Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Elena Chiappini, Chiara Petrolini, Elena Sandini, Ameila Licari, Lorenza Pugni, Fabio A Mosca & Gianluigi Marseglia (2019): Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology., Expert Review of Vaccines, DOI: 10.1080/14760584.2019.1604230

To link to this article: https://doi.org/10.1080/14760584.2019.1604230

Accepted author version posted online: 05 Apr 2019.

Publisher: Taylor & Francis

Journal: *Expert Review of Vaccines*

DOI: 10.1080/14760584.2019.1604230

Review

Update on vaccination of preterm infants: a systematic review about safety and efficacy/effectiveness. Proposal for a position statement by Italian Society of Pediatric Allergology and Immunology jointly with the Italian Society of Neonatology.

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Abstract

Introduction: Preterm infants (PIs) are at increased risk of vaccine preventable diseases (VPDs). However delayed vaccination start and low vaccine coverage are still reported.

Areas covered: This systematic review includes 37 articles on preterm vaccination published in 2008-2018 in PubMed. Both live attenuated and inactivated vaccines are safe and well tolerated in PIs. Local reactions, apnea and reactivity changes are the most frequently reported adverse events. Lower gestational age and birth weight, preimmunization apnea, longer use of continuous positive airway pressure (CPAP) are risk factor for apnea. The proportion of PIs who develop protective humoral and cellular immunity is generally similar to full terms although later gestational age is associated to increased antibody IgG concentrations (i.e. against certain pneumococcal serotypes, influenza, hepatitis B virus and poliovirus 1) and increased mononuclear cells proliferation (i.e. after inactivated poliovirus). However vaccinated PIs have lower hospitalizations, ambulatory visits and notifications of VPDs.

Expert opinion: PIs can be safely and adequately protected by available vaccines with the same schedule used for full terms. However data at this regard have been almost exclusively retrieved by studies using a 3-dose primary series for pneumococcal and hexavalent vaccines, while further studies are needed regarding the 2+1 schedule. Apnea represents a nonspecific stress response in PIs, thus those hospitalized at 2 months should have cardio-respiratory monitoring for 2 days after their first vaccination.

Keywords: preterm infant, vaccinations, safety, immunogenicity, efficacy, effectiveness.

Article highlights

- Despite recommendation to vaccinate preterm infants at the same scheduled age as full-term children, a delay is commonly experienced in these population.
- Preterm children may experience vaccine preventable diseases, which tend to be more severe, due to an impaired immune response
- Based on our research the overall safety and tolerability of the scheduled vaccines showed no differences in preterm and full-term infants, and live attenuated vaccines as well are considered safe.
- Postponing vaccination is justified only in clinically unstable infants
- Preterm infants already hospitalized at the time of first vaccination should receive their first dose in the neonatal ward, particularly those infants born≤31 weeks of gestation, those with a birth weight 2 ≤kg, those suffering from apnoea/bradycardia and those with severe bronchopulmonary dysplasia. There should then be monitoring of the clinical conditions and the cardio-respiratory system as inpatients for two days.

1- Introduction

Among the nearly 13 million preterm births occurring each year worldwide, approximately 500,000 occur in Europe where the preterm birth rate varies between 5% and 9% [1,2]. In Italy, the proportion of preterm (<37 weeks gestation) and very preterm (<32 weeks gestation) births are about 7% and 1%, respectively, corresponding approximately to 38,000 and 5500 live births annually [3]. -Preterm infants (PIs) may develop several long term adverse consequences, such as cerebral palsy, sensory deficits, respiratory illnesses, cognitive and behavioral disabilities [4–6], and are at increased risk of infections due to defects in external barriers, lower levels of passively transferred maternal antibody, innate and adaptive immunity impairment, with the latter resulting in suboptimal B and T cell function [7-9]. Therefore, preterm infants may experience vaccine preventable diseases (VPD) with increased frequency and severity in the first months of life [10–12], such as pertussis [13], pneumococcal infections [14], and influenza [15].
According to the international recommendations preterm infants, who are otherwise healthy, should follow the same vaccination schedule used for full-term infants, based on their chronological age rather than corrected gestational age and regardless of their birth weight. Moreover, vaccine dosages normally given to full term infants should not be reduced or divided when given to PIs [16-21].
However, low vaccination coverage and schedules' delayed start have been reported in PIs [22-29]. Delayed beginning of vaccines' schedules seems to be associated with low birthweight, lower gestational age, hospitalization after discharge from the neonatal intensive care units (NICUs), paternal/maternal unemployment, increasing numbers of siblings in the family, lower socioeconomic status and ethnicities other than white [22, 30]. Fear of a weaker response to vaccines or of adverse events in preterm infants could be other reasons for the delay [31–34]; however several studies show that PIs are generally able to mount a protective adaptive immune response to most vaccines used in infant vaccination programmes [31, 35-36]. Moreover even if some adverse events like apnea and/or bradycardia have been reported to occur between 0 and 47% following vaccination in PIs, they are self-limiting non specific stress responses that commonly complicate other medical procedures without any long term sequelae [33-39]. The aim of the present study is to systematically review the available literature about vaccinations in PIs focusing on safety and immunogenicity/effectiveness.

2- Methods

A literature search was performed covering papers published from January 1st 2008 to 31st October 2018. The PubMed MEDLINE and Cochrane Library databases were systematically searched using the following terms combined using Boolean operators ("infant, preterm"[MeSH Terms]) AND "vaccination"[MeSH terms]). Only papers published in English were included. Reference lists of the retrieved articles were reviewed to identify other possible pertinent publications. Titles and abstracts of studies identified during the primary search were screened for inclusion, and papers containing prospective or retrospective

observational studies and clinical trials focusing on vaccination in PIs were included in this review. We included also studies assessing a comparison between full-term and PIs. Articles not pertinent to vaccines in PIs, commentaries, letters, case series (including less than 10 infants), case reports, reviews, duplicates and papers not written in English were excluded. Data were independently extracted by two different authors (CP and ES) and any disagreements or conflicts were discussed with a third author (EC). The following data were extracted for each study: year of publication, study type and location, gestational age (GA) of the study population, number of children included, type of vaccination administered, study outcomes (i.e.: laboratory indicators of immunogenicity; clinical indicators of efficacy or effectiveness; reported adverse events for vaccines' safety), follow up and possible biases and limitations of the study. The PRISMA Statement has been used for reporting of the systematic review filling a 27-item checklist (Table 1) and a four-phase flow diagram (Figure 1) [40].

3-Results

Initially, 61 studies were identified through the search strategy (Table 2) and additionally another 15 studies were retrieved after evaluation of the studies' references; 39 articles were excluded relying on studies' abstracts or titles because they didn't satisfy eligibility criteria (Figure 1).
Finally, 37 relevant articles were included in this systematic review: 24 articles had as the main objective vaccines' safety in preterm infants [34-35, 41-62]; while 18 and 4 articles investigated immunogenicity [31, 41-42, 46-50, 53-54, 63-67, 70,72,73] and effectiveness [45, 68-69, 71] as the main objective respectively.

3.1-Studies on vaccine safety.

Safety was the main objective of 24 studies, overall including 789,165 preterm infants (Table 3) [34, 35, 41-62].

3.1.1-Studies on live attenuated vaccines'safety.

Live attenuated vaccines were investigated in 6 studies [41-46]. Measles vaccination's safety was evaluated by *Ichikawa et al.* in a prospective study including 17 PIs <34 weeks of gestation who received an early vaccination at 6 months of age in order to prevent the disease. No adverse reaction was reported, but the number of vaccinated infants in the present study was limited [41].
Saroha et al. in a prospective randomized trial found that Bacille Calmette-Guérin (BCG) vaccine may be safely given at birth to moderately PIs (31–33 weeks). The only complication observed in 3.4% of the 117 patients enrolled in the study was left axillary lymphadenopathy [42]. Another two studies aimed to determine the safety of BCG vaccination [43-44]. *Kjærgaard et al*. performed two randomized multicenter clinical trials in Denmark, overall involving 4262 children, of which 144 were aged 32 to 37 weeks of gestation. No difference was observed on either susceptibility of infections, growth, body composition or psychomotor development between patients that received or did not receive BCG vaccination at birth [43-44].
Two studies investigated safety of rotavirus vaccination in PIs [45-46]. A large population-based study by *Rouè et al.* showed no significant difference in severe adverse events incidence following rotavirus vaccination between preterm and full-term infants. [45]. *Omenaca et al*. in their phase IIIb randomized double blinded placebo-controlled trial including 165 PIs vaccinated with live-attenuated rotavirus observed a similar frequency of severe adverse events (SAEs) in the vaccinated and placebo groups (P = 0.266) [46]. The proportion of all and grade 3 solicited general adverse events (AEs) reported during the 15-day postvaccination follow-up period were similar in both the vaccinated and placebo groups, with irritability as the most common AE [46]. The most commonly reported unsolicited AEs were fever, irritability, gastrointestinal disorders and upper respiratory tract infections.

3.1.2-Studies on inactivated or subunit vaccines' safety.

Inactivated or subunit vaccines were investigated in 18 studies [34-35,47-62] (Table 3). *Tsuda et al.* in a prospective cohort study reported local redness as the only AE after *Haemophilus influenzae* (Hib) vaccination in 54 PIs [47]. Influenza A/H1N1 MF59-adjuvanted vaccination were studied by *Esposito et al*. in an open randomized trial including 101 infants. No difference in safety and tolerability were found between term and PIs. The only systemic adverse event consistently observed in all groups was fever, which was significantly more frequent after the first dose than after the second in all the groups [48].

