ABSTRACT

Objective: to identify, in the scientific literature, evidence related to post-vaccination adverse events.
Method: integrative review to answer the guiding question ‘What is the evidence of post-vaccination adverse events of the national immunization program?’ To do so, a search for evidence was carried out between 2010 and 2015, in the SciELO library and in the LILACS and PUBMED / MEDLINE databases, with the descriptors: vaccines; adverse effects and immunization, considering the pre-established inclusion and exclusion criteria. 14 articles were selected, that were submitted to reