT and anti-Prn IgG GMC 1 month after primary series

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Anti-PT EL.U/ml	Anti-Prn EL.U/ml
Casadei Pistilli 1995 (28)	Prospective controlled	26-37 (32)	aP (Acelluvax®)	Primary 2 + 4 + 6 / 3 + 5 + 7 / 4 + 6 + 8 months	87	90.6	145.6
		Above 37			83	129.7	131.9
Faldella 1998 (29)	Prospective controlled	Below 30+6 (29.3)	GSK DTaP-HBV (Produced by GSK)	Primary 3 + 5 months Booster 11 months	10	21.9	82.3
		31-35 (33.2)			24	41.7	177.8
		38 - 42			28	37.1	182.0
Slack 2004 (31)	Prospective controlled	Below 32 (29.1)	DTaP-Hib (Infanrix-Hib®)	Primary 2 + 3 + 4 months	130	21.0	82.6
		Above 36+6			54	33.4	86.6
Slack 2005 (30)	Prospective controlled	Below 32 (28.5)	DTaP-IPV-Hib (Pediacel®)	Primary 2 + 3 + 4 months	50	76.8	38.8
		Above 36+6			60	86.4	34.1
Omenaca 2005 (32)	Prospective controlled	24-36 (31.1)	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 16-18 months	93	61.3	155.3
		37-42			89	60.4	200.3
Vasquez 2008 (33)	Prospective observational	24-35 (29.5)	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 18-24 months	79	25.5	110.1
		30-36 (32.8)			82	36.6	115.7
Vermeulen 2010 (34)	Prospective observational	25-30 (28)	DTaP-IPV (Tetravac®)	Primary 2 + 3 + 4 months	18	38.0	n.a.

Table A2 Anti-PT and anti-Prn IgG GMC 1 month after booster

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Anti-PT EL.U/ml	Anti-Prn EL.U/ml
Faldella 1998 (29)	Prospective controlled	Below 30+6 (29.3)	GSK DTaP-HBV (Produced by GSK)	Primary 3 + 5 months Booster 11 months	10	40.7	173.8
		31-35 (33.2)			24	57.5	331.1
		38 - 42			28	66.0	501.2
Omenaca 2007 (35)	Prospective controlled	24-36 (31.1)	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 16-18 months	94	58.9	456.5
		37-42			89	63.1	544.4
Vasquez 2008 (33)	Prospective observational	24-35 (29.5)	DTaP-IPV-Hib-HepB (Infanrix hexa®)	Primary 2 + 4 + 6 months Booster 18-24 months	59	44.4	312.5
		30-36 (32.8)			56	56.1	418.3

Table A3 Anti-pneumococcal IgG GMC per serotype 1 month after primary series

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Anti-pneumococcal IgG GMC per serotype (µg/ml)												
						1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
D'Angio 2010 (41)	Prospective observational	23-32 (27.8)	PCV7	Primary 2 + 4 + 6 months	244	-	-	1.78	-	-	1.9	-	1.63	6.02	2.08	-	2.56	1.41
Moss 2010 (44)	Prospective controlled	23-35 (28.6)	PCV7	Primary 2 + 3 + 4 months	132	-	-	1.02	-	-	0.2	-	0.94	3.8	1.05	-	1.67	0.58
		36-42 (39.7)			53	-	-	1.61	-	-	0.29	-	1.07	3.8	1.39	-	2.64	1.46
Martinon-Torres 2015 (43)	Prospective observational	Below 37 (30.8)	PCV13	Primary 2 + 3 + 4 months Booster 12 months	99	1.26	0.83	1.96	0.56	1.22	0.73	2.14	1.26	7.48	1.93	2.85	2.21	0.86
		Above 36+6 (39.5)			97	1.79	0.86	2.46	1.03	2.01	1.3	3.02	1.7	6.08	1.93	3.35	3.05	1.36
Kent 2016 (42)	Randomized controlled	24-34 (29.6)	PCV13	Primary 2 + 4 months Booster 12 months	64	0.76	0.42	0.97	0.29	0.49	0.16	1.51	0.44	3.56	0.96	0.84	2.85	0.32
		23-34 (30)		Primary 2 + 3 + 4 months Booster 12 months	59	0.84	0.54	1.12	0.33	0.63	0.35	1.35	0.84	5.66	1.12	2.03	2.48	0.48
		23-34 (30)		Primary 2 + 4 + 6 months Booster 12 months	68	1.58	0.62	1.36	0.63	2.02	0.98	2.95	1.02	8.49	1.46	1.68	3	1.11
Omenaca 2011 (40) and GSK technical reports (45, 46)	Prospective controlled	27-30	PCV10	Primary 2 + 4 + 6 months Booster 16-18 months	41	0.97	-	1.53	1.45	-	0.85	1.87	1.43	3.52	3.28	-	3.6	1.05
		31-36			80	1.1	-	1.88	1.93	-	1.11	2.37	1.69	3.28	4.86	-	4.8	1.33
		≥ 37			129	1.35	-	2.42	2.31	-	1.18	2.69	2.41	3.71	5.22	-	4.56	1.54

