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IMMUNOGENICITY AND SAFETY OF DTPW-HEPB-HIB (PRP-T) VACCINE (PENTAVAC) IN INFANTS AGED 2–7 MONTHS: A POST MARKETING PHASE 4 CLINICAL TRIAL STUDY

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Abstract. *Background.* Vaccines play a critical role in safeguarding public health, particularly for children. It is imperative to proactively address safety concerns to uphold trust in their effectiveness and safety. Skepticism surrounding vaccines can have significant adverse effects on the overall well-being of the entire population, potentially leading to individuals opting out of vital vaccinations, thereby posing risks to public health. Thus, ensuring confidence in vaccine safety remains paramount. *Materials and methods.* This phase four clinical trial was conducted as a post-marketing study (PMS) on 2 to 7 month old healthy infants (N = 539) to evaluate immunity and safety of Indian pentavalent vaccine containing Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b [DTPW-HEP B-HIB (PRP-T)/PENTAVAC] in four different centers at Tehran province. Blood samples were collected from eligible infants before receiving the vaccine (2 months of age) and 1 month after the third dose (7 months of age) to determine antibodies against all antigens in the pentavalent vaccine using ELISA. *Results.* The results indicated that the immune responses demonstrated seroprotection and protective antibody levels after three doses of the vaccine for Haemophilus influenza b, diphtheria, tetanus, hepatitis B virus and *Bordetella pertussis* were 99.1%, 98.7%, 99.8%, 99.4% and 69.6%, respectively. Statistical analysis showed that the P-value for all vaccine components was similar ($P < 0.001$). The five most common side effects reported were mild fever (10%), erythema at the vaccination site (9.1%), inflammation (4.3%), pain at the vaccination site (3.3%), and restlessness (2.6%). *Conclusion.* This study's findings demonstrated a significant increase in antibody levels against all five vaccine components. In light of these results, it can be concluded that the Pentavalent vaccine is not only effective in enhancing immunity against multiple diseases but also presents minimal risk of side effects in the study population. These findings contribute to the body of evidence supporting the safety and efficacy of vaccines, underscoring their crucial role in protecting public health.

Key words: *immunity, infants, pentavalent vaccine, antibody levels, side effects, children's health.*

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ИММУНОГЕННОСТЬ И БЕЗОПАСНОСТЬ ВАКЦИНЫ DTPW-HEP B-HIB (PRP-T) (ПЕНТАВАК) У МЛАДЕНЦЕВ В ВОЗРАСТЕ 2–7 МЕСЯЦЕВ: КЛИНИЧЕСКОЕ ИСПЫТАТЕЛЬНОЕ ПОСТМАРКЕТИНГОВОЕ ИССЛЕДОВАНИЕ 4 ФАЗЫ

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Резюме. Вакцины играют критически важную роль в охране общественного здоровья, особенно для детей. Крайне важно активно решать проблемы безопасности для поддержания доверия к вакцинации. Скептицизм вокруг вакцин может иметь существенные неблагоприятные последствия для общего благополучия всего населения, потенциально приводя к тому, что люди отказываются от жизненно важных прививок, тем самым создавая риски для общественного здравоохранения. Следовательно, обеспечение уверенности в безопасности вакцин остается первостепенной задачей. *Материалы и методы.* Настоящее клиническое испытание четвертой фазы было проведено в качестве постмаркетингового исследования (PMS) на здоровых младенцах 2–7 месяцев (N = 539) для оценки иммунитета и безопасности индийской пятивалентной вакцины против дифтерии, столбняка, коклюша, гепатита B и *Haemophilus influenza* типа b [DTPW-HEPB-HIB (PRP-T)/PENTAVAC] в четырех различных центрах в провинции Тегеран. Образцы крови обследованных младенцев были собраны до введения вакцины (возраст 2 месяца) и через 1 месяц после третьей дозы (возраст 7 месяцев) для определения антител против всех антигенов пятивалентной вакцины методом ELISA. *Результаты.* Показано, что уровни серозащиты и защитных антител после трех доз вакцины против антигенов *Haemophilus influenza* типа b, дифтерии, столбняка, вирус гепатита B и коклюша составили 99,1%, 98,7%, 99,8%, 99,4% и 69,6% соответственно. Статистический анализ показал, что величина P для всех компонентов вакцины была сопоставима ($P < 0,001$). Пять наиболее распространенных побочных эффектов применения вакцины были представлены в виде умеренной лихорадки (10%), эритемы в месте вакцинации (9,1%), воспаления (4,3%), боли в месте вакцинации (3,3%) и беспокойства (2,6%). *Выводы.* Результаты настоящего исследования продемонстрировали выраженное увеличение уровня антител против всех пяти компонентов вакцины. В свете полученных результатов можно заключить, что вакцина Пентавалент не только эффективна в повышении иммунитета против указанных заболеваний, но и несет минимальный риск побочных эффектов в исследуемой популяции. Приводимые результаты вносят вклад в совокупность доказательств, подтверждающих безопасность и эффективность вакцин, подчеркивая их решающую роль в защите общественного здравоохранения.

Ключевые слова: *иммунитет, младенцы, пентавалентная вакцина, уровни антител, побочные эффекты, здоровье детей.*

Introduction

Vaccines are usually used for the health of the general public, especially children. Any concerns about efficacy and safety of vaccines should be seriously investigated [3]. If Suspicion about a vaccine may increase, it could create dangerous consequences for everyone's health as some people will avoid vaccination of their children [20]. It is important to evaluate the safety of vaccines, especially in the case of vaccines that have been used in a more limited way and there are fewer reports of their side effects.

Pentavalent vaccine includes Diphtheria, Tetanus, Pertussis, Hepatitis B and *Haemophilus influenza* type b. This vaccine has entered the national vaccination program for children in Iran since 2014 and is usually given at the ages of 2, 4, and 6 months [9].

Pentavalent vaccination aims to protect infants against five major life threatening diseases, including diphtheria, whooping cough, tetanus, hepatitis B, and *Haemophilus influenza* [13]. To date, no vaccine has been 100% effective and safe for all individuals and because of the antigen or other substances in the vaccine some show a reaction to it [22]. Equally in the case of neonatal vaccination, the health promotion of infants should also be considered; therefore it is important to evaluate the efficacy and safety in infants following pentavalent vaccination.

In this study we assessed the immunogenicity and safety of pentavalent vaccine administrated at 2, 4, 6 months of age, as well as the possible complications after the injection of the pentavalent vaccine within the first 48 hours, one week and 2 months after injection.

Materials and methods

Study group. Participants for this study included healthy male and female infants aged 2–6 months who were referred to four Health Centers in two districts of Tehran, covered by Iran University of Medical Sciences, who were scheduled to receive routine pentavalent vaccine between July 2, 2018, and February 20, 2019.

Inclusion criteria included the infant's with armpit temperature of less than 38.5, and normal clini-

cal examination at the time of vaccination, who were born from a normal pregnancy with a gestational age of 38–42 weeks from a mother seronegative for HBsAg, and received the 2/4/6 months vaccination in the same clinic and were available up to two months after the last vaccination. Infants with the history of transfusion of blood or blood products or use of immunoglobulin since birth, with significant and chronic heart, respiratory, kidney, liver and blood disease, history of any type of allergic disease or any type of sensitivity that may be exacerbated by vaccine components, history of seizures or neurological disorders, congenital or genetic immunodeficiency were excluded. Moreover, the participants who used any type of vaccine or investigational drug except the study vaccine during the study, or received one of the other routine vaccines during the study except BCG and OPV, were also excluded.

Vaccine. The PENTAVAC vaccine [DTPW-HEPB-HIB (PRP-T)] used in this study is manufactured by the Serum Institute of India and contained a combination of: Diphtheria toxoid < 25 Lf (> 30IU), Tetanus toxoid > 2.5 Lf (> 40 IU), *Bordetella pertussis* (whole cell) < 16 OU (> 4.0 IU), HBsAg (rDNA) > 10 μg, Purified capsular Hib polysaccharide (PRP) conjugated to Tetanus Toxoid (carrier protein) 10 μg, < 0.01% Thiomersal as preservative and Al^{3+} content as aluminum phosphate < 1.25 mg.

The pentavalent vaccination was administrated based on the routine national protocol of vaccination and the infants were observed for 30 min after each vaccination for immediate effects and then for 48 hours, one week and 2 months after injection following the vaccination for any complications such as fever ≥ 38.3°C, drowsiness, restlessness, persistent crying, seizure, and anaphylaxis which were registered in the questionnaire form for possible complications by parents.

Serology. For determination of antibodies against all antigens in the pentavalent vaccine, blood samples were collected at 2 months of age (pre-first vaccination) and at 7 months of age (1-month after the third vaccination). The trial was registered with the Trial Registry of Iran (IRCT2016042027498N1), the sampling protocols were approved by the Ethics Committee of Iran University of Medical Sciences, and written consent was obtained from parents/guardians of patients prior to data collection.

Antibody titers were measured by ELISA kits from DeMeditec Diagnostics GmbH (Germany). The seroprotection was considered as immune if antibody concentration were defined as follows: Anti Diphtheria IgG antibody titer of ≥ 0.1 IU/ml, Anti Tetanus IgG antibody titer of ≥ 0.1 IU/ml, Anti Pertussis IgG titer of ≥ 16 IU/ml, Anti HepB IgG antibody titer of ≥ 10 IU/ml, and Anti PRP IgG titer of ≥ 0.15 μg/ml.

Data analysis. The categorical variables were expressed as frequencies, percentages and mean, and differences in variables were assessed by Fisher's exact test. The data were analyzed using SPSS software version 22. Two-sided P values of less than 0.05 were considered statistically significant.

Results

In the first stage, a total of 658 participants entered the study and received the first dose of vaccination. As some of the parents refused to continue participating in the project due to traveling and changing their place of residence, in the second stage, the number of participants was reduced to 553. Fourteen other samples were discarded due to tube breakage, lack of volume and presence of clots, and eventually the blood samples of 539 infants including 261 girls (48.4%) and 278 boys (51.6%) who participated in both sampling times were included in results. The participant's flowchart is shown in Figure.

Tables 1 and 2 present the immunogenicity data for the pentavalent vaccine. The observed immune responses to each vaccine component considering the cut-off point of ELISA-IgG or the protective antibody showed that the average anti-Bordetella antibody titer in 2- and 7-month-old infants was 9.336±0.411 and 24.380±0.574, respectively, and 69.6% have been immunized against *Bordetella pertussis*. The average anti-*Haemophilus influenzae* antibody in 2-month-olds is 0.490±0.04 and in 7-month-olds it is 5.491±0.169 and 99.1% of 7-month-olds have been immunized against *Haemophilus influenzae* type b after 3 doses of the vaccine. The average anti-diphtheria antibody titer in 2- and 7-month-olds was 0.2420±.014 and 0.919±0.016, respectively, and after 3 doses of the vaccine 98.7% of 7-month-olds have been immunized against diphtheria. The average level of anti-tetanus antibody in a 2-month-old infant before vaccine injection was 1.127±0.047 and after three doses of vaccine was 3.497±0.078, and 99.8% got immunized against tetanus. The average antibody titer against surface antigen of hepatitis B virus (HBs-Ab) was 40.15±5.137 and 544.67±12.183 in 2 and 7-month-olds, respectively, and 99.4% protection have been achieved against hepatitis B virus. Comparison of the level of the antibodies and side effects of 5 vaccine in boys and girls revealed no significant differences in all 4 medical centers. As indicated in Table 3, inspecting the side effects after receiving each dose of the vaccine, which were monitored 48 hours, one week and two months later in person or by phone, showed mild fever (38–38.9) with 10%, erythema at the vaccination site with 9.1%, inflammation with 4.3%, pain with 3.3% and restlessness with 2.6% were five common vaccine side effects. Complications such as abscess, lymphadenitis, encephalopathy and encephalitis, meningitis, convulsions, drowsiness, anaphylactic shock were not observed in any of the children.

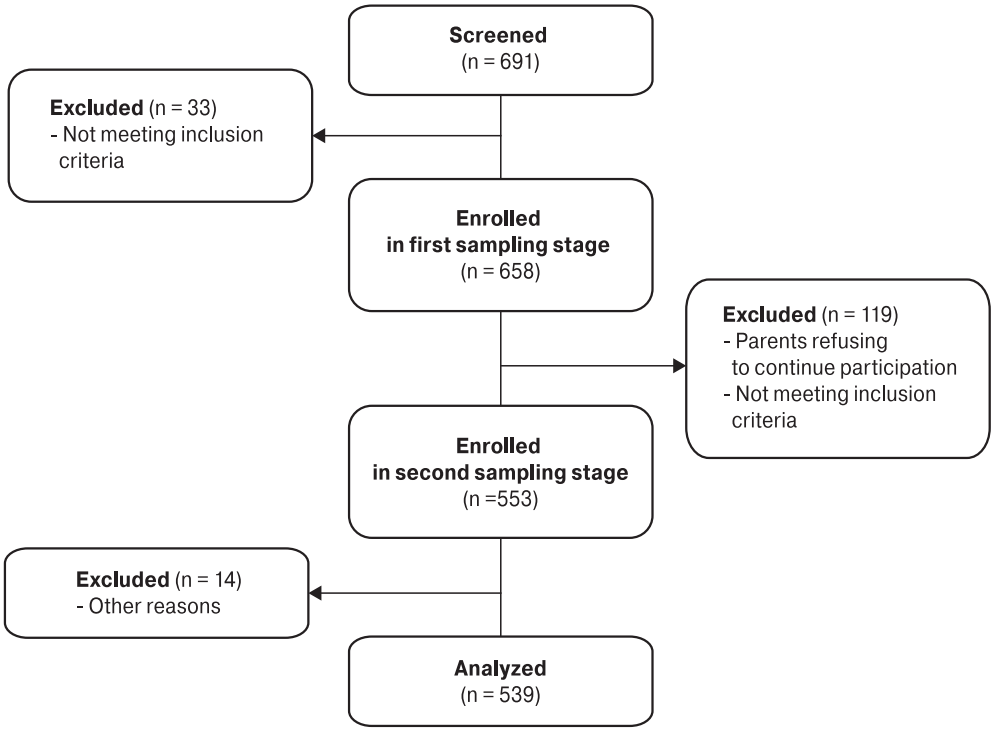

Figure. The participant's flowchart

Table 1. Antibody titers before (2 months old) and after (7 months old) Immunization

Variables	Before Vaccination, No = 539		After Vaccination, No = 539		p
	Non-Immune N (%)	Immune N (%)	Non-Immune N (%)	Immune N (%)	
Tetanus IgG	< 0.1 IU/ml 36 (6.7)	≥ 0.1 IU/ml 503 (93.3)	< 0.1 IU/ml 1 (0.2)	≥ 0.1 IU/ml 538 (99.8)	< 0.001
HBs Ab IgG	< 10 IU/ml 251 (46.5)	≥ 10 IU/ml 288 (53.4)	< 10 IU/ml 3 (0.6)	≥ 10 IU/ml 536 (99.4)	0.053
Diphtheria IgG	< 0.1 IU/ml 272 (50.5)	≥ 0.1 IU/ml 267 (49.5)	< 0.1 IU/ml 7 (1.3)	≥ 0.1 IU/ml 532 (98.7)	0.008
Hib Anti PRP IgG	< 0.15 ug/ml 175 (32.5)	≥ 0.15 ug/ml 364(67.5)	< 0.15 ug/ml 5 (0.9)	≥ 0.15 ug/ml 534 (99.1)	0.028
Pertussis IgG	< 16 IU/ml 453 (84)	≥ 16 IU/ml 86 (16)	< 16 IU/ml 164 (30.4)	≥ 16 IU/ml 375 (69.6)	< 0.001

