Hexavalent vaccines in preterm infants: an update by Italian Society of Pediatric Allergy and Immunology jointly with the Italian Society of Neonatology

E. Chiappini* 1, C. Petrolini 2, C. Caffarelli 3, M. Calvani 4, F. Cardinale 5, M. Duse 6, A. Licari 7, S. Manti 8, A. Martelli 9, D. Minasi 10, M. Miraglia Del Giudice 11, GB. Pajno 12, C. Pietrasanta 13, L. Pugni 13, MA. Tosca 14, F. Mosca 13 and GL. Marseglia 7

Abstract

Hexavalent vaccines, protecting against six diseases (diphtheria, tetanus, pertussis [DTaP], poliovirus, hepatitis B virus [HBV], and Haemophilus influenzae type b [Hib]), are routinely the standard of care in Europe. The use of combined vaccines allows the reduction of number of injections and side effects, the reduction of costs, and the increase in adherence of the family to the vaccination schedule both in terms of the number of doses and timing. The safety profile, efficacy and effectiveness of hexavalent vaccines have been extensively documented in infants and children born at term, and data are accumulating in preterm infants. Hexavalent vaccines are particularly important for preterm infants, who are at increased risk for severe forms of vaccine preventable diseases. However, immunization delay has been commonly reported in this age group. All the three hexavalent vaccines currently marketed in Italy can be used in preterm infants, and recent data confirm that hexavalent vaccines have a similar or lower incidence of adverse events in preterm compared to full-term infants; this is likely due to a weaker immune system response and reduced ability to induce an inflammatory response in preterm infants. Apnoea episodes are the adverse events that can occur in the most severe preterm infants and/or with history of respiratory distress. The risk of apnoea after vaccination seems to be related to a lower gestational age and a lower birth weight, supporting the hypothesis that it represents an unspecific response of the preterm infant to different procedures. High seroprotection rates have been reported in preterm infants vaccinated with hexavalent vaccine. However, a lower gestational age seems to be associated with lower antibody titres against some vaccine antigens (e.g. HBV, Hib, poliovirus serotype 1, and pertussis), regardless of the type of hexavalent vaccine used. Waiting for large effectiveness studies, hexavalent vaccines should be administered in preterm infants according to the same schedule recommended for infants born at term, considering their chronological age and providing an adequate monitoring for cardio-respiratory events in the 48–72 h after vaccination, especially for infants at risk of recurrence of apnoea.

Keywords: Vaccines, Preterm infants, Hexavalent vaccines
Introduction

In Italy, as well as in most European countries, hexavalent vaccines, protecting against six diseases (diphtheria, tetanus, pertussis [DTaP], poliovirus, hepatitis B virus [HBV], and Haemophilus influenzae type b [Hib]), are routinely the standard of care [1–6]. Combined vaccines allow the reduction of the number of injections and number of side effects, the reduction of costs and the increase in adherence of the family to the vaccination schedule both in terms of the number of doses and timing [7, 8]. As a consequence, in countries which have adopted a program based on hexavalent vaccines, the coverage rates in the first year of life are high (from 90 to 99%) and higher than those obtained in countries that use other multivalent vaccines as the only option or as an alternative to hexavalent vaccination (70–90%) [8]. According to the Italian 2017–2019 National Vaccine Prevention Plan (PNPV) schedule (Fig. 1), the primary immunization cycle with hexavalent vaccines includes 3 doses, to be administered at 3–5–11 months of age, followed by booster doses in preschool age (at 6 years) with DTaP and inactivated poliovirus vaccines (DTPa-IPV) and with dTaP-IPV in adolescents (12–18 years) and adults, to be repeated every 10 years [9]. This strategy has been associated with a dramatic reduction in the number of cases of infectious diseases targeted by the hexavalent vaccines in Italy [10]. Currently, three hexavalent vaccines are marketed in Italy, Infanrix Hexa®, Hexyon® and Vaxelis®, which can be administered in preterm infants. The European Medicines Agency (EMA) authorizes the use of the three hexavalent vaccines even in the most severe preterm infants (11–13 Fig. 2).