An open-label prospective multicenter randomized controlled trial by *Kent et al.* evaluated the safety of the conjugate vaccine containing thirteen pneumococcal serotypes (PCV13) on PIs aged <35 weeks of gestation with different timing of administration: reduced schedule of PCV13 (at 2 and 4 months of age), accelerated schedule (at 2, 3 and 4 months of age) and extended schedule (at 2, 4 and 6 months of age) [49]. There was no significant difference in the frequency or severity of local and systemic AEs between vaccination schedules at any time point and no serious AEs were considered vaccine related [49].
Several studies found a similar or sometimes lower frequency of AEs related to multivalent vaccines in PIs compared to full term infants, probably as the result of a reduced immune response and ability to mount an inflammatory process [50-54].
Klein et al. described adverse events related to diphtheria, tetanus, acellular pertussis (DTaP), hepatitis B (HBV), inactivated polio (IPV), pneumococcal vaccine (PCV) during the 30 days after each of 3 doses, comparing the frequency of AEs in preterm and full-term infants in 83 patients: no increase of medical attended events (MAEs) was found in the two groups comparing to the control period (postvaccination days 31–60)[50]. Moreover, in one retrospective study by *McCrossan et al*. none of the 344 PIs displayed an AE [51]. In a large observational self-controlled case series by *Wilson et al.* children acted as their own control counting the rate of events per day in an "at risk" period (i.e. immediate 3 days post vaccination at 2 months of age with DTaP-HBV-IPV-PCV) compared with the rate of events in a control period during which it would be unlikely that the exposure produced the outcome (9–18 days post-vaccination)[52]. Overall 771,453 children, of which 49,220 children <37 weeks of GA and 7,392 children ≤ 32 weeks of GA, were enrolled in the study, showing a progressive reduction in admission to emergency room department or to hospital 3 days after vaccination at 2 months of age with increasing category of prematurity [52].
Omeñaca et al. enrolled 313 term and PIs in an open controlled prospective multicenter study. Local symptoms in the 4 days following the combined *Haemophilus influenzae* type B-*Neisseria meningitidis* serogroup C vaccine (Hib-MenC-TT) were lower compared with DTaP-HBV-IPV-PCV vaccine [53]. Large injection-site swellings after the booster dose were reported less frequently in the preterm group than in full-term group, occurring mainly at the DTaP-IPV injection site. No difference in grade 3 AEs were found between groups [53]. Similarly, in another study, assessing the safety of the 10-valent pneumococcal non typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in 149 term and 137 PIs, the incidence of solicited general symptoms (i.e: fever, irritability, drowsiness, loss of appetite) was generally similar across the groups [54]. Considering local symptoms, such as redness or swelling, their incidence was lower in PIs than in the term group [54]. None of the reported serious AEs was considered causally related to vaccination. The most frequently reported unsolicited AEs in all groups were upper respiratory tract infections, together with injection site nodules after primary and booster vaccination in the term group. One episode of apnea was reported in a PI after the first primary dose, but it was not considered to be associated to the vaccination and resolved without sequelae [54].
Wilinska et al. studied 138 children born before 37 weeks of gestation (73 born ≤28 weeks GA and 65 born >28 weeks GA), who underwent vaccination as inpatient and monitored their cardiac and respiratory functions as well as body temperature over 72 hours after DTaP-IPV-PCV-Hib vaccination. Apnea and changes in reactivity (i.e. change in infants' behavior valued by Multidimensional Neonatal Infant Pain Scale-NIPS) were the relatively most frequent reported AEs. Infants who experienced apneas had significantly more frequently late onset sepsis and a history of longer use of continuous positive airway pressure (CPAP)[55].
Several studies found an increased incidence of apnea in PIs following vaccination with DTaP-IPV-PCV-Hib vaccine [34-35, 56-60]. Incidence of these reactions even if different in the reported studies declined with age, supporting the hypothesis that these cardiorespiratory events essentially represent nonspecific stress responses of very low birth weight (VLBW) PIs, whose maturity progresses with chronological age [34-35, 56-60]. In the study by *Anderson et al*. the incidence of apnea after the first DTaP-IPV- PCV-Hib vaccination was 8.4% in extremely PIs, while there was no reaction following the second dose at 4 months. Infants with apnea following the 2-month vaccine displayed significantly lower GA and birth weight. Unfortunately, only 50% cases with apnea after the first vaccination dose at 2 months were evaluated through a cardiorespiratory monitoring after the second dose at 4 months [56]. Similarly, in a prospective study by *Furck et al.* the risk of apnea decreased with increasing GA [57]. In this study the frequency of apnea/bradycardia after the first dose of DTaP-IPV-PCV-Hib vaccine in 473 preterm infants with a weight

<1500 g was 10.8% [57]. In a retrospective observational study by *Flatz-Jequier et al*. including 64 very low birth weight PIs aged <32 weeks, 33 infants developed a cardiorespiratory event after the first dose of DTaP-IPV-Hib vaccination and 6 of them required medical interventions after the second vaccine for a similar event, identifying a positive history of previous analogous AE as a significant risk factor for the recurrence of a cardiorespiratory event [35]. In the study by *Clifford et al.* evaluating the frequency of apnea and bradycardia up to 48 hours after DTPa-IPV-HBV-Hib-PCV7 and oral rotavirus vaccine at 2 and 4 months of age, 7 out of 38 preterm infants developed recurrent apnea after vaccination. Lower birth weight and ongoing hospitalization for complications related to prematurity increased the risk of a recurrent apnea following vaccination [34]. Accordingly, a large multicenter retrospective cohort study by *De Meo et al.* including 13926 extremely PIs showed an increase in the respiratory support need in the 3 days following vaccination compared with the 3 days preceding the procedure, particularly in infants of 23-34 weeks of GA compared with older PIs [58].
Other studies investigated possible risk factors for post-vaccination apnea other than lower GA, lower birth weight, lower chronological age and positive history of previous similar events [59-60].
A retrospective cohort study by *Hacking et al*. including 411 extremely PIs observed a higher incidence of apnea in PIs who had previously experienced septicemia and had a greater mean total accumulated time on CPAP prior to vaccination [59]. A multivariate analysis by *Klein et al.* identified age ≤31 weeks of gestation, increased initial illness severity scores at birth, birth weight <2 kg and the presence of pre-vaccination apnea as independent risk factors for post-vaccination apnea [60].
Conversely, the only available randomized blinded controlled multicenter study investigating the incidence of apnea in PIs found no increased incidence of post-vaccination apnea[61]. They investigated the frequency of cardiorespiratory events after DTaP vaccination at 2 months of age in 191 PIs with a GA<37 weeks. Infants were randomly assigned to a group that received DTaP vaccine or a control group that did not. No significant differences in apnoea or bradycardia frequency were found between the two groups [61].
A randomized double blinded placebo controlled trial by *Ben Jmaa et al.* included 56 PIs <32 weeks of gestation vaccinated at 2 months of age randomized in two group: the ibuprofen treatment group and the placebo group. Ibuprofen treatment significantly attenuated the variation of cardio-respiratory event following first vaccine. Authors speculated that the inflammatory processes triggered by vaccine might be responsible for the respiratory depression often observed in PIs and suggested a possible protective role of ibuprofen [62].

3.2-Studies on vaccine immunogenicity and efficacy/effectiveness.

Immunogenicity and efficacy/effectiveness was assessed in 22 studies overall including 1,566,350 infants (Table 4-5) [31, 41-42, 45- 50, 53-54, 63-72].

3.2.1-Studies on live attenuated vaccines' immunogenicity and efficacy/effectiveness.

Live attenuated vaccines were investigated in 6 studies [41, 42, 45, 46, 63, 64]. The immunogenicity of the early *vs.* delayed BCG vaccination (BCG at birth vs BCG at 34 weeks gestational age) in moderately preterm infants was studied by in-vivo (i.e. Mantoux test and scar formation 6 months after BCG vaccination) and in-vitro methods (i.e. rise IFN-ɤ after BCG vaccination) by *Saroha et al*. The overall immunogenicity of BCG in this study was 98.3% independently from the time of vaccine administration. [42]. Even *Faridi et al.* in a prospective observational study evaluated the immunogenicity of BCG administered to infants of 31–41 weeks gestation within 7 days after birth. The 95.8% of enrolled patients had either a reactive Mantoux test or positive leukocyte migration inhibition test 6 months after BCG vaccination [63].
Ichikawa et al. investigated immunogenicity of anti-measles vaccine at 6 months of age in PIs<34 weeks of gestation. Early vaccination at 6 months reached protective antibody titers in all cases 1 month after vaccination without a decay during the 12 months after vaccine [41].
A prospective study by *Ferreira et al.* compared the immune response to measles and varicella vaccination in infants born prematurely with those born full-term. The proportion of infants with protective humoral titers to measles and varicella after vaccination were similar in both groups [64].

Two studies focused on rotavirus vaccine immunogenicity and effectiveness [46, 45]. *Omenaca et al.* assessed immunogenicity of rotavirus vaccine dosing IgA specific antibody 30–83 days post-dose 2 in a randomized double blind multicenter controlled trial. Seroconversion rate was 85.7% in the vaccine group and 16.0% in the placebo group [46]. Effectiveness of rotavirus vaccination was the topic of the study performed by *Roué et al*. with the aim to evaluate the impact of the pentavalent rotavirus vaccine on the number of hospitalizations for rotavirus diarrhoea in preterm infants. A significant decrease in the number of hospitalizations for rotavirus infection in infants younger than 3 years of age in the three epidemic seasons following the vaccine introduction was found [45].

3.2.2-Studies on inactivated or subunit vaccines' immunogenicity and efficacy/effectiveness.

Tsuda et al. evaluated the immunogenicity of Hib vaccine in PIs evaluating antibody anti-polyribosylribitolphosphate (PRP) geometric mean concentrations (GMCs) after the third dose of vaccine. The seroconversion rate was lower, but not significantly, in preterm than in full term infants (85.2% vs. 92.4%) [47].

Immunogenicity of pneumococcal vaccine was investigated in 6 studies [31, 49, 54, 65, 66, 67], while the assessment of the PCV effectiveness was the aim of one study [68]. Regarding immunogenicity results are discordant. Two studies [54,65] reported protected specific antibody levels in high proportion of PIs, however several other authors found lower titers, especially against some serotypes such as 6B and 23F [31,49].

A trial by *Omenaca et al*. assessed immunogenicity of the PHiD-CV in two groups of preterm infants (those born between 27 and 30 weeks vs. those born between 31-36 weeks). At least 93% and 97.6% of infants in each group reached protective antibody titers 1 month after primary vaccination and after the booster dose respectively, without any difference in antibody titers between groups [54]. *Szynczewska et al.* assessed the concentration of specific IgG against serotypes of PCV7 in 60 PIs [65]. Ninety-one % and 100% of patients reached protective antibody concentrations after administration of three doses of the vaccine and after the booster dose respectively. Serotypes 6B and 23F were the least immunogenic ones[65].

On the other hand, only 36% term infants and 34% PIs achieved protective levels against all PVC7 vaccine serotypes following the primary vaccination [31]. Preterm birth adversely affected the GMCs to serotypes 4, 6B, 14, 19F, and 23F [31]. Immunogenicity of PCV13 was investigated in one RCT by *Kent et al.* including 199 PIs <35 weeks of GA, randomized to receive a reduced, accelerated and extended schedule of PCV13 [49]. Lack of seroprotection toward more than one-half of the PCV13 serotypes was seen in 25%, 12%, and 3% of participants receiving the reduced, accelerated and extended schedules respectively. Waning of pneumococcal antibody concentrations was evident at 12 months of age. Later gestational age was associated with an increase in post-primary vaccination IgG concentrations for some serotypes, while receipt of antenatal steroids was associated with decreased odds of seroprotection after primary vaccination for some serotypes [49].