Table A4 Anti-pneumococcal IgG GMC per serotype 1 month after booster

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Anti-pneumococcal IgG GMC per serotype (µg/ml)											
						1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Martinon-Torres 2015 (43)	Prospective observational	Below 37 (30.8)	PCV13	Primary 2 + 3 + 4 months Booster 12 months	99	3.32	0.52	2.57	2.63	5.64	4.42	4.25	2.3	9.24	2.37	5.57	7.38	2.45
		Above 36+6 (39.5)			97	4.09	0.57	3.97	3.72	7.84	7.27	5.13	3.06	11.02	2.81	8.84	11.67	4.03
Kent 2016 (42)	Randomized controlled	24-34 (29.6)	PCV13	Primary 2 + 4 months Booster 12 months	64	4.05	1.2	2.74	1.71	8.34	4.39	4.01	2.34	14.96	1.88	9.32	10.36	4.51
		23-34 (30)		Primary 2 + 3 + 4 months	59	3.75	1.18	2.51	1.57	6.49	4.5	3.68	1.92	13.21	1.46	6.16	7.38	3.58
		23-34 (30)		Primary 2 + 4 + 6 months	68	2.26	0.86	1.82	1.33	5.21	3.91	3.7	1.73	8.76	1.5	5.03	6.01	3.1
Omenaca 2011 (40) and GSK technical reports (45, 46)	Prospective controlled	27-30	PCV10	Primary 2 + 4 + 6 months Booster 16-18 months	41	1.57	-	2.98	1.84	0.7	2.44	3.11	2.87	4.88	9.51	0.65	6.83	2.7
		31-36			66	1.74	-	3.67	2.38	0.77	2.46	4.16	3.47	5.14	13.2	0.93	9.78	3.45
		≥ 37			118	1.98	-	4.23	2.58	0.79	2.67	3.93	4.17	5.98	12.38	1.1	9.72	3.3

Table A5 Proportion with anti-pneumococcal IgG GMC > 0.35µg/ml (> 0.20 µg/ml) 1 month after primary series

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Proportion with anti-pneumococcal IgG GMC > 0.35µg/ml (> 0.20 µg/ml) (%)												
						1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
D'Angio 2010 (41)	Prospective observational	23-32 (27.8)	PCV7	Primary 2 + 4 + 6 months	90	-	-	95.8	-	-	76.3	-	94.1	97.5	97.5	-	99.2	79.7
Moss 2010 (44)	Prospective controlled	23-35 (28.6)	PCV7	Primary 2 + 3 + 4 months	132	-	-	88	-	-	39	-	86	96	91	-	96	71
		36-42 (39.7)			53	-	-	96	-	-	38	-	90	98	96	-	100	96
Omenaca 2011 (40)	Prospective controlled	28.6 (27-30)	PCV10	Primary 2 + 4 + 6 months Booster 16-18 months	41	97.6	-	97.6	100	-	92.7	100	97.6	100	100	-	100	95.1
		33.5 (31-36)			80	100	-	98.8	100	-	95.1	100	100	100	100	-	100	96.3
		≥ 37 wks (37-42)			129	99.2	-	100	100	-	93.9	100	100	100	98.5	-	100	95.4
Martinon-Torres 2015 (43)	Prospective observational	Below 37 (30.8)	PCV13	Primary 2 + 3 + 4 months Booster 12 months	99	94	86	97	72	83	73	99	97	100	97	99	99	86
		Above 36+6			97	96	91	99	91	95	88	99	97	100	97	99	99	93
Kent 2016 (42)	Randomized controlled	24-34 (29.6)	PCV13	Primary 2 + 4 months	64	85	61	92	36	58	20	91	59	94	88	83	97	47
		23-34 (30)		Primary 2 + 3 + 4 months	59	80	66	88	47	72	52	97	85	98	87	95	100	63
		23-34 (30)		Primary 2 + 4 + 6 months	68	94	80	94	74	94	78	100	93	99	96	96	100	83