In term infants the three hexavalent vaccines have been proved to be not inferior to each other for immunogenicity and safety profile, even in co-administration with anti-pneumococcal and anti-rotavirus vaccination [11–15]. Moreover, large effectiveness studies have been performed in several European countries (including Sweden, Denmark, and Germany) concerning diseases such as pertussis and invasive Hib [16–18]. The safety data collected in the clinical studies on hexavalent vaccines have also demonstrated good tolerability of these vaccines, confirmed by phase IV post-
marketing surveillance studies, reporting a higher percentage, but not statistically significant, of fever and mild, transitory, local symptoms compared to vaccines with fewer components [11–13, 19, 20]. It was estimated that in 2018 approximately 500,000 preterm infants have been vaccinated with Hexyon®, while a similar number of preterm infants in the same year were vaccinated with Infanrix Hexa® and Vaxelis® [8]. A recent publication by a panel of Italian experts from the Italian Society of Hygiene and Preventive Medicine, the Italian Society of Pediatrics and the Italian Federation of Pediatrics confirmed that all the three hexavalent vaccines can be used in preterm infants (Tables 1 and 2), [7]. The panel underlined that no delay in undertaking the national vaccination schedule can be justified in preterm infants, as well as reluctance in the co-administration of other vaccines, including anti-pneumococcal vaccine and anti-rotavirus vaccines. Once the absolute contraindications are excluded, vaccination should be executed basing on the chronological age of the child [6, 21–24]. This is particularly important considering that high prevalence of sepsis [25–28], pertussis [29], and other diseases [30, 31] have been reported in preterm infants.

Despite the national and international recommendations, however, several studies have shown low vaccination rates and delays in the majority preterm infants [32–35]. A post-marketing surveillance study on vaccination with Infanrix Hexa® and Hexyon® vaccines found that only 57.6% of preterm infants of the Puglia in 2017 had been vaccinated by their 90th day of life [36]. The ACTION follow-up project (Access to Intensive Care and Neonatal Obstetrics, Access to Obstetrical and Neonatological Intensive Care follow-up project) evaluated preterm infants at 22–31 weeks of EG in 5 Italian regions in 2003–2005 (Friuli-Venezia-Giulia, Tuscany, Marche, Lazio, Calabria) and showed that the delay in starting vaccination was correlated to a lower weight and EG at birth, to a second hospitalization after discharge from the neonatal intensive care unit (NICU), to maternal / paternal unemployment, the number of children within the family, lower socio-economic status, positive anamnesis for cerebral palsy and ethnicity other than Caucasian [33]. Some possible reasons of the vaccination delay in preterm infants concern safety and efficacy of hexavalent vaccines in these children [37–40]. Hereby, we reviewed and summarized the recent literature regarding safety, efficacy and effectiveness of hexavalent vaccines in preterm infants, which further support the national and international recommendations.

Table 1 Sub-categories of preterm birth, based on gestational age. From WHO. Preterm birth. Fact sheet. 2016. www.who.int/mediacentre/factsheets/fs363/en/. (modified)

| Subcategory of preterm birth | Gestational age |
|-----------------------------|----------------|
| moderate to late preterm     | 32 to 37 weeks |
| very preterm                | 28 to 32 weeks |
| extremely preterm           | < 28 weeks    |

Preterm is defined as babies born alive before 37 weeks of pregnancy are completed.

Fig. 2 Infanrix Hexa®, Hexyon® e Vaxelis®. Summary of product characteristics as reported by EMA (European Medicine Agency). Paragraph regarding safety in preterm infants, including those born with ≤28 weeks of gestational age and/or recent history of respiratory distress.
Methods
A systematic search of the literature published from 1 January 2008 to 30 June 2019 was performed on PubMed MEDLINE and Cochrane Library databases, using the following Boolean expression (“infant, preterm” [MeSH Terms]) AND “vaccination” [MeSH terms] AND “hexavalent vaccines” [MeSH terms]) and selecting only articles published in English. The reference of articles retrieved by this search strategy were also examined in order to recover any further relevant publications. A first screening of the selected articles was carried out on the basis of the title and the abstract. We included all prospective or retrospective observational studies and clinical trials regarding efficacy, effectiveness or safety profile of hexavalent vaccines in preterm infants. Studies that carried out a comparison between the hexavalent vaccination in full-term and preterm infants and studies in which hexavalent vaccines was co-administered with other vaccination types (e.g. anti-pneumococcal, anti-rotavirus, anti-VRS, anti-influenza) were included. The non-pertinent articles, commentaries, letters, case series concerning < 10 children cases, reviews, duplicates and articles not written in English were excluded. For each study the following data were evaluated and summarized in the tables: year of publication, study design, gestational age (GA) of the population, number of study included, type of vaccination administered, outcomes (e.g. laboratory parameters for immunogenicity, clinical indicators for efficacy and reported adverse events for safety), follow-up period and any study bias / limits.