An open-label, multicenter trial by *Martinón-Torres et al*. evaluated antipneumococcal antibody responses elicited by PCV13 with a longer follow up, evaluating specific IgG antibody 1 and 2 years after the fourth dose (toddler dose) in PIs compared with term infants. IgG GMCs in both infant groups at the 1-year and 2-year follow-up visits were lower than GMCs 1 month after the toddler dose for all serotypes. Particularly IgG GMCs in PIs were statistically significantly lower at both follow-up time points for serotypes 6B, 18C, 19A, 19F and 23F, while IgG GMCs for serotypes 5, 6A and 9V were statistically significantly lower in PIs at the 1-year follow-up only [67].

Despite controversial immunogenicity results the only study investigating antipneumococcal effectiveness found reassuring results. Authors assessed the impact of PCV7 on invasive pneumococcal disease (IPD) in PIs comparing those born in 2000 (prior to the recommendation to vaccinate with PCV7 preterm infants) with those born in 2007. A reduction in notifications of IPD in 2007 was found both in full term and in PIs, although this reduction was not significant in the latter. No PIs with reported IPD received full vaccination with booster dose according to the recommended schedule. In two IPD cases were both not vaccinated and presented with a serotype included in PCV7 [68].

Two studies focused on influenza vaccine [48,69]. *Esposito et al.* evaluated the immunogenicity of influenza A/H1N1 MF59-adjuvanted vaccine measuring antibody immediately before administration of dose 1 and 2 and 4 weeks after the dose 2. GMCs were significantly higher after the second dose and significantly lower in PIs <32 weeks of gestation, thus confirming that a very low GA may lead to a reduced immune response.

However seroprotection rates were >90% after the first dose in all the groups, suggesting that a single dose of vaccine administered after the sixth month of life can protect almost all children aged <23 months [48].
Shen et al. examined influenza-related healthcare use outcomes among preterm and full-term children aged 6–23 months. The effectiveness of seasonal influenza vaccination was evaluated by examining influenza-coded ambulatory visits (physician office and ED visits) during influenza season periods over five years in more than 600,000 patients. Full vaccination was associated with an overall 19% reduction in ambulatory visits, however a significant reduction was observed only in full term infants [69].
Klein et al. investigated the immunogenicity of the primary series of IPV given as part of a combined vaccine evaluating poliovirus type 3–specific memory T cell, poliovirus type 3–specific cell-mediated immunity and neutralizing antibody response against poliovirus serotypes 1, 2 and 3. Preterm and term infants developed comparable mean frequencies of poliovirus-specific memory T cell responses. Considering mononuclear cells proliferation (PBMCs), PIs were significantly less likely to have a positive stimulation index (SI) than term infants, while all infants had a seroprotective antibody response to all 3 poliovirus serotypes. However the GMCs to poliovirus serotype 1 was significantly lower in both the group of all preterm infants [50].
Two studies investigated immunogenicity or effectiveness of pertussis vaccination in PIs [70-71]. *Vermeulen et al*. assessed the persistence of the specific immune responses against *Bordetella pertussis* in three groups of one-year old children born prematurely: one group received a whole cell vaccine (Pw) for the primary vaccination and a two components acellular vaccine (Pa) as booster dose; the second group received a two component Pa vaccine for every dose of the schedule, the third group received a three component Pa vaccine. The antigen specific cellular immune response persisted at year of age, however acellular vaccines induced a lower specific Th1 type immune response compared with Pw vaccine [70].
Hviid in a large retrospective nationwide Danish study observed a reduced immunogenicity of whole cell pertussis vaccine in PIs after the first dose but the completed primary series was equally effective in preterm and full-term children [71].
Omenaca et al. found an optimal immunogenicity of Hib-MenC-TT vaccine in 309 PIs [53]. In the same study anti-HBV IgG levels were also measured as secondary objectives after concomitant coadministration of DTaP-HBV-IPV showing a gestational age-related profile, with the lowest levels observed in infants aged ≤31 weeks. Similar findings were evident in another study suggesting that PIs have lower humoral response to HBV than full-term infants in terms of GMCs but not in term of seroprotection rates[73].

4-Conclusion

Our findings are in general reassuring regarding the safety and immunogenicity of vaccines in PIs. Studies on BCG, rotavirus and measles vaccination found no increased risk of AEs. Considering inactivated/subunit vaccines, pain, redness and swelling in the injection site are frequently reported, as expected. However, large injection-site swellings after the booster dose have been reported less frequently in the preterm than in full-term infants by some authors [53, 54, 74], but not by others [75-77]. Some authors postulated that a reduced immune response in PIs could result in fewer AEs immediately following vaccination [52]. Apnea and changes in activity (i.e. drowsiness, irritability and loss of appetite) were other frequently reported adverse events [53-55]. Incidence of cardiorespiratory events vary widely (from 1% to 59.1% of PIs) [34-35, 56-62]. Most cardiorespiratory events resolved spontaneously or required minimal intervention [35]. A causal relationship between vaccination and the occurrence of cardiorespiratory events continues to be widely debated. This may be due to the lack of a control group in many studies, their retrospective nature, sample sizes too small to demonstrate statistically significant differences, the difficulty in distinguishing apnea due to vaccination from background instability and the frequent presence of confounding factors (i.e.: periventricular hemorrhage, bronchopulmonary dysplasia, history of sepsis during hospitalization). Moreover, the incidence of post vaccination apnea could be influenced by the so-called “healthy vaccinated” effect, by which clinicians wait until infants are more stable to immunize, thus reducing the observed incidence of adverse events. However, the chance of experiencing an apnea after vaccination seems to be related with lower GA and birth weight [56, 60], supporting the hypothesis that these cardiorespiratory events essentially represent nonspecific stress responses of preterm infants [35,58]. Moreover, newborns who experienced apnea after vaccination were those with a previous severe clinical condition such as late onset sepsis or requiring long time CPAP support [55, 59]. One important risk factor

for recurrence of cardiorespiratory event seems to be a positive history of previous similar adverse reaction, particularly in the 24 h prior to vaccine [35, 50, 60, 78].
Notably, the only controlled prospective randomized study by *Carbone et al.* [61] suggested that vaccination does not directly contribute to cardiorespiratory events showing no difference in occurrence or severity of apnea/bradycardia in vaccine recipients vs. controls. In this study clinical reviewers were blinded to vaccination status and study phase (before or after vaccination), but one possible bias of the study could be that PIs with unstable vital signs were excluded as were infants who required assisted ventilation.
In conclusion given the risks of cardio-respiratory events but also the increased risk of VPDs, PIs who are still hospitalized at 2 months of age should be vaccinated prior to discharge from hospital and should be monitored for 48–72 h after vaccination. This is particularly important in PIs with VLBW with a previous history of cardiorespiratory events, especially in the 24 h prior to vaccination. When a cardiorespiratory AE to the first dose is suspected, consideration should be given to administering the second vaccination under controlled circumstances.
Considering immunogenicity, the proportion of PIs who developed humoral immunity were generally similar in preterm compared with full term infants for many vaccines, with contrasting results for PCV vaccines, even if PCV7 effectiveness was found to be high in preterm infants in one study [64, 66, 73]. Good seroprotection rate for Hib, MenC, HBV, influenza and IPV vaccinations were reported in PIs [47, 48, 50, 53, 72], even if lower gestational ages were associated to lower GMCs
in most of the studies and for most valences (i.e. HBV, Hib, IPV, influenza, pneumococcal and pertussis vaccine), suggesting a lower immunogenicity for PIs [31, 48, 50, 53, 67, 73].
Even if a possible impairment of Th1 response in PIs has been suggested [79-80], several results of studies documented an appropriate cellular immune response toward several vaccines (BCG, pertussis, IPV) [42, 50, 63, 70]. One study reported imbalance in Th1/Th2 response in recipients of acellular pertussis vaccination, depending on the vaccine type, but clinical impact of such a finding is unclear [70].
Unfortunately, only 4 studies evaluating vaccine effectiveness (rotavirus, influenza, PCV, and pertussis) were retrieved [45,68,69,71]. Notably, all the large population based studies documented no differences in vaccine effectiveness between preterm and full term infants.
Our review presents several limitations: our literature search might have missed some studies. However, two authors independently performed literature searches in order to minimize this possibility. The study design of the retrieved papers varied and some of them included small datasets, especially for live attenuated vaccinations, thus further investigations are required. In addition, data about extreme PIs are poor and a distinction of results according to grade of prematurity is not always performed in the studies enrolled.

5-Expert opinion

Neither gestational age nor birth weight should delay the decision to start vaccination in clinically stable PIs. Postponing vaccination is justified only in clinically unstable infants. If PIs are still hospitalized at the time at which they should be vaccinated they should receive their first vaccine in the neonatal ward monitoring them for 48–72 h after vaccination. This is particularly important for infants born ≤31 weeks of GA, with birth weight <2 Kg, with pre-vaccination apnea episodes or with severe bronchopulmonary dysplasia. Educational programs for health professionals and caregivers should be improved in order to avoid delay in vaccination of these infants.
Most of the available studies comparing the immunogenicity of DTaP-IPV-Hib-HBV and PCV in preterm and full term infants apply a 3-dose primary series of vaccination [31, 45, 50, 53-54, 65, 67-71, 73] as recommended by the Centers for Disease Control and Prevention [81]. Even if many countries like United Kingdom, Australia and Canada adopt a 3-dose primary series, other European countries, including Italy, apply a 2+1-dose primary series for hexavalent/pentavalent and pneumococcal vaccination.
Currently only one study compared different schedules of immunization with PCV13 [49], showing lower specific IgG GMCs with the reduced schedule after the primary course but superior antibody concentrations after the booster dose in comparison with extended or accelerated schedules. According to some experts' opinions, it could be preferable to vaccinate very PIs with a 3-dose primary series of DTaP-IPV-HBV-Hib and PCV. However, further studies are needed in order to better understand the immunogenicity of the 2+1 schedule in very PIs (< 32 weeks of gestational age).