Note. HBs: hepatitis B surface antigen; Hib: *Haemophilus influenzae* type b; PRP: polyribosyl ribitol phosphate.

Table 2. Average antibody concentration before (2 months old) and after (7 months old) Immunization

Vaccine components	Immunization state	Mean	Std. Error Mean	p
Hib	Before	0.49027	0.040869	< 0.001
	After	5.49169	0.169185	
HBs	Before	40.15051	5.137379	< 0.001
	After	544.67656	12.183976	
Diphteria	Before	0.24237	0.014602	< 0.001
	After	0.91907	0.016916	
Tetanus	Before	1.12727	0.047490	< 0.001
	After	3.49705	0.078262	
Bordetella	Before	9.33689	0.411791	< 0.001
	After	24.38097	0.574530	

Note. Hib: *Haemophilus influenzae* type b; HBs: hepatitis B surface antigen.

Table 3. Observed adverse effects associated with pentavalent vaccination

Symptoms	Primary	First Booster	Second Booster	p
Fever	54 (10)	55 (10.2)	37 (6.9)	0.043
Pain	12 (2.2)	18 (3.3)	17 (3.2)	0.461
Erythema	3 (0.6)	10 (9.1)	8 (1.5)	0.128
Inflammation	23 (4.3)	14 (2.6)	8 (1.5)	0.015
Restlessness	8 (1.5)	14 (2.6)	22 (2.4)	0.022
Anorexia	5 (0.9)	2 (0.4)	1 (0.2)	0.197
Allergic symptoms	0	3 (0.6)	0	–
Vomiting	0	0	5 (0.9)	–
Long-term crying	0	1 (0.2)	0	–

Note. Variables are represented by No. (%).

Discussion

There are many benefits for combination vaccines, such as reduced number of injections, patient's discomfort and costs. Whereas the complications

in this context are mainly pain, erythema, fever, restlessness, weakness, vomiting, irritability or sensitivity, diarrhea and unusual crying [23]. In recent years the pentavalent vaccination has been widely used for the prevention of DTP, hepatitis B and Hib [12], and different studies have been conducted to highlight its preventive effect.

Our results showed that one month after the third dose of the Pentavalent vaccine, immunogenicity levels increase significantly and the participants had no serious complications. In the study of Aspinall et al. which evaluated the immunogenicity and safety of Quinvaxem vaccine used in Switzerland, it was found that one month after the injection of the vaccine in 90% of the infants showed increased levels of immunity to all three antigens and the injection of the vaccine had not any complications [1]. Also, in another study in El Salvador, it was found that Quinvaxem vaccine was highly effective in terms of immunogenicity and safety [21].

In this study the protective antibody levels for *Haemophilus influenza* b, diphtheria, tetanus, hepatitis B virus and *Bordetella pertussis* was 99.1%, 98.7%, 99.8%, 99.4% and 69.6%, respectively. In a study conducted in India, which investigated two types of pentavalent vaccines (PENTAVAC and Eastfive), the immunogenicity of both vaccines was 100% for all vaccine components, except *Bordetella pertussis*, which was 95% and 96% for PENTAVAC and Eastfive, respectively [18].