Results
Initially, 101 articles were retrieved by the search strategy. Sixteen articles regarding hexavalent vaccination in preterm infants have been identified, of which 13 and 5 concerned safety ([39, 40, 42]; Table 3) and efficacy/effectiveness (Table 4), respectively. In all these studies hexavalent vaccines were administered according to the primary 3-dose immunization schedule, as recommended by the Centers for Disease Control and Prevention [43]. Among the 13 safety studies, 11 had hexavalent vaccination [39, 40, 42], as main objective, while 2 studies had, as their main objective, other types of vaccines (anti-pneumococcal and anti-rotavirus) in co-administration with hexavalent vaccines. In 9 out of 11 safety studies on hexavalent vaccines, other vaccines were co-administered [39, 40, 42].
| Author (year)          | Study design       | Number of children | Gestational age (EG) in weeks (s) | Vaccine                              | Target | Follow-up (FU) after the vaccine | Results                                                                 | Bias                                                                 |
|-----------------------|--------------------|--------------------|----------------------------------|--------------------------------------|--------|----------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| Wilinska et al. (2016)| Observational perspective | 138                | 73 ≤ 28 s 65 > 28 s              | DTPa, IPV, HBV, Hib, Co-administration: PCV7 | Evaluate incidence of adverse events after vaccination by monitoring CR parameters and body temperature | 72 h    | • Apnea and reactivity alterations are the most frequent adverse events (4 and 9% respectively)  
  • Those born preterm who present apnea also have experienced a statistically more frequent lateonset sepsis ($p = 0.028$) and a more prolonged use of continuous positive air pressure (CPAP) ($p = 0.033$) | • No group of control vaccinated effect  
• Clinicians more readily document adverse events that occur in the immediate vicinity of the vaccine administration |
| DeMeo et al. (2015)   | Multi-center cohort retrospective | 13926              | ≤ 28 s                          | DTPa, IPV, HBV, Hib, Co-administration: PCV7 | Evaluate the number of tests for sepsis (blood culture sampling), the increased need for respiratory support, convulsions and death in 3 days after the vaccination | 3 days | • The incidence of findings for sepsis and the need for respiratory support increases after vaccination  
• Children with an EG of 23–24 weeks demonstrate an increased incidence of sepsis tests and an increased need for respiratory support compared to children with major EG (2728 weeks)  
• Gram-positive + A history of sepsis is associated with a hearing impaired incidence of investigations for sepsis after vaccination administration | • Healthy vaccinated effect  
• Clinicians more readily document adverse events that occur in the immediate vicinity of the vaccine administration |
| McCrosan et al. (2015)| Retrospective       | 344                | < 37 s                          | DTPa, IPV, HBV, Hib, Co-administration: PCV7 | Evaluate the safety of preterm vaccines | No child presented adverse events | No child presented adverse events | • Studio retrospecting scope  
• Not clear the period of follow-up |
| Anderson et al. (2012)| Retrospective       | 203                | ≤ 28 s                          | DTPa, IPV, HBV, Hib, Co-administration: PCV7 | Evaluate apnea in the 48 h following vaccination to 2 months of life | 48 h    | • 17 preterm have presented a framework clinically compatible with apnea (incidence 8.4%) after vaccinations nation than 2 months  
• Children who have experienced apnea at 2 months of age have a statistically significant lower EG and a lower birth weight  
• No reaction to subsequent vaccination doses | • Limited sample  
• Lack of cardio-saturimetric monitoring in 50% of cases at the 4 month vaccine dose |
| Clifford V et al. (2011) | Retrospective observational | 46                 | 38 < 37 s 8 ≥ 37 s             | DTPa, IPV, HBV, Hib, Co-administration: PCV7, rotavirus | Evaluate the occurrence of adverse events in the 48 h following the vaccine at 2 and 4 months of life  
• Investigate any risk factors for apnea recurrence | 48 h    | • 35/38 preterm has apnea after the 2 month vaccine, 3/38 after the 4-month vaccine  
• 7/38 (18%) has a recurrence of apnea  
• A lower birth weight ($p = 0.04$) and hospitalization due to | • Limited sample  
• Studio retrospecting scope |
| Author (year)                  | Study design                           | Number of children | Gestational age (EG) in weeks (s) | Vaccine Co-administration: | Target | Follow-up (FU) after the vaccine | Results                                                                 | Bias                                                                                                      |