Specific issues should be considered regarding rotavirus vaccination considering the risk of transmission of the live attenuated virus in the stool of immunized PIs still hospitalized in NICUs. Several international guidelines recommend that rotavirus vaccine should be administered within 6 to 14 weeks and 6 days of age in order to minimize the potential risk of intussusception [82,83,84]. Canadian and American guidelines suggest rotavirus vaccine administration at or following discharge from the NICUs to prevent the spread of vaccine virus in the hospital setting with the risk of missing possible cardiorespiratory events but also the risk of missing the benefit of rotavirus vaccination in term of immunogenicity overcoming the specific time of administration of vaccine [82-83]. A possible compromise could be policy adopted by British guidelines recommending to vaccine PIs still hospitalized applying routine standard infection control precautions [84]. Further studies are needed to develop evidence-based recommendations regarding the necessity to monitor PIs with suspected cardio-respiratory event following the first vaccine when the second immunisation is performed, considering also direct and indirect costs of a prolonged hospitalization.

Although several studies have been retrieved, limited data are available regarding vaccine effectiveness in preterm infants, particularly after the schedule 2+1 for the hexavalent vaccine and PCVs. Therefore, further studies are needed in this respect, especially focusing on the more recently marketed vaccines (i.e. PCV13 and anti-meningococcal vaccines) and on the need for eventual additional booster doses. Moreover, future studies should analyse the potential differences between subgroups of preterm infants, such as extremely preterm ones (<29 weeks gestational age) to assess whether they need additional vaccine or earlier booster doses.

Funding
This paper was not funded.

Declaration of interests
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

Acknowledgments
The authors would like to show their gratitude to Duse M., Minasi D., Miraglia Del Giudice M. , Cardinale F. , Caffarelli C. , Calvani M. , Martelli A., Pajno GB. , Tosca M., Manti S as members of the governing board of the Italian Society of Pediatric Allergology and Immunology (SIAIP) and thank the reviewers for their insights.

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Table and figure legends

Table 1: PRISMA 2009 Checklist filled out [40].

Table 2: Sixty-one articles identified with the search details (infant, preterm"[MeSH Terms]) AND "vaccination"[MeSH terms] and exclusion criteria for the screening relying on studies' abstracts or titles.

Table 3: Studies regarding vaccine safety in preterm infants.

[Notes: DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H.influenzae protein D conjugate vaccine; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II); AOR=adjusted odd ratio; CI=confidence interval**].**

Table 4: Studies regarding vaccine immunogenicity in preterm infants
[Notes: DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H. influenzae protein D conjugate vaccine; FHA=filamentous haemagglutinin; PT=pertussis toxin; PRN=pertactin; OPA=opsonophagocytic activity; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II), MMR=measles, mumps, and rubella vaccine; GMCs= geometric mean concentrations; PRP= anti-polyribosylribitolphosphate; IPD= invasive pneumococcal disease; LMIT=leukocyte migration inhibition test; SBAMenC=seroprotective serum bactericidal activity thresholds against meningococcal serogroup C vaccine].

Table 5: Studies regarding vaccine effectiveness in preterm infants.

[**Notes:** DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H. influenzae protein D conjugate vaccine; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II), MMR=measles, mumps, and rubella vaccine; GMCs= geometric mean concentrations; PRP= anti-polyribosylribitolphosphate; IPD= invasive pneumococcal disease; LMIT=leukocyte migration inhibition test, IC=interval confidence; ED=emergency department; HR= Adjusted hazard ratios; Pw=pertussis whole vaccine; Pa=pertussis acellular vaccine].

Figure 1: Four-phase flow diagram of the systematic review in accordance with PRISMA guidelines [40].

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 Table 2 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3 Table 3-5

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3 Table 3-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3-4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-13 Table 3-5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4-13 Table 3-5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3-5
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency" in accordance with the text in the Explanation and Elaboration document.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3-5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the	16

		systematic review.	

***Table 1*:** PRISMA 2009 Checklist filled out [40].

References	Excluded/ included	Reason
Omeñaca F, Vázquez L, Garcia-Corbeira P, Mesaros N, Hanssens L et al. Immunization of preterm infants with GSK's hexavalent combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine: A review of safety and immunogenicity.Vaccine.2018;36:986-96.	Excluded	Review
Ferreira CSM, Perin MCAA, Moraes-Pinto MI, Simão-Gurge RM, Goulart AL et al. Humoral immune response to measles and varicella vaccination in former very low birth weight preterm infants. Braz J Infect Dis.2018;22:41-6. [64]	Included (immunogenicity)	
Sisson H, Gardiner E, Watson R. Vaccination timeliness in preterm infants: An integrative review of the literature. J Clin Nurs.2017:26;4094-104.	Excluded	Review
Cuna A, Winter L. Quality Improvement Project to Reduce Delayed Vaccinations in Preterm Infants. Adv Neonatal Care.2017;17:245-49.	Excluded	Not pertinent
Wilińska M, Warakomska M, Głuszczak-Idziakowska E, Jackowska T. Risk factors for adverse events after vaccinations performed during the initial hospitalization of infants born prematurely. Dev Period Med.2016;20:296-305. [55[	Included (safety)	
Martinón-Torres F, Wysocki J, Center KJ, Czajka H, Majda-Stanislawska E, et al. Circulating Antibody 1 and 2 Years After Vaccination With the 13-Valent Pneumococcal Conjugate Vaccine in Preterm Compared With Term Infants. Pediatr Infect Dis J.2017;36:326-32. [67]	Included (immunogenicity)	
Kucukoglu S, Aytekin A, Celebioglu A, Celebi A, Caner I, et al. Effect of White Noise in Relieving Vaccination Pain in Premature Infants. Pain Manag Nurs.2016;17:392-400.	Excluded	Not pertinent
Kent A, Ladhani SN, Andrews NJ, Scorrer T, Pollard AJ, et al. Schedules for Pneumococcal Vaccination of Preterm Infants: An RCT. Pediatrics.2016;138:e20153945-58[49]	Included (immunogenicity and safety)	
Kilich E, Sadarangani M. Use of rotavirus vaccines in preterm babies on the neonatal unit. Expert Rev Vaccines.2016;15:1463-65.	Excluded	Not pertinent
Kjærgaard J, Stensballe LG, Birk NM, Nissen TN, Thøstesen LM, et al. Bacillus Calmette-Guérin vaccination at birth: Effects on infant growth. A randomized clinical trial. Early Hum Dev.2016;100:49-54 [43]	Included (safety)	
Higgins RD, Shankaran S. The Neonatal Research Network: History since 2003, future directions and challenges. Semin Perinatol.2016;40:337-40.	Excluded	Not pertinent
Olsen SJ, Mirza SA, Vonglokham P, Khanthamaly V, Chitry B et al. The Effect of Influenza Vaccination on Birth Outcomes in a Cohort of Pregnant Women in Lao PDR, 2014-2015. Clin Infect Dis.2016;63:487-94.	Excluded	Not pertinent
Kjærgaard J, Stensballe LG, Birk NM, Nissen TN, Foss KT et al. Lack of a Negative Effect of BCG-Vaccination on Child Psychomotor Development: Results from the Danish Calmette Study - A Randomised Clinical Trial. PLoS One.2016;11:e0154541. [44]	Included (safety)	
Navarro-Alonso JA, Taboada-Rodríguez JA, Limia-Sánchez A; Toward a New Immunization Schedule in Spain, 2016 (Part 2). Rev Esp Salud Publica.2016;90:E3.	Excluded	Review
McArdle AJ, Mugisha G, Birahinduka D. QUESTION 2: Vaccinating preterm infants in resource-poor settings: what is the incidence of apnoea, bradycardia and need for respiratory support? Arch Dis Child 2016;101:290-3.	Excluded	Commentary
Salamouras D, Levy J. Vaccination of premature infants, a population at high risk of infection. Rev Med Brux.2015;36:223-8	Excluded	Review in French
Saroha M, Faridi MM, Batra P, Kaur I, Dewan DK. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31-33 weeks) infants. Hum Vaccin Immunother.2015;11:2864-71 [42]	Included (safety and immunogenicity)	
McCrossan P, McCafferty C, Murphy C, Murphy J. Retrospective review of administration of childhood primary vaccination schedule in an Irish tertiary neonatal intensive care unit. Public Health.2015;129:896-8.	Included (safety)	