Table A6 Proportion with anti-pneumococcal IgG GMC > 0.35µg/ml (> 0.20 µg/ml) 1 month after booster dose

Reference	Study design	GA in weeks (mean)	Vaccine	Schedule	N	Proportion with anti-pneumococcal IgG GMC > 0.35µg/ml (> 0.20 µg/ml) (%)												
						1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Omenaca 2011 (40)	Prospective controlled	28.6 (27-30)	PCV10	Primary 2 + 4 + 6 months Booster 16-18 months	41	100	-	100	100	-	100	100	100	100	100	-	100	97.6
		33.5 (31-36)			80	100	-	100	100	-	98.5	100	100	100	100	-	100	100
		Above 36+6 (37-42)			129	99.2	-	100	100	-	100	100	100	100	99.2	-	100	99.2
Martinon-Torres 2015 (43)	Prospective observational	Below 37 (30.8)	PCV13	Primary 2 + 3 + 4 months Booster 12 months	99	100	71	100	100	100	98	100	100	100	100	100	100	99
		Above 36+6 (39.5)			97	100	79	100	100	100	100	100	100	100	99	100	100	100
Kent 2016 (42)	Randomized controlled	24-34 (29.6)	PCV13	Primary 2 + 4 months Booster 12 months	64	98	89	100	98	98	98	98	98	100	100	100	100	98
		23-34 (30)		Primary 2 + 3 + 4 months	59	100	93	98	97	98	97	100	98	100	97	100	100	100
		23-34 (30)		Primary 2 + 4 + 6 months	68	100	87	99	93	100	99	100	99	100	94	100	100	97

Table A7 Vaccine effectiveness of pertussis and invasive pneumoccal disease

Reference	Study design and groups	Vaccine /schedule	Age at vaccination	Effectiveness by dose (95%CI) Preterm full-term	Outcome, comment
Hviid 2009 (56) Denmark	National cohort Preterm, GA 20-36 weeks, N= 59311 Full-term, GA 37-41 weeks, N=820113	Whole cell, SSI, 5*-, 9 weeks, 10 months. *: 1/2 dose Years 1990-96.	preterm mean age 1st dose 11.8 weeks, 2nd dose 21.4 weeks, 3rd dose 11.5 months	1st -23(-90;-21) 36(20;49) 2nd 47(14;67) 66(58;73) 3rd 95(62;99) 87(80;91)	Pertussis hospitalization, compared to full-term infants a reduced response was observed after the 1st dose, but not after the 2nd and 3rd dose
		Acellular, pertussis toxoid vaccine, 40 µg, Baxter, 3, 5 and 12 months. Years 1997-2004	preterm mean age 1st 4,7 months, 2nd 6.8 months, 3rd 13.3 months	1st 45(12;65) 51(41;60) 2nd 77(57;88) 85(81;89) 3rd 90(69;97) 96(93;98)	Pertussis hospitalization, preterm vs. full-term similar effectiveness
Riise 2017 (1) Norway	National cohort Preterm, GA 23-36 weeks, N=36913 Full-term, GA 37 weeks or older, N=676253	Acellular, Infanrix and Infanrix-polio+Hib, GSK, Rixensart, Belgium 3, 5 and 12 months, Year 1998-2010	age at administration is not reported	1st 71.2(30;88) 60.7(46;72) 2nd 93.8(72;99) 90.6(82;95) 3rd 88.7(54;97) 91.1(79;96)	Pertussis hospitalization, similar vaccine effectiveness, the model also included interaction terms between number of vaccine doses and a prematurity indicator variable
				1st 73.0(44;87) 52.5(46;72) 2nd 80.1(64;89) 81.9(75;87) 3rd 93.0(86;97) 88.8(84;92)	Pertussis disease, preterm and full-term had similar vaccine effectiveness
Shinefield 2002 (53) USA Black 2002 (57) USA	RCT, GA 32 to < 38 weeks, N=4340	7-valent pneumococcal conjugate vaccine (PCV7; Prevenar) or meningococcal C conjugate vaccine (MCV) concomitantly with routine childhood vaccines	2, 4, 6 and 12-15 months.	Nine children had invasive pneumococcal disease in the MCV group and zero in the PCV7 group, giving a vaccine efficacy of 100%.	Invasive pneumococcal disease caused by vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F. For the main efficacy analysis, the disease had to be caused by vaccine serotypes and with disease onset more than 14 days after the 3rd dose in addition to occurring in a subject vaccinated according to protocol. Children at least 16 months of age were considered fully vaccinated after receipt of the 4th dose.