|-------------------------------|----------------------------------------|--------------------|-----------------------------------|---------------------------|--------|---------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Furck et al. (2010)           | Observational perspective              | 473                | < 37 s                            | DTPa, Hib, HBV, IPV       | Germany | Evaluate the adverse events within the next 48 h the vaccine | 48 h                                                                                       | The frequency of adverse events is 10.8 and 2.8% for apnea / bradycardia and local / fever reactions, respectively.  
If incidence of apnea / bradycardia increases in co-administration with PCV7 but not in a statistically significant manner.  
The risk of experiencing episodes of apnea decreases with increasing EG  
Fever is statistically more significant in children with grade 3–4 cerebral haemorrhage or with leucomalacia periventricular (OR 8.7 and 82 respectively)  
The 3 groups do not have the same number of children  
The EG at the time of vaccination is reduced with advancing years. |
| Hacking et al. (2010)         | retrospective cohort study             | 411                | 27 s                              | DTPa, Hib, HBV, IPV       | Australia | Assess the need for support respiratory (CPAP) or of ventilation in positive international pressure sender (IPPV) within 7 days after the vaccine at 2 months | 7 days                                                                                     | 22/411 (9%) pre-term experience a worsening of respiration in the following 3 days the vaccine attributable only to immunization.  
Children who needed respiratory support after the disease have a greater previous incidence of sepsis (p = 0.02) and a greater average cumulative time of use of CPAP before the vaccine (p = 0.03). |
| Klein et al. (2010)           | Prospective self-controlled case series approach | 83                | 33 < 37 s 50 ≥ 37 s | DTPa, Hib, HBV, IPV       | United States of America | Describe the AE 30 days after each vaccination dose confrontation one frequency in preterm and born at term | 30 days                                                                                     |  No adverse events reported in the 2 groups  
The self-controlled case series analysis showed no increase in adverse events in full-term and pre-term births after no vaccination.  
Limited sample |
| Carbone et al. (2008)         | Perspective, randomized, controlled, double-blind, multicentric | 197                | < 37 s                            | DTPa, IPV, Hib, HBV       | United States of America | Evaluate the increase in CR events after vaccination in preterm | 48 h                                                                                       | No increase in CR events in the vaccine group compared to the control group  
No long-term follow-up in the control group |
| Author (year) | Study design | Number of children | Gestational age (EG) in weeks (s) | Vaccine | Target | Follow-up (FU) after the vaccine | Results | Bias |
|--------------|--------------|-------------------|-----------------------------------|---------|--------|-------------------------------|---------|------|
| Flatz et al. (2008) [40] | retrospective | 135 | < 32 s | Switzerland | DTPa, IPV, HIB, HBV, Co-administration: PCV7, anti VRS | Evaluate the frequency of CR events later hexavalent vaccination in VLBW children in the next 48 h the second dose of vaccine | 48 h | 34/135 VLBW (25%) presented a CR event after a 2-month vaccination dose |
| Klein et al. (2008) | retrospective | 497 | 456 ≤ 30 s 41 31–41 s | United States of America | DTPa, IPV, HIB, Hib Co-administration: PCV, influenza | Evaluate the factors associated with post-vaccination apnea | 48 h | 95% post-vascular apnea (62/65) occurs in preterm born ≤31 weeks of EG |
| Omenaca et al. (2012) | prospective, multicentric, randomized, controlled, double-blind trial | 250 | ≥ 27 < 37 | France, Portugal, Poland, Spain | Rotavirus Co-administration: DTPa, IPV, Hib, HBV | Evaluate the incidence of adverse events at 15 and 31 days after vaccination and any serious adverse events | 31 days | Similar frequency of adverse events reported in the vaccine group and in the placebo group (p = 0.266) |
| Omenaca et al. (2011) | prospective trial | 286 | 50 27–30 s | Spain, Greece | PHID-CV Co-administration | Evaluate the safety of PHID-CV e of vaccines co-administered with 2–4-6 | 31 days (6) | The most frequently observed systemic adverse events are |
Table 3: Studies concerning the safety of hexavalent vaccine co-administered with other types vaccine in pre-term infants (Continued)