Kilich E, Anthony M. Rotavirus vaccination in preterm infants: a neonatal guidance chart to aid timely immunisation. Arch Dis Child Fetal Neonatal Ed.2015;100:F465.	Excluded	Letter
Mehler K, Ulbrich L, Börner S, Joachim A, Becker I, et al. Multidimensional response to vaccination pain in very preterm, moderate- to-late preterm and full-term infants at age three months. Early Hum Dev.2015;91:199-204	Excluded	Not pertinet
Ochoa TJ, Zea-Vera A, Bautista R, Davila C, Salazar JA et al. Vaccine schedule compliance among very low birth weight infants in Lima, Peru. Vaccine.2015;33:354-8.	Excluded	Not pertinent
Czajka H, Lauterbach R, Pawlik D. Vaccination of preterm infants by polyvalent vaccines: immunogenicity and safety- review of literature. Dev Period Med.2014;18:360-6	Excluded	Review
Erener-Ercan T, Aslan M, Vural M, Erginoz E, Kocazeybek B et al. Tetanus and diphtheria immunity among term and preterm infant-mother pairs in Turkey, a country where maternal and neonatal tetanus have recently been eliminated. Eur J Pediatr.2014;174:339-44	Excluded	Not pertinent
Tozzi AE, Piga S, Corchia C, Di Lallo D, Carnielli V et al. Timeliness of routine immunization in a population-based Italian cohort of very preterm infants: results of the ACTION follow-up project. Vaccine.2014;32:793-9.	Excluded	Not pertinent
Woestenberg PJ, van Lier A, van der Maas NA, Drijfhout IH, Oomen PJ et al. Delayed start of diphtheria, tetanus, acellular pertussis and inactivated polio vaccination in preterm and low birth weight infants in the Netherlands. Pediatr Infect Dis J.2014;33:190-8.	Excluded	Not pertinent
Szynczewska E, Chlebna-Sokół D. Immunogenicity of heptavalent conjugate vaccine against Streptococcus pneumoniae in premature babies with low birth weight. Pediatr Neonatol.2014 Apr;55(2):101-7 [65]	Included (immunogenicity)	
Shen S, Campitelli MA, Calzavara A, Guttmann A, Kwong JC. Seasonal influenza vaccine effectiveness in pre- and full-term children aged 6-23 months over multiple seasons. Vaccine.2013;31:2974-8 [69]	Included (effectiveness)	
Wilson K, Hawken S, Holdt Henningsen K, Kwong JC, Deeks SL et al. On-time vaccination coverage in premature infants in Ontario, 2002-2009. Can J Public Health.2012;10:e359-62	Excluded	Not pertinent
Vermeulen F, Dirix V, Verscheure V, Damis E, Vermeylen D, et al. Persistence at one year of age of antigen-induced cellular immune responses in preterm infants vaccinated against whooping cough: comparison of three different vaccines and effect of a booster dose. Vaccine.2013;31:1981-6 [70]	Included (immunogenicity)	
Ichikawa T, Tsuji A, Fujino M, Kusano R, Sugiyama R et al. Effect of early measles vaccination (AIK-C strain) for preterm infants. Pediatr Int.2013;55:163-8.	Included (safety and immunogenicity)	
Esposito S, Fumagalli M, Principi N. Immunogenicity, safety and tolerability of vaccinations in premature infants. Expert Rev Vaccines.2012;11:1199-209.	Excluded	Review
Ahrens K, Lash TL, Louik C, Mitchell AA, Werler MM. Correcting for exposure misclassification using survival analysis with a time-varying exposure. Ann Epidemiol.2012 ;22:799-806	Excluded	Not pertinent
Wilson K, Hawken S. Incidence of adverse events in premature children following 2-month vaccination. Hum Vaccin Immunother.2012;8:592-5 [52]	Included (safety)	
Zhang L, Zhai XJ, Li YP, Zhang W, Zhu FC, Huang T, et al. Multi-center matching study on antibody response between preterm and full-term infants after primary immunization of hepatitis B vaccine. Zhonghua Liu Xing Bing Xue Za Zhi.2012;33:185-8.	Excluded	Not written in english
Meinus C, Schmalisch G, Hartenstein S, Proquitté H, Roehr CC. Adverse cardiorespiratory events following primary vaccination of very low birth weight infants. J Pediatr (Rio J). 2012 Mar-Apr;88(2):137-42	Excluded	Not written in english
Gaudelus J, Lachassinne E, de Pontual L. Immunization of the preterm infant. Rev Prat.2012;62:382-3	Excluded	Not written in english
Lin TH, Lin SY, Lin CH, Lin RI, Lin HC et al. AdimFlu-S(®) influenza A (H1N1) vaccine during pregnancy: the Taiwanese Pharmacovigilance Survey. Vaccine.2012 Mar 30;30(16):2671-5.	Excluded	Not pertinent
Buijs SC, Boersma B. Cardiorespiratory events after first immunization in premature infants: a prospective cohort study]. Ned Tijdschr Geneeskd.2012;156:A3797.	Excluded	Not written in english
Omenaca F, Sarlangue J, Szenborn L, Nogueira M, Suryakiran PV, et al. Safety, reactogenicity and immunogenicity of the human rotavirus vaccine in preterm European Infants: a randomized phase IIIb study. Pediatr Infect Dis J.2012;31:487-93	Included (safety and immunogenicity)	
Tsuda K, Iwasaki S, Horiguchi H, Mori M, Nishimaki S, et al. Immune response to Haemophilus influenzae type b conjugate vaccine in preterm infants. Pediatr Int. 2012;54:64-7 [47]	Included (safety and immunogenicity)	
Mullooly JP, Schuler R, Mesa J, Drew L, DeStefano F et al. Wheezing lower respiratory disease and vaccination of premature infants.	Excluded	Not pertinent

Vaccine.2011;29:7611-7		
Omeñaca F, Arístegui J, Tejedor JC, Moreno-Perez D, Ruiz-Contreras J et al. Combined Haemophilus Influenzae type B-Neisseria meningitidis serogroup C vaccine is immunogenic and well tolerated in preterm infants when coadministered with other routinely recommended vaccines. Pediatr Infect Dis J.2011;30:e216-24 [53]	Included (safety and immunogenicity)	
Omeñaca F, Merino JM, Tejedor JC, Constantopoulos A, Papaevangelou V, Kafetzis D. Immunization of preterm infants with 10-valent pneumococcal conjugate vaccine. Pediatrics 2011;128:e290-8 [54]	Included (safety and immunogenicity)	
Calderón C G, Moore V R, Pittaluga P E, Potin S M. Adherence to immunizations in newborns less than 1500 gr at birth and/or younger than 32 weeks, in two chilean centers. Rev Chilena Infectol.2011;28:166-73	Excluded	Not written in english
Clifford V, Crawford NW, Royle J, Lazzaro T, Danchin M, et al. Recurrent apnoea post immunisation: Informing re-immunisation policy. Vaccine.2011;29:5681-7. [33]	Included (safety)	
Esposito S, Pugni L, Daleno C, Ronchi A, Valzano A et al. Influenza A/H1N1 MF59-adjuvanted vaccine in preterm and term children aged 6 to 23 months. Pediatrics.2011 May;127:e1161-8. [48]	Included (safety and immunogenicity)	
Zanoni G, Gottin L, Boner A, Piacentini G, Peroni D et al. Case discussion of an immediate serious reaction to hexavalent vaccine mistaken for anaphylaxis. Br J Clin Pharmacol.2010;70:916-7.	Excluded	Case report
Mirpuri J, Jain L. Issues of prematurity and HIV infection. Clin Perinatol.2010;37:887-905	Excluded	Not pertinent
Baxter D. Premature infants and vaccination. Hum Vaccin.2010;6:493.	Excluded	Comment on
Trück J, Pollard AJ. Challenges in immunisation against bacterial infection in children. Early Hum Dev.2010;86:695-701.	Excluded	Not pertinent
Dhillon S. Spotlight on DTPa-HBV-IPV/Hib Vaccine (Infanrix hexa). BioDrugs.2010;24:299-302	Excluded	Review
Baxter D. Vaccine responsiveness in premature infants. Hum Vaccin.2010;6:506-11	Excluded	Review
Baxter D. Impaired functioning of immune defenses to infection in premature and term infants and their implications for vaccination. Hum Vaccin.2010;6:494-505.	Excluded	Review
Tinnion RJ, Berrington JE. Flu vaccination for ex-preterms and infants under 6 months--are we getting it right? Arch Dis Child.2010 May;95:400-1	Excluded	Letter
Baxter D, Ghebrehewet S, Welfare W, Ding DC. Vaccinating premature infants in a Special Care Baby Unit in the UK: results of a prospective, non-inferiority based, pragmatic case series study. Hum Vaccin.2010;6:512-20.	Included (immunogenicity)	
Pinquier D, Adde-Michela C, Ploin D, Levêque C, Marret S; Vaccination rate of premature infants at 6 and 24 months of age: a pilot study. Arch Pediatr.2009 Dec;16:1533-9.	Excluded	Not written in english
Esposito S, Serra D, Gualtieri L, Cesati L, Principi N. Vaccines and preterm neonates: why, when, and with what. Early Hum Dev 2009;85:S43-5.	Excluded	Review
Fleischer L, Syed SS. Hepatitis B surface antigenemia in a neonate following vaccination with Pediarix. Clin Pediatr.2009;4:311-2.	Excluded	Case report
Ryan MA, Gumbs GR, Conlin AM, Sevick CJ, Jacobson IG et al. Evaluation of preterm births and birth defects in liveborn infants of US military women who received smallpox vaccine. Birth Defects Res A Clin Mol Teratol.2008;82:533-9	Excluded	Not pertinent
Klein NP, Massolo ML, Greene J, Dekker CL, Black S et al. Risk factors for developing apnea after immunization in the neonatal intensive care unit. Pediatrics.2008;121:463-9 [60]	Included (safety)	

Table 2: Sixty-one articles identified with the search details (infant, preterm"[MeSH Terms]) AND "vaccination"[MeSH terms] and exclusion criteria for the screening relying on studies' abstracts or titles.

Author (year)	**Design**	**No of pts**	**Gestational Age in weeks (w)**	**Location**	**Vaccine**	**Objectives**	**Follow up (FU) after vaccine**	**Results**	**Bias**
Ben Jmaa et al. (2017) [62]	Prospective randomized, double blinded, placebo-controlled	56	< 32 w	Canada	DTPa,IPV, Hib, PCV10	To analyze cardio-respiratory Events (CREs) 48 hours after vaccination and inflammatory eesponse after primary Immunization	48 h	-Significant correlation between Δ C-reactive protein and Δ Total CRE/patient/24 hours; -CRE/patient/24 hours was unchanged before versus after immunization (6.7 ± 7.7 before versus 6.8 ± 9.7 after, P = 0.9) in the ibuprofen group	

Kjærgaard et al. (2016) [43]	Prospective randomized, multicenter clinical trial	4262 (144 born 32-37 w)	32-37 w	Denmark	BCG	Effects of BCG vaccination on early childhood infections, growth and development in term and preterm infant	22 months	There was no effect of BCG on either incidence of infections, growth, body composition or psychomotor development	
Kjærgaard et al. (2016) [44]	Prospective randomized, multicenter clinical trial	4262 (144 born 32-37 w)	32-37 w	Denmark	BCG	To assess the non-specific effect of Bacillus Calmette-Guérin (BCG) vaccination at birth on psychomotor development	22 months	Lack of a Negative Effect of BCG-Vaccination on Child Psychomotor Development	
Kent et al (2016) [49]	Phase IV, open-label, prospective, multicenter, randomized controlled trial	199	<35 w	UK	PCV13 in association with other polyvalent vaccines	To evaluate solicited adverse events (AEs)	28 days	- no significant differences in the frequency or severity of local and systemic AEs between vaccination schedules at any time point - 77 serious AEs, of which 1 possibly related to vaccination unexpected serious adverse reaction from each randomized group	
Wilińska et al (2016) [55]	Observational prospective	138	73 ≤ 28 w 65 >28 w	Poland	DTPa-IPV-HBV-Hib-PCV	To assess incidence of adverse events following vaccination (AEFV) monitoring cardio-respiratory functions and body temperature	72 hours	- Apnea and activity dysfunctions were the relatively most frequent AEFI. -Preterm newborns who experienced apnea show significantly more frequent late onset sepsis (p=0.028) as well as a history of longer use of continuous positive air pressure (CPAP) (p=0.033)	-no control group -small sample size
De Meo et al (2015) [58]	Multicenter retrospective cohort study	13,926	≤28 w	USA	DTPa, IPV, HBV, Hib, PCV7	To assess sepsis evaluation (collection of blood culture), need of increased respiratory support, seizures and death in the 3 days following vaccination	3 days	-The incidence of sepsis evaluation and increased respiratory support increase from the pre-immunization period to the post-immunization period -Infants 23–24 weeks of gestation demonstrated an increased incidence of sepsis evaluation and increased respiratory support compared to older infants (27– 28 weeks gestation) -A prior history of gram-positive sepsis was associated with an increased rate for sepsis evaluation in the post-immunization period. -There was no difference in the incidence of adverse events in combination vaccines versus single-dose vaccines.	-"healthy vaccinated "effect -physicians may be more likely to document adverse events that are occurring in close proximity to the administration of immunizations
McCrossan et al (2015) [51]	Retrospective	344	<37 w	Ireland	DTPa, IPV, HBV, PCV, Hib	To assess delay in administration and safety of vaccines in preterm		None of the patients had a documented adverse reaction	-Retrospective study -not clear the period of follow up
Saroha et al (2015) [42]	Prospective randomized comparative trial	117	31-33 w	India	BCG	To compare complications of BCG vaccine in preterm infants aged 31–33 weeks immunized at birth or at 34 completed weeks	6 months	-Left axillary lymphadenopathy was the only complication seen in 3.4% of patients in in both groups -BCG vaccine may be safely given to moderately preterm infants (31–33 weeks) at birth	
Roué et al (2014) [45]	Population-based study	7150	6883>37 w 267<37 w	France	Rotavirus vaccine	To analyze the cause of hospitalizations for up to 42 days after the last dose of Rotavirus vaccine	42 days	-No significant differences in severe AEs following vaccination between premature and term infants were found (5.2% versus 8.1%, p = 0.09) . -No case of intussusception nor of Kawasaki disease were reported.	
Ichikawa et al (2013) [41]	Prospective	17	<34 w	Japan	Measles vaccine	To evaluate immunogenicity and safety of early vaccination with measles vaccine at 6 months.	12 months after birth	AEs did not occur	Small sample
Anderson et al (2012) [56]	Retrospective	203	≤28 w	Australia	DTaP, IPV, Hib, PCV	To evaluate likely/possible apneic reaction within 48 hours following 2 months vaccination	48 h	-18 preterm infants had a vaccine reaction, 17 with likely/possible apnea reaction (incidence 8,4%) after 2 months vaccination -Babies reacting to the 2-month vaccine were statistically of lower birth gestation and birth weight - There were no reactions to the following vaccine doses	-Small case numbers -lack of cardiorespiratory monitoring for the 4-month immunizations in approximately 50% of