Table A8 Studies included in the safety assessment of apnea/ABD events after first vaccination

Reference	Study design	GA (weeks, mean)	N	Vaccine	Age at first vaccination	Incidence of apnea/ Apnea Bradycardia Desaturation, within 48-72 hours post-vaccination period
Anderson 2013 **(62)**	Retrospective observational	26.3	203	DTaP-HepB (Infanrix®-hepB) DTaP-IPV+Hib+HepB (Infanrix hexa®) Menb-Hib(Pedvax®) PCV7 (Prevenar®)	71 days (mean)	8.4 %
Buijs 2012 **(74)**	Prospective observational	30.8	41	DTaP-IPV-Hib (Pediacel®) DTaP-IPV-Hib-HepB (Infanrix hexa®) PCV7 (Prevenar®)	9.2 weeks (mean)	0
Carbone 2008 **(60)**	Randomized controlled	26.9	93	DTaP (Infanrix®) DTaP-IPV-HepB (Pediarix®)	57.5 days (mean)	16.1 %
Ellison 2005 **(58)**	Prospective observational	26.4	48	DTaP (Infanrix®) Hib-conj-Men-HepB (Comvax®)	76 days (mean)	23 %
Faldella 2007 **(71)**	Prospective observational	28.4	81	DTaP–IPV–Hib–HepB	73 days (mean)	6.2 %
Furck 2010 **(61)**	Prospective observational	27.6	260 group C	DTaP-IPV+Hib+HepB (Infanrix hexa®) PCV7 (Prevenar®)	9.8 weeks (median)	15.0 %
Schulzke 2005 **(59)**	Retrospective observational	28	53	DTaP- IPV-HIB (Infanrix®-IPV+Hib) or DTaP-IPV+Hib+HepB (Infanrix hexa®)	67 days (mean)	13 %
Wilinska 2016 (a) **(63)**	Prospective observational	27	73	DTaP-IPV-Hib (Infanrix-IPV-HIB®) PCV7 (Prevenar®)	49 days (mean)	7 %
Wilinska 2016 (b) **(63)**		30 (29-36)	65		44 days (mean)	2 %

Search documentation

Database: Cochrane Library Date: June 2nd 2017 Database provider: Wiley			
Search #	Search field	Search terms	Number of hits
Population			
1	MeSH	MeSH descriptor: [Infant, Low Birth Weight] explode all trees	2074
2	MeSH	MeSH descriptor: [Infant, Premature] explode all trees	3315
3	Title/Abstract	born near/1 premature*:ti or born near/1 premature*:ab	194
4	Title/Abstract	(premature or preterm or pre-term) next (birth or infant or infants or newborn or newborns or baby or babies or child or children or neonate or neonates):ti or (premature or preterm or pre-term) next (birth or infant or infants or newborn or newborns or baby or babies or child or children or neonate or neonates):ab	8551
5	Title/Abstract	born next (preterm or pre-term):ti or born next (preterm or pre-term):ab	137
6	Title/Abstract	prematurity or preterms:ti or prematurity or preterms:ab	1557
7	Title/Abstract	immature next (infant or infants):ti or immature next (infant or infants):ab	37
8	Title/Abstract	"low birth weight" or LBW or VLBW:ti or "low birth weight" or LBW or VLBW:ab	3005
9		#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	12068
Intervention			
10	MeSH	MeSH descriptor: [Immunization] explode all trees	4802
11	MeSH	MeSH descriptor: [Vaccines] explode all trees	8806
12	Title/Abstract	vaccin* or immunization or immunogenicity or "immune response":ti or vaccin* or immunization or immunogenicity or "immune response":ab (Word variations have been searched)	18315
13		#10 OR #11 OR #12	19585
Combined search			
14		#9 AND #13	166
15		#14. Filter: publication year 1986-2017	165*/**