| Author (year) | Study design | Number of children | Gestational age (EG) in weeks (s) | Vaccine | Target | Follow-up (FU) after the vaccine | Results | Bias |
|---------------|--------------|--------------------|-----------------------------------|---------|--------|----------------------------------|---------|------|
| 87            |              | 31–36 s            | with DTPa, IPV, Hib, HBV          | months and 16–18 months Evaluate the local and systemic adverse events 31 days after the vaccine dose and serious adverse events within 6 months following the booster dose | months for severe adverse events | irritability, drowsiness, fever and loss of appetite, but the incidence of high-grade systemic adverse events is low (e.g., 0.8–1.5% with regard to fever > 39°C in the 4 days following the doses of the primary cycle, 7.1% as regards the subsequent one the booster dose) | | |
|               |              | 149 ≥ 37 s         |                                   |         |        |                                  | The incidence of grade 3 local adverse events is low (< 5.3%) in both groups but greater after the booster dose in full-term births | | |
|               |              |                    |                                   |         |        |                                  | No severe adverse events were reported to be correlated with the vaccine | | |
|               |              |                    |                                   |         |        |                                  | It was noted an episode of apnea in preterm infants after the first dose vacSino but has not been considered to be related to the vaccine and left no sequelae | | |

DTPa: Diphtheria, tetanus, acellular pertussis, IPV: Polio inactivated vaccine, HBV: Hepatitis B vaccine, PCV7: Heptavalent pneumococcal vaccine, PCV13: Pneumatic anti-pneumococcal vaccine, Hib: H. influenzae type b vaccine, SNAP-II: Score for Neonatal Acute Physiology II, VLBW: Very Low Birth Weight, PHID-CV: Decavalent pneumococcal vaccine (PCV10) conjugated to the non-typable D protein of H. influenzae, CR: Cardio-respiratory, d: days
Table 4: Studies concerning the immunogenicity of hexavalent vaccination in preterm

| Author et al. (year) | Study | Number of children | Gestational age (EG) in weeks (s) | Sed | Vaccine | Target | Results | Bias |
|----------------------|-------|--------------------|----------------------------------|-----|---------|--------|---------|------|
| Vermeulen et al. (2013) | Prospective cohort observation | 68 | < 31 s | Belgium | 3 types: Pw, Pa-2, Pa-3 | Evaluate the 1-year specific cellular response in the preterm by cytokine secretion after antigenic stimulation | • More than half of the preterm vaccinated with Pw or Pa-2 develops a response at 3 and 6 months • IFNɤ to FHA and PT • No effect of the booster dose on FHA or PTTinduced IFNɤ secretion in the 3 groups • The Pa vaccine induces a greater secretion of Th2 cytokines in response to FHA and PT, compared to children vaccinated with Pw | Limited sample |
| Omeñaca et al. (2011) | Prospective | 286 | | Spain, Greece | PHID-CV Co-administration DTPa, IPV, HBV, Hib, PCV | Evaluate the immunogenicity of PHID-CV at 2, 4, 6 months by evaluating the antibody titre as OPA or GMC 1 month after the primary vaccination cycle and 1 month after the booster dose | • The percentage of subjects with a concentration of anti-PRP antibodies compatible with seroprotection is ≥99% in all groups • The booster dose induces a marked increase in anti-iPRP GMC, after a reduction in the percentage of subjects with seroprotective titres before the booster dose • At least 97.5% of the subjects in each group have concentrations of anti-HBs antibodies > 10 mIU / ml at 1 month after the third vaccination dose • The titer of anti-HBV antibodies after dose 3 is significantly lower in preterm than group I compared to those born with larger EGs | |
| Omeñaca et al. (2011) | Phase IIIb prospective, controlled, multicentric | 309 | | Spain | Hib-MenC-TT to 2, 4, 6 months and 16–18 months Co-administration DTPa, IPV, HBV, Hib, PCV, rotavirus | Evaluate the immunogenicity of Hib-MenC-TT in preterm by measuring the specific antibody titer 1 month after the third dose and 1 month after the booster dose | • Preterms and those born at term develop comparable levels of memory response of T cells to type 3 polioviruses • With regard to lympho-monocellular proliferation Preterms present less frequently a positive stimulation index compared to those born at term (p=0.03) • All subjects have serumprotective antibody titers for the 3 types of poliovirus • The GMC towards the sierotipo 1 polio was | |
| Klein et al. (2010) | Observational perspective | 88 | | United States of America | DTPa, IPV, HBV, Hib PCV co-administration | Compare the humoral and cellular response of preterm vs full term babies after the primary vaccination cycle | • Preterms and those born at term develop comparable levels of memory response of T cells to type 3 polioviruses • With regard to lympho-monocellular proliferation Preterms present less frequently a positive stimulation index compared to those born at term (p=0.03) • All subjects have serumprotective antibody titers for the 3 types of poliovirus • The GMC towards the sierotipo 1 polio was | |
### Table 4: Studies concerning the immunogenicity of hexavalent vaccination in preterm (Continued)