									cases
Omenaca et al (2012) [46]	randomized double blinded placebo-controlled trial	250	≥27 and <37 w	France, Portugal, Poland, Spain	Rotavirus vaccine	To assess the occurrence of any solicited and unsolicited AEs during the 15- and 31-day postvaccination follow-up period after each dose, respectively and severe adverse event (SAE)	31 days	- Frequency of AEs recorded in the vaccine and placebo groups were similar (P = 0.266). -During the 31-day postvaccination follow-up period, at least 1 unsolicited AE was reported in 196 (29.3%, 95% CI: 25.8–32.9%) and 138 (40.7%, 95% CI: 35.4–46.1%) infants in the vaccine and placebo groups, respectively (P < 0.05). - The percentage of all and grade 3 solicited general AEs recorded during the 15-day postvaccination follow-up period were similar in both groups (P > 0.05) with irritability being the most common AE reported	- coadministration of other polyvalent vaccines
Tsuda et al (2012) [47]	prospective cohort study	54 preterm infants	<37 w	Japan	Hib	To assess immunogenicity and side-effects after vaccination		-Side-effects after vaccination were rare, with only one case of local redness	-small number of samples -not clear the follow up period
Wilson et al (2012) [52]	Retrospective self-controlled case-series	771453	-49220 born 33-36 w -7392 born ≤ 32 w	Canada	DTPa-IPV-HiB-PCV	-to evaluate rates of emergency room visits and hospital admissions within 3 days following 2 months vaccination	3 days	-Reduced AEs (as emergency room visits and hospital admission) were observed in preterm infants when compared to small for gestational age term children. When compared with all term children this decrease in risk was not statistically significant.	-the healthy vaccine effect - emergency room visits and hospital admissions within 3 days following vaccination could not be related to vaccination
Clifford V et al (2011) [34]	Observational retrospective	46	-38 born < 37 w -8 born ≥37 w	Australia	DTPa-IPV-HBV-HiB+PCV7 and rotavirus vaccine	-To determine recurrence rates for AEs following 2 or 4 month immunisations over 48 hours after vaccination. -To explore potential risk factors for recurrence of apnea	48 hours	-35/38 preterm infants had an apnoea following their 2-month vaccine, 3/38 had an apnea after their 4-month vaccine -7/38 (18%) preterm infants had recurrent apnoea -Lower birth weight (p = 0.04) and ongoing hospitalisation for complications relating to prematurity (p = 0.01) increased the odds of a recurrent apnoea AEFI. - No infant with recurrent apnoea at 4-months suffered a third apnoea AEFI at their 6-month immunisations	-small sample size - overestimation of the number of infants with a first apnoea AEFI maybe because of the retrospective nature of the study without the possibility to confirm the apnoea diagnosis
Esposito et al. (2011) [48]	Prospective, randomized open trial	101	-34 born <32 w -35 born 32-36 w -32 born ≥37 w	Italy	Influenza A/H1N1 MF59-adjuvanted vaccine	To assess immunogenicity, safety and tolerability of influenza A/H1N1 MF59-adjuvanted vaccine in preterm and term children aged 6 to 23 months	14 days	-The incidence of local AEs was 2,9-3,1% in all children -The only systemic AE consistently recorded was fever, more frequently after the first dose than after the second dose in all the groups(P<0.05) -None of the enrolled children experienced any severe AE.	
Omeñaca et al (2011) [53]	open, controlled prospective multicenter study	313	-56 born <31w -107 born 31-36 w -150 full term	Spain	Hib-MenC-TT	To assess immunogenicity and safety profile in preterm infants compared with full-term born infants. To record specific local and general solicited adverse events for 4 days after each vaccination and	31 days	-solicited local symptoms tended to be lower than those observed after DTPa-HBV-IPV-PCV7 -Grade 3 local symptoms were reported by no more than 7.6% -No evidence of increasing reactogenicity with an increasing number of doses in any group. -Grade 3 general symptoms were	-open design -no randomization

						to record unsolicited adverse events for 31 days after vaccination		reported by no more than 9.3% and 2.8% of patients after primary vaccination and after the booster dose respectively	
Omeñaca et al(2011) [54]	Prospective clinical trial	286	-50 born 27-30 w -87 born 31-36 w -149 full term	Spain, Greece	PHID-CV	To evaluate immunogenicity and safety to PHiD-CV and coadministered vaccine at 2-4-6 month of age, followed by a booster dose at 16-18 months of age. To evaluate local and general adverse events for 4 days after each vaccine dose and unsolicited adverse events for 31 days after vaccine and serious adverse events for 6 months after booster vaccination.	6 months	-The most frequently reported solicited general AE were irritability, drowsiness, fever and loss of appetite, but the incidence of high grade of general AE was low (i.e. 0,8-1,5% incidence of fever > 39°C within 4 days after each of the vaccine doses, 7.1% after the booster dose) -Incidence of grade 3 solicited local AEs was low in both groups, but higher after booster vaccination in the term group. -SAEs were reported but no one were considered as causally related to vaccination - One episode of apnea was reported in a preterm infant after the first primary dose but was not considered to be related to study vaccination and resolved without sequelae.	
Furck et al (2010) [57]	prospective observational trial	473	<37 w	Germany	DTPa, Hib, HBV, IPV, PCV7	To assess AEs for up to 48h following vaccination	48 hours	-The frequency of side effects was 10.8% and 2.8 % for apnea/bradycardia and local reaction/fever respectively -The chance of suffering from apnea decreased with increasing gestational week at birth -Fever was significantly more frequent in infants with cerebral hemorrhage grade 3–4 or with periventricular leukomalacia (OR 8,7 and 8,2 respectively)	-The 3 groups did not have the same number of infants -the gestational age as the time of vaccination decreased over the years
Hacking et al. (2010) [59]	Retrospective historical cohort study	411	27 w	Australia	DTPa, Hib, HBV, OPV/IPV, PCV7	To evaluate initiation of respiratory support (CPAP) or intermittent positive pressure ventilation (IPPV) within 7 days of the 2-month scheduled vaccination	7 days	-22 preterm infants experienced some respiratory deterioration in the first 3 day after vaccination attributed solely to the immunization -infants requiring respiratory support following vaccination had a higher incidence of previous septicaemia (p = 0.02) and had a greater mean total accumulated time on CPAP prior to receiving immunizations (p=0.03)	- retrospective nature of the study cannot suggest that immunization was a causative factor
Klein et al (2010) [50]	open-label prospective study, self-controlled case series approach	83	-33 born <37w -50 born≥37 w	USA	DTPa, Hib, HBV, IPV, PCV	to describe potential vaccine-related AEs during the 30 days after each of 3 doses comparing the frequency of these events in preterm and term infants	30 days	-No AEs like fever, seizure, or swelling were reported for either preterm or term infants -Self-controlled case series analyses showed no increase in AEs among preterm and term infants after any vaccine dose	Small sample size
Carbone et al. (2008) [61]	Randomized, controlled, blinded multicenter study	197	< 37 w	USA	DTPa	To evaluate increase in cardiorespiratory events after DTPa in preterm infants	48 hours	Absence of increase in cardiorespiratory events in DTaP group versus the control group	no long-term observation of the untreated control group.
Flatz-Jequier et al (2008) [35]	Retrospective study	64	<32 w	Switzerland	DTPa-IPV/HIB/-PCV/anti VRS	To evaluate occurrence of cardiorespiratory events after first DTPw or DTPa immunization in VLBW during the first 48 hours after second dose of vaccine	48 hours	-33/64 showed significant cardiorespiratory event after the 2 months vaccine. -6/33 require medical intervention (i.e. oxygen supplementation through nasal cannula in 4 patients, tactile stimulation in 1 patients, mask ventilation in 1 patients) after the 4 months vaccine -None showed significant cardiorespiratory event after the third vaccine -A previous AE to vaccine was a risk factors for recurrence of cardiorespiratory events.	- retrospective study
Klein et al. (2008) [60]	Retrospective study	497	456 born ≤30 w	USA	DTPa-IPV-HBV-Hib-	To assess factors associated with	48 hours	- 95% episodes of postimmunization apnea (62 of 65 episodes) occurred	

			41 born 31-41 w		PCV	postimmunization apnea		among infants born at ≤31 weeks of gestation -Bivariate analysis revealed that postimmunization apnea was markedly associated with the presence of preimmunization apnea ($P < 0.0001$) - Multivariate analysis conducted exclusively among infants without apnea before immunization similarly found that SNAP-II >10 (AOR: 4.2; 95% CI: 1.2–14.3), chronological age of <67 days (AOR: 2.3; 95% CI: 1.1–4.8)and weight of <2 kg (AOR: 2.1; 95% CI: 1–4.5) were associated with postimmunization apnea.	