*Cochrane Database of Systematic Reviews: 11, Database of Abstracts of Reviews of Effect: 1, Cochrane Central Register of Controlled Trials: 150, Cochrane Methodology Register: 1, Health Technology Assessment Database: 1, NHS Economic Evaluation Database: 1
**Result exported to EndNote

Database: Scopus Database provider: Elsevier		Date: June 2nd 2017	
Search #	Search field	Search terms	Number of hits
Population			
1	Title, Abstract, Keywords	TITLE-ABS-KEY ((born W/1 premature*) OR ((premature OR preterm OR pre-term) PRE/1 (birth OR infant OR newborn OR baby OR child OR neonate)) OR (born PRE/1 (preterm OR pre-term)) OR prematurity OR preterms OR "immature infant" OR "low birth weight" OR lbw OR vlbw)	173684
Intervention			
2	Title, Abstract, Keywords	TITLE-ABS-KEY (vaccin* OR immuni?ation OR immunogenicity OR "immune response")	776692
Combined searches			
3	Title, Abstract, Keywords	#1 AND #3	3812
4		#3. Filtered by publication year 1986-2017	3523*

*Result exported to EndNote

Database: PubMed Database provider: NLM		Date: June 2nd 2017	
Search #	Search field	Search terms	Number of hits
Population			
1	MeSH	"Infant, Low Birth Weight"[Mesh] OR "Infant, Premature"[Mesh]	68823
2	Title/Abstract	born prematurely[Title/Abstract] OR prematurely born[Title/Abstract] OR preterm birth[Title/Abstract] OR premature birth[Title/Abstract] OR born preterm[Title/Abstract] OR premature infants[Title/Abstract] OR premature infant[Title/Abstract] OR premature neonates[Title/Abstract] OR premature neonate[Title/Abstract] OR premature babies[Title/Abstract] OR premature baby[Title/Abstract] OR premature child[Title/Abstract] OR premature children[Title/Abstract] OR premature newborn[Title/Abstract] OR premature newborns[Title/Abstract] OR pre-term infants[Title/Abstract] OR pre-term infant[Title/Abstract] OR preterm	90071

		infants[Title/Abstract] OR preterm infant[Title/Abstract] OR pre-term children[Title/Abstract] OR pre-term child[Title/Abstract] OR preterm children[Title/Abstract] OR preterm child[Title/Abstract] OR pre-term babies[Title/Abstract] OR pre-term baby[Title/Abstract] OR preterm babies[Title/Abstract] OR preterm baby[Title/Abstract] OR pre-term newborns[Title/Abstract] OR pre-term newborn[Title/Abstract] OR preterm newborns[Title/Abstract] OR preterm newborn[Title/Abstract] OR pre-term neonate[Title/Abstract] OR pre-term neonates[Title/Abstract] OR preterm neonate[Title/Abstract] OR preterm neonates[Title/Abstract] OR prematurity[Title/Abstract] OR immature infants[Title/Abstract] OR immature infant[Title/Abstract] OR preterms[Title/Abstract] OR low birth weight[Title/Abstract] OR LBW[Title/Abstract] OR VLBW[Title/Abstract]	
3		#1 OR #2	113606
Intervention			
4	MeSH	"Immunization"[Mesh] OR "Vaccines"[Mesh]	286697
5	Title/Abstract	vaccine[Title/Abstract] OR vaccines[Title/Abstract] OR vaccination[Title/Abstract] OR vaccinations[Title/Abstract] OR immunization[Title/Abstract] OR immunisation[Title/Abstract] OR immunogenicity[Title/Abstract] OR immune response[Title/Abstract]	407959
6		#4 OR #5	500865
Combined search			
7		#3 AND #6	1728
8		#7. Filters activated: Publication date from 1986/01/01	1589*

*Result exported to EndNote

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