| Author (year) | Study | Number of children | Gestational age (EG) in weeks (s) | Sed | Vaccine | Target | Results | Bias |
|---------------|-------|-------------------|-----------------------------------|-----|---------|--------|---------|------|
| Omeñaca et al. (2010) | Prospective trial | 182 | 93 < 37 s<br>89 ≥ 37 s | Spain | DTPa, IPV, HBV, Hib | Evaluate the response to hepatitis B vaccine in preterm after the primary vaccination cycle and the booster dose | 93.4 and 95.2% of preterm and full-term babies respectively show seroprotection against HBV after the primary vaccination cycle<br>The GMCs for HBV after primary cycle are lower in the Group of preterm born than in the group of term births, although not in a statistically significant manner<br>6 preterm (6.59%) respond neither to the primary cycle nor to the booster dose<br>Non-responders have an EG ≤ 31 s of which 2 are severe IUGR |
in the same vaccination session. Regarding the safety of hexavalent vaccines in preterm infants, several studies showed a similar or lower incidence of both local and systemic adverse events in preterm compared to full-term infants, probably due to the lower ability to induce an inflammatory response in preterm infants, even when co-administered with pneumococcal vaccine. None of the serious adverse events observed in these studies were considered causally related to the vaccination. Apnoea and alterations in reactivity in preterm infants were the most frequently reported adverse events. Numerous studies have shown an increase in the incidence of apnoea episodes in preterm infants after hexavalent vaccination [40–42]. Preterm infants who have experienced apnoea episodes after hexavalent vaccination are generally those in more critical clinical conditions (e.g. previous late-onset sepsis), who required greater support through continuous positive airway pressure, and who have a positive history for similar episodes, particularly in the 24 h prior to the administration of the vaccine [40–42]. A lower birth weight (<2 kg), a lower GA (≤ 31 weeks) and chronological age (< 67 days), a positive history for similar episodes and hospitalization for complications related to prematurity are risk factors of recurrence of post-vaccination apnoea [40] also at the second dose of the vaccination schedule with variable percentage in the datasets (4.4–18%) [39, 40]. However, a causal relationship between the vaccine and the appearance of cardio-respiratory events continues to be, widely debated. The available studies are often retrospective, with no control group and with numbers of included children too limited to demonstrate a statistically significant difference in the incidence of these events in preterm infants. Furthermore, it is difficult to distinguish apnoea related to vaccination from those due to the clinical instability of preterm infants due to other associated comorbidities (e.g. periventricular hemorrhage, bronchopulmonary dysplasia or late onset sepsis). Indeed, the only available prospective randomized controlled trial by Carbone et al. suggests that the hexavalent vaccine administration is not associated with cardio-respiratory events, showing no difference in the frequency and severity of apnoea / bradycardia episodes in those who had received vaccination compared to controls. Given the potential risk of apnoea reported in several studies, however, preterm infants still hospitalized at 2 months of life should be vaccinated before discharge from the NICU with a clinical and respiratory monitoring for the 48–72 h following vaccination, particularly with regard to the very low birth weight (VLBW) preterm with a positive medical history for cardio-respiratory events, especially in the 24 h prior to the administration of the vaccine. If a cardio-respiratory episode has occurred after the first vaccine dose, the second dose should be administered in a protected environment in those individuals at high risk of recurrence.