Table 3. Studies regarding vaccine safety in preterm infants [Notes: DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H.influenzae protein D conjugate vaccine; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II); AOR=adjusted odd ratio; CI=confidence interval**].**

Study (year)	Design	No of pts	Gestational Age in weeks (w)	Location	Vaccination	Objectives	Results	Bias
Ferreira et al. (2018) [64]	Prospective study	121 -65 preterm infants -56 full-term infants	25–34.4 w	Brazil	MMR	to compare the immune response to measles and varicella vaccination in infants born prematurely with those born at full-term measuring measles antibodies at 12 and 15 months (before and after MMR vaccine) and varicella antibodies at 15 and 18 months (before and after vaccine)	- The percentages of infants with humoral immunity to measles and varicella after vaccination were similar in both groups - antenatal corticosteroid use reduced the level of measles antibodies ($p = 0.009$), while breastfeeding for more than six months increased antibody levels after varicella vaccination ($p = 0.023$).	
Martinón-Torres et al. (2017) [67]	open-label, 2-arm, multicenter, parallel-group study	200 -100 full term infants -100 preterm infants	-25 born <29 w -50 born 29–31 w -25 born 32–36 w	Spain and Poland	PCV13	To evaluate antipneumococcal antibody responses elicited by PCV13 1 and 2 years after the fourth dose (toddler dose) in formerly preterm infants compared with term infants	-IgG GMCs in both infant groups at the 1-year and 2-year follow-up visits were lower than GMCs 1 month after the toddler dose for all serotypes. -Compared with term infants, IgG GMCs in preterm infants were statistically significantly lower at both follow-up time points for serotypes 6B, 18C, 19A, 19F and 23F; IgG GMCs for serotypes 5, 6A and 9V were statistically significantly lower in preterm infants at the 1-year follow-up only	
Kent et al. (2016) [49]	Open label, randomized, controlled multicenter clinical trial	199	<35 w	UK	PCV13 -group 1: reduced schedule (vaccine at 2 and 4 months of age) -group 2 accelerated schedule (vaccine at 2, 3,	To assess the immunogenicity of 3 commonly used PCV13 priming schedules in premature infants and their response to a 12-month booster dose.	-Lack of seroprotection for more than one-half of the PCV13 serotypes was seen in 25%, 12%, and 3% of participants receiving the reduced, accelerated, and extended schedules, respectively ($P < 0.001$). -A reduced priming schedule of PCV13 resulted in higher post-booster IgG concentrations but lower post-primary	

					and 4 months of age) -group 3 extended schedule (vaccine at 2, 4, and 6 months of age)		concentrations. -Later gestation was associated with an increase in post-primary vaccination IgG concentrations for some serotypes, while receipt of antenatal steroids was associated with decreased odds of seroprotection at 2 months and after primary immunization for some serotypes.	
Saroha et al. (2015) [42]	Prospective randomized comparative trial	117 -69 received BCG at birth (group 1) -48 received BCG at 34 w(group 2)	31-33 w	India	BCG	To evaluate immunogenicity of early vs delayed BCG vaccination in moderately preterm (31-33 weeks) infants.	-the rise of IFN-g levels measured 6 months after BCG in 2 groups was comparable ($p > 0.05$) -In group 1, 39.1% infants had positive Mantoux reaction (5–9 mm) 6 months after BCG whereas 37.5% infants in group 2 had positive Mantoux test ($p = 0.473$) -Six infants (5.12%) failed to develop BCG scar - the overall immunogenicity of BCG was 98.3%	
van den Berg (2015) [66]	Prospective randomized trial	113 divided into 2 groups: -1 group received enteral oligosaccharides mixture during days 3–30 of life -1 group received placebo	<32 w	The Netherlands	PCV 7 (4 doses at 2, 3, 4 and 11 months of age)	to investigate the specific antibody levels against the 7 pneumococcal vaccine serotypes 4–6 weeks after the third pneumococcal immunization and 4–8 weeks after the booster dose	- IgG antibody levels in preterm infants supplemented with oligosaccharides were similar to those of term infants at 5 months of age, while IgG antibody levels in preterm infants supplemented with placebo were higher for 5 of the 7 vaccine serotypes (serotypes 4, 6B, 9V, 19F, 23F; $P < 0.05$) than those in term infants. -At 12 months of age, there was a significant booster response in both preterm groups and the GMCs of pneumococcal antibody levels after the booster dose for all serotypes were not different in the two groups -preterm infants with higher gestational age showed higher pneumococcal antibody concentrations of certain serotypes at 5 and 12 months	
Szynczewska et al (2014) [65]	Observational prospective	60 -Group I 23 born with birth weight <1000 g; -Group II 37 born with birth weight ≥1000 g	24-34 weeks	Polonia	PCV7	To assess concentration of specific immunoglobulin G against all seven serotypes of PCV7 4 weeks after the primary vaccination; prior and 4 weeks later the booster dose administration.	- After primary immunization, an increase in the average concentration of antibodies for all serotypes was observed in most children, with no significant differences between groups. -Serotypes 6B and 23F proved to be the least immunogenic following the primary vaccination -Prior to administration of the booster dose at age 16 months a significant decrease in antibody titer was observed in all children - The last vaccination resulted in another significant increase in the concentration of antibodies in both groups.	
Ichikawa et al (2013) [41]	Observational prospective Clinical trial	161 (17 received early vaccination at 6 months)	< 34 w	Japan	Measles	To evaluate antibody titers before and after early vaccination at 6 months for measles	-The antibody titers at birth was significantly lower in preterm infants born <28 weeks ($P < 0.05$) and with a weight <1000 g ($P < 0.01$). -At 3–6 months of age, none of the 108 infants tested had protective antibody titers. -Preterm infants who received early vaccination at 6 months kept antibodiy titers positive in all cases 1 month after vaccination. -Titers did not decay during the 12 months after vaccination	Small sample size
Vermeulen et al. (2013) [70]	Observational prospective cohort study	68 -22 vaccinated with whole cell pertussis vaccine (Pw) -24 vaccinated with two components	<31 w	Belgium	3 type of vaccines: Pw, Pa bicomponent, Pa multicomponent	To assess at one year of age the specific cellular immune responses in the preterm infants (through cytokine	-more than half of premature infants vaccinated with the Pw vaccine or with the 2 component Pa vaccine developed at 3 and/or at 6 months of age an IFN-ɤ response to FHA and/or PT	Small sample size

		acellular vaccine (Pa) -22 vaccinated with three component Pa vaccine.				secretion after antigenic stimulation)	- no effect of the booster dose was observed on the FHA or PT-induced IFN- ɤ secretion in the 3 groups - Pa vaccine induced more secretion of Th2 cytokines in response to FHA and to PT, compared to infants primed with a Pw vaccine	
Omenaca et al. (2012) [46]	phase IIIb, randomized double blind, multicenter, placebo-controlled trial	228	≥ 27 and <37 w	France, Portugal, Poland, Spain	Rotavirus	To assess immunogenicity of a human rotavirus vaccine dosing IgA specific antibody concentrations 30–83 days post-dose 2	seroconversion rate at 30–83 days post dose 2 of vaccine/placebo was 85.7% (95% CI: 79.0–90.9%) in vaccine group and 16.0% (95% CI: 8.8–25.9%) in the placebo group	
Tsuda et al. (2012) [47]	Observational prospective cohort	54	<37 w	Japan	Hib	to evaluate vaccine immunogenicity in preterm infants by measuring antibody PRP titers as GMCs before and 1 month after the third dose	- after three doses of vaccine, GMCs increased from 0.06. to 2.89 mg/mL (P < 0.001). -The seroconversion rate was 85.2% - the seroconversion rate after vaccination of infants with a history of antenatal exposure to steroids was higher than those without antenatal exposure (P = 0.046). - the seroconversion rate of group vaccinated at the age of 2 months was close to being significantly worse than the group vaccinated at the age of >3 months (P = 0.060)	Small sample size
Esposito et al. (2011) [48]	Prospective, randomized study	101	-34 born <32w -35 born 32-36 w -32 born ≥37w	Italy	Influenza A/H1N1 MF59-adjuvanted vaccine	To assess immunogenicity of influenza A/H1N1 $_{MF59}$-adjuvanted vaccine in preterm and term children aged 6 to 23 months evaluating antibody titers collected immediately before administration of dose 1, dose 2 and 4 weeks later the dose 2.	-the first dose was able to determine seroprotection in all of the preterm born between 32 and 36 weeks of gestation -After the administration of the vaccine, there was a significant increase in the GMCs of all the children (P <0.05) -The preterm subjects with a gestational age <32 weeks aged 6 to 11 months had significantly lower absolute GMCs than the subjects in any of the other groups (P<0.05)	
Omeñaca et al. (2011) [54]	Prospective clinical trail	286	-preterm group I (between 27and 30 w); -preterm group II (between 31 and 36 w -term group	Spain, Greece	PHiD-CV	To evaluate immunogenicity to PHiD-CV at 2, 4, and 6 months of age evaluating antibody titers like OPA o GMC 1 month after primary vaccination, and 1 month after booster vaccination.	-at least 92.7% of infants in each group had antibody GMCs concentrations>0.2µg/mL and at least 93.2% of subjects had OPA titers >8 1 month after primary immunization. -preterm infants showed lower antibody titers for certain serotypes -at least 97.6% of subjects in each group developed antibody concentrations >0.2 µg/mL 1 month after booster dose. -One month after both primary and booster vaccination, all subjects were seroprotected/seropositive for antibodies against the antigens of the coadministered vaccines, except 1 subject in preterm group I after primary vaccination who was not seroprotected against polio type 3.	
Omenaca et al, (2011) [53]	phase IIIb open, controlled multicenter prospective study	309	-56 preterm I: ≤31 w - 107 preterm II between 32 and 36 w -150 full term infants	Spain	Hib-MenC-TT and PCV7 at 2, 4, 6 months and at 16 to 18 months of age	to evaluate the immunogenicity of Hib-MenC-TT in formerly preterm infants measuring antibody specific titers 1 month postdose 3 and 1 month after the booster dose.	-the percentage of subjects with seroprotective anti-PRP antibody concentrations was ≥99% in all groups. -Booster vaccination induced marked increases in anti-PRP antibody GMCs, after a reduction of the percentage of subjects with seroprotective anti PRP before the booster -At least 99.0% and 97,3% of	Open design