In the study of Roa et al. which was conducted for three types of pentavalent vaccines common in India, the immunogenicity rate obtained for pertussis is 89.94%, 76.60% and 92.39% in Shan5, Easy five and TritanrixHB vaccines, respectively [4]. Although this study showed that the immunogenicity of the pertussis is less immunogenic than other antigens of the pentavalent vaccine, compared to this study, our results indicate lower amounts of anti-pertussis immunogenicity. Not only development of antibody to pertussis is less than other vaccines but also antibody against pertussis wanes overtime. To combat this issue more researches is needed and additional booster doses of vaccine should be used [14, 16].

In this study, 67.5% of 2 months old infants showed protective antibodies against *Haemophilus influenzae* b before receiving the vaccine that has reached to nearly 100% after receiving three doses, which is similar to other studies [6, 10, 15, 19]. Increased levels of antibody before vaccination is due to mothers' immunogenicity levels, which indicates the high prevalence *Haemophilus influenzae* infection in the society, as the mothers had not have a history of receiving *Haemophilus influenzae* vaccine.

In this study, 93.3% of the infants due to maternal immunity were immune against tetanus before vaccination, which increased to 99.8% at the time of second evaluation 1 month after the third dose of the vaccine. Other studies also showed similar results [7, 11]. Our results also showed that 53.4%, 49.5% and 16% of the infants were immune against Hepatitis B virus, Diphtheria and Pertussis before vaccination, respectively, which is similar to the results of other studies [2, 5, 6].

The five most common complications of the vaccine were mild fever, erythema, inflammation, pain and restlessness, which is similar to observations documented in other studies [6, 11, 17]. No complications such as abscess, lymphadenitis, encephalopathy and encephalitis, meningitis, convulsions, drowsiness, anaphylactic shock were observed in any of the children who received the vaccine.

In another study conducted on 1119 children less than one year of age, the side effects of Pentavalent vaccine 48 hours after injection showed 15.8% inflammation, 10.9% erythema, 44.2% pain, 12.6% mild fever, 15.0% decreased appetite, 32.9% irritability, 4.6% nausea and 5.5% continuous crying, and none of the children showed complications such as seizures or encephalopathy [8].

Conclusion

According to the results, this study effectively evaluated the immunogenicity of the PENTAVAC vaccine in infants, demonstrating promising out-

comes. Despite preliminary participant deduction, the analysis became primarily based on samples from 539 cases, revealing significant immune responses to all five vaccine components (diphtheria, tetanus, pertussis, Hib and hepatitis B) with significant immunogenicity levels. Furthermore, the monitoring of vaccine side effects showed that slight fever, erythema, inflammation, pain, and restlessness have been the most commonplace, without any severe complications determined. These findings support the effectiveness and safety of the pentavalent vaccine in infants. Overall, this research offers precious insights for healthcare specialists and policymakers, highlighting the significance of successful vaccination programs for infant health.

Additional information

Ethical clearance. The sampling protocols were approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.REC. 1394.26616) and written consent was obtained from parents/guardians of patients prior to data collection.

Conflict of interest. The authors had no financial interest in the vaccine nor were related to the sponsor in any way and declare that there is no conflict of interest to publish the content of this article.

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Data availability. The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Author contributions. HMA contributed to the conception of the work, MF and AN designed the study, MF and RA acquired the data, HRB and EJ analyzed the data, EJ wrote the first draft and prepared the figure, HMA and AN reviewed it critically and HRB edited the work. All authors approved the final version to be published.

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Abbreviations. BCG: bacille Calmette–Guerin; DTP: diptheria, tetanus toxoids and pertussis Vaccine; ELISA: enzyme-linked immunoassay; HBsAg: hepatitis B surface antigen; HepB: Hepatitis B; Hib: *Haemophilus influenzae* type b; IU: International Units; Lf: Limits of Flocculation; OPV: Oral poliovirus vaccines; OU: Opsonophagocytic Units; PRP: polyribosyl ribitol phosphate; rDNA: recombinant DNA.

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