Focusing on the immunogenicity of hexavalent vaccines, high seroprotection rates have been reported in preterm infants. However, a lower GA seems to be associated with lower antibody titres against some vaccine antigens (eg HBV, Hib, poliovirus serotype 1, and pertussis), regardless of the type of hexavalent vaccine used. These data are in agreement with previous studies in which the seroprotection rates reached 98.7–100% in preterm infants [43, 44]. Lower seroprotection rates, although still high, have been reported with respect to pertussis and Hib (92.4 and 92.5% respectively) [44]. Although lower GA and birth weight seem to be associated with lower antibody titres against Hib, a booster dose of hexavalent vaccine was able to induce a protective serological response (evaluated as anti-PRP [anti-polyribosyl ribitol phosphate] antibody concentration > 1 μg/mL) in 98.2% of preterm infants, suggesting an adequate immunological memory in this population [45]. On the other hand, the ability to induce an adequate humoral response to HBV in preterm infants is still debated. In large studies the seroprotection rates for HBV were similar in very low birth weight (VLBW) and low birth weight (LBW) (93.7% vs. 94.9% respectively). However, seroprotection rates were reinforced (≥98%) by booster vaccination for all antigens except for HBs in VLBW children: only 88.7% of those had anti-HBs antibody concentrations > or = 10 mIU/mL, compared with 96.5% of LBW children (the difference was not statistically significant) [43]. In contrast, Omenaca et al. did not observe no difference in the humoral response to HBV vaccination in preterm infants of lower GA and birth weight neither after primary nor after a booster dose [46]. Only one study investigated the T cell-mediated response in preterm infants, showing comparable levels of memory T lymphocyte response for poliovirus antigens in full-term and preterm infants after hexavalent vaccination, but the latter demonstrate several non-specific and poliovirus-specific functional T cell limitations. Moreover, although all infants developed seroprotective poliovirus antibody titers, serotype 1 titers were lower among preterm infants (P = 0.03).

The immunogenicity of the hexavalent vaccines in co-administration with other types of vaccines was evaluated in several studies [47]. Effectiveness studies regarding the use of hexavalent in preterm infants are very scarce at the moment. Furthermore, in the available studies, a 3 + 1 schedule was used characterized, as recommended by the Centers for Disease Control and Prevention [48], while in some European countries, including Italy, a reduced (2 + 1) vaccination schedule is employed. Further studies are needed in order to define in greater detail the immunogenicity and effectiveness of hexavalent vaccines with reduced schedule in preterm infants, focusing also on the potential
differences in the subgroup of severe preterm infants (< 29 weeks of EG), in order to assess the need for additional vaccine doses or for early administration of booster doses.

Conclusions

Hexavalent vaccines administered to preterm infants display a good safety and immunogenicity profile even when co-administered with other vaccines included in the Italian schedule. Summarizing the results of the present review, it should be bared in mind that: the three hexavalent vaccines available in Italy have the same indications and can be administered in preterm infants; • although further studies are needed regarding their effectiveness, no delay in vaccination of clinically stable preterm infants is justifiable; • preterm infants must be immunized according to their chronological age, in the same time and manner as those born at term; • severe preterm infants who are still hospitalized at the time when they should be vaccinated should receive the first dose during the hospitalization, particularly in the case of preterm infants ≤ 31 weeks, with a birth weight < 2.0 kg, with previous episodes of apnoea / bradycardia before vaccination and / or with severe bronchopulmonary dysplasia, in order to provide monitoring for cardiorespiratory events for the 48–72 h following vaccination; • if a cardio-respiratory episode has occurred after the first vaccination dose, the second dose should be administered in a protected environment; • the specific recommendation for the administration of hexavalent vaccines in the most severe preterm infants (≤ 28 weeks) or with a recent history of respiratory distress, as reported by EMA, includes an additional respiratory monitoring for 48 to 72 h after the vaccination.

Acknowledgements

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest with respect to the topics discussed in the article.

Authors’ contributions

Contributions to conception, CE, PC, CC; design of the work: MF, MGL; acquisition, analysis: CE, PC, CC; have drafted the work and revised it: CM. 4 Contributions to conception, CE, PC, CC; design of the work: MF, MGL; 5 Mendation for the administration of hexavalent vaccines EMA, includes an additional respiratory monitoring for cardiorespiratory events for the 48–72 h following vaccination. 48 to 72 h after the vaccination.

Competing interests

The authors declare that they have no competing interests.