							subjects in each age stratum had rSBAMenC titers ≥1:8 postprimary vaccination and post booster dose respectively. - At least 97.5% of infants in each age stratum had anti-HBs concentrations >10 mIU/mL at 1 month postdose 3 -The postdose 3 anti-HBV GMCs was significantly lower in the preterm I group than in the preterm II and full-term groups		
Baxter et al (2010) [72]	Prospective pragmatic case series	131	<32 w	UK	DT-Hib-MenC-PCV	to show antibody response in premature infants to DT-Hib-MenC-PCV, in a routine clinical situation	-98.3% and 100% of premature infants respectively developed a minimum protective antibody response; -86.6% premature infants were protected against Men C. However, only 67.8% preterm infants achieved anti-polyribosyl ribitolphosphate (PRP) antibodies >0.15µg against Hib -Responses to the different pneumococcal serogroups ranged from 67.5% to 92.5%. - In comparison to term infants, preterm infants were less likely to achieve protective levels against MenC and Hib -Protection was inferior to expected based on published premature infant clinical trial data for Hib, some pneumococcal serotypes and Men C.		
Klein et al. (2010) [50]	Observational open-label prospective study	88 -33 ≤33 w -50 >37 w	≤33-37 w	USA	IPV	To compare the humoral and cellular immune responses of preterm infants to those of term infants after the primary series of IPV given as part of a combination vaccine	-preterm and term infants developed comparable mean frequencies of poliovirus-specific memory T cell responses - About mononuclear cells (PBMCs) proliferation preterm infants were significantly less likely to have a positive stimulation index (SI) than term infants (P=0.03) - All infants with serum available for testing had a seroprotective antibody response to all 3 poliovirus serotypes -The GMCs to poliovirus serotype 1 was significantly lower in both the group of all preterm infants		
Moss et al. (2010)	Observational prospective	184	-132 preterm infants -52 full term infants	UK	PCV7 administered with Neisseria meningitidis group C (MCC), diphtheria, tetanus, pertussis, polio, and Hib vaccines	To assess pneumococcal serotype-specific IgG antibody concentrations for all PCV7 4 weeks following the third immunization, and either at 12 months of age or 4 weeks after a booster dose of PCV7	- only 36% term infants and 34% preterm infants achieved putatively protective levels against all 7 vaccine serotypes, - At 12 months of age, only 22% term infants and 11% preterm infants had putatively protective levels against all vaccine serotypes - There was a significant increase in GMCs for both term and preterm infants for all serotypes, including the 2 control serotypes from post-primary immunizations to post-fourth dose ($P < 0.01$) - Preterm birth adversely affected the GMCs to serotypes 4, 6B, 14, 19F, and 23F ($P < 0.01$).		
Omeñaca et al. (2010) [73]	Open label trial	182 -93 preterm infants -89 full term infants	-93 preterm infants -89 full term infants	Spain	DTPa, IPV, HBV, Hib	To assess Hepatitis B response of premature infants after primary and booster immunisation with hexavalent vaccine	-A total 93.4% preterm and 95.2% full-term infants responded to primary vaccination -Six preterm infants (6.59%) did not respond to primary immunization and failed to respond to the booster dose -No responders had a gestational age of at least 31 weeks and, except for two, were severe IUGR		
Faridi et al. (2009) [63]	Observational prospective	143	31-41 w	India	BCG	To evaluate immunogenicity of	-95.8% had either a reactive Mantoux test or positive LMIT 6		

	study					BCG in preterm infants through Mantoux test conversion at 12 weeks and 6 months of age in babies vaccinated with BCG at birth	months after BCG vaccination. -There were only 6 babies (4.2%) who did not show adequate responses to BCG vaccination.	

Table 4. Studies regarding vaccine immunogenicity in preterm infants [Notes: DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H. influenzae protein D conjugate vaccine; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II), MMR=measles, mumps, and rubella vaccine; GMCs= geometric mean concentrations; PRP= anti-polyribosylribitolphosphate; IPD= invasive pneumococcal disease; LMIT=leukocyte migration inhibition test].

Study (year)	**Design**	**No of pts**	**Gestational Age**	**Location**	**Vaccination**	**Objectives**	**Results**	**Bias**
Roué et al. (2014) [45]	Observational prospective population-based study	201	<37 w	France	Rotavirus vaccine	To evaluate the impact of the pentavalent rotavirus vaccine on the number of hospitalizations for rotavirus diarrhoea in preterm infants enrolled in the IVANHOE study.	- After introduction of the vaccination program, a 2.6-fold (95% CI, 1.3 to 5.2) and an 11-fold (95% CI, 3.5 to 34.8) decrease in the number of hospitalizations for rotavirus was detected in two epidemic seasons in prematurely born infants younger than 3 years of age	
Shen et al. (2013) [69]	Observational retrospective	683,354 (52903 preterm infants)	Preterm and full-term infants	Canada	Influenza	to estimate the effectiveness of seasonal influenza vaccination in all pre- and full-term infants aged 6–23 months examining influenza-coded ambulatory visits (physician office and ED visits) during influenza season periods.	-Full vaccination was associated with an overall 19% reduction in ambulatory visits (HR = 0.81; 95% CI, 0.68–0.97) -Among preterm children, full vaccination was associated with a non-significant, 28% reduction (HR = 0.72; 95% CI, 0.40–1.29). -Partial vaccination appeared ineffective in all groups.	
Rückinger et al (2010) [68]	active prospective surveillance trial	766,999 in 2000 684,862 in 2007	number of preterm born children was estimated based on the assumption that about 7% of children in Germany are born preterm.	Germany	PCV7	To evaluate the impact of PCV7 on IPD in preterm born infants comparing children born in 2000 (the only birth cohort of unvaccinated children) with those born in 2007	- A reduction in notifications of IPD per 100,000 from 15.0 to 8.5 ($P < 0.001$) in 2007 was found. -A reduction in notification rate from 26.1 to 16.7 per 100,000 comparing the 2000 with the 2007 was found also in preterm birth cohort but it was not significant ($P = 0.39$) - No preterm infants with reported IPD had received full vaccination with booster dose according to the recommended scheme. In two cases a serotype included in PCV7 was found. These two cases had not received pneumococcal vaccination prior to disease onset, although they were at an appropriate age.	- exact number of preterm born infants in Germany is unknown

Hviid (2009) [71]	Observational retrospective nationwide cohort study	879,424 -preterm infants 59,311 -full term infants 820,113	≥20	Denmark	Pw and Pa vaccine	Effectiveness of two pertussis vaccines in preterm Danish children through evaluation of pertussis hospitalisation	-For whole-cell vaccinated children, the difference in effectiveness estimated between preterm and full-term children was statistically significant (p = 0.0134). -We found that preterm children were at 91% increased risk (95% CI, 21–200%) compared to full-term children after one dose of whole-cell vaccine.	

Table 5 Studies regarding vaccine effectiveness in preterm infants. [Notes: DTaP=diphtheria, tetanus, acellular pertussis vaccine; IPV= inactivated polio vaccine; OPV=oral polio vaccine; HBV=hepatitis B vaccine; PCV7 heptavalent antipneumococcal vaccine; PCV13= tridecavalent antipneumococcal vaccine; Hib= type B Haemophilus influenzae vaccine; Hib-MenC-TT= Haemophilus influenza type B-Neisseria meningitidis serogroup C vaccine; BCG= Bacille Calmette-Guérin vaccine; PHID-CV =PCV10-non typeable H. influenzae protein D conjugate vaccine; SNAP-II: Score for Neonatal Acute Physiology II (SNAP-II), MMR=measles, mumps, and rubella vaccine; GMCs= geometric mean concentrations; PRP= anti-polyribosylribitolphosphate; IPD= invasive pneumococcal disease; LMIT=leukocyte migration inhibition test, IC=interval confidence; ED=emergency department; HR= Adjusted hazard ratios; Pw=pertussis whole vaccine; Pa=pertussis acellular vaccine].

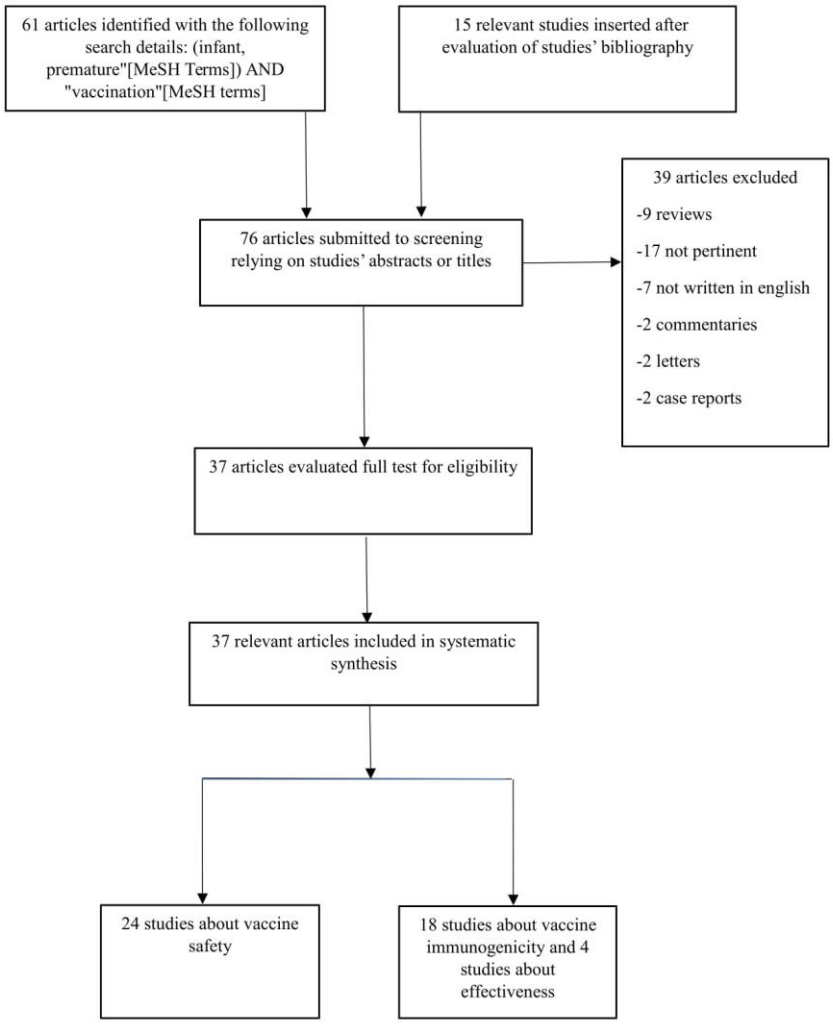

Figure 1: Four-phase flow diagram of the systematic review in accordance with PRISMA guidelines[40].

Figure 1

Four-phase flow diagram of the systematic review in accordance with PRISMA guidelines[40].