Author details

1 SODc Malattie Infettive AOU Meyer, Dipartimento di Scienze della Salute, Università di Firenze, Firenze, Italy. 2 Dipartimento di Scienze della Salute, Università di Firenze, Firenze, Italy. Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy. 4 Dipartimento di Pediatría, Ospedale S. Camillo-Forlanini, Roma, Italy. 5 UOC Pediatría, Servizio di Allergologia e Pneumologia Pediatrica, Azienda Ospedaliera-Universitaria “Consorziale-Policlinico”, Ospedale Pediatrico Giovanni XXIII, Bari, Italy. 6 Dipartimento di Pediatría, Policlinico Umberto I, Università Sapienza di Roma, Roma, Italy. 7 Clinica Pediatrica, Fondazione IRCCS Policlinico “S. Matteo”, Università di Pavia, Pavia, Italy. 8 Dipartimento di Medicina Clinica e Sperimentale, Unità di Bronconeumologia Pediatrica, Università di Catania, Catania, Italy. 9 UOC Pediatría, Azienda Ospedaliera G. Salvini, Ospedali di Garbagnate Milanese e Bollate, Milano, Italy. 10 Unità Pediatrica, Ospedale di Polistena, Reggio Calabria, Italy. 11 Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Università della Campania Luigi Vanvitelli, Napoli, Italy. 12 Dipartimento di Pediatría, Unità di Allergología, Università di Messina, Messina, Italy. 13 Terapia intensiva neonatale, Fondazione IRCCS “Ca’ Granda”, Ospedale Maggiore Policlinico; Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Milano, Italy. 14 Allergologia Pediatrica, Istituto Gianninina Gaslini, Genova, Italy.

Received: 2 October 2019 Accepted: 23 October 2019

Published online: 19 November 2019

References

1. Agenzia Italiana del Farmaco. Vaccinazioni come strumento di sanità pubblica: le conclusioni del Consiglio UE. Available at the website: www. aifa.gov.it/content/vaccinazioni-come-strumento-di-sanità-pubblica-le- conclusioni-del-consiglio-ue. Last accessed 23rd September, 2019.
2. Skibinski D, Bauder B, Singh MO, et al. Combination vaccines. J Global Infect Dis. 2011;3:63–72.
3. Decker MD. Principles of pediatric combination vaccines and practical issues related to use in clinical practice. Pediatr Infect Dis J. 2001;20:10–8.
4. Maman K, Zollner Y, Greco D, et al. The value of childhood combination vaccines: from beliefs to evidence. Hum Vacc Immunother. 2015;11:2132–41.
5. Vidor E, Soubyrand B. Manufacturing DTaP-based combination vaccines: industrial challenges around essential public health tools. Expert Rev Vaccines. 2016;15:1575–82.
6. Obando-Pacheco P, Rivero-Calle I, Gomez-Rial J, et al. New perspectives for hexavalent vaccines. Vaccine. 2018;36:5485–94.
7. Onsi A, Azazi C, Bozza A, et al. Hexavalent vaccines: characteristics of available products and practical considerations from a panel of Italian experts. J Prev Med Hyg. 2018;59:E107–19.
8. White paper to understand the market structure of pediatric pertussis combination vaccines. Disponibile online al link: www.reportlinker.com/ insight-white-paper-understand-market-structure-pediatric-pertussis- combination-vaccines.html.
9. Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017–2019.
10. Pezzotti P, Bellino S, Prestinari F, et al. The impact of immunization programs on 10 vaccine preventable diseases in Italy: 1900-2015. Vaccine. 2018;36:1435–43.
11. Infanrix Hexa®, RCP. Available at the website: https://farmaci.agenziafarmaco.gov.it/af/a/ser/Qt/PdfDownloadServlet?pdfFileName=footer_000231_03496_0_RCP&sety=0&syt=0&bar1=13. Last accessed 23rd September, 2019.
12. Hegoxy®, RCP. Available at the website: https://farmaci.agenziafarmaco.gov.it/af/a/ser/Qt/PdfDownloadServlet?pdfFileName=footer_000737_042817_FL.pdf&sety=0&syt=0&bar1=13. Last accessed 23rd September, 2019.
13. Vaxelis®, RCP. Available at the website: https://www.ema.europa.eu/en/documents/product-information/vaxelisepar-product-information_it.pdf. Last accessed 23rd September, 2019.
14. Veselka T, Silvendar S, Jordanov E, et al. A randomized controlled study of DTaP-IPV-HEP-PRP-T, a fully liquid hexavalent vaccine administered in a 3, 5 and 11 to 12 month schedule. Pediatr Infect Dis J. 2017;36:87–93.
15. Silvendar S, Icardi G, Vesikari T, et al. A phase III randomized double blind clinical trial of an investigational hexavalent vaccine given at 24 and 11-12 months. Vaccine. 2016;34:3810–6.
pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine: a review of safety and immunogenicity. Vaccine. 2018;36:986–96.

62. Robinson CL, Bernstein H, Romero JR, et al. Advisory committee on immunization practices recommended immunization schedule for children and adolescents aged 18 years or younger United States, 2019. Weekly. 2019;68:112–4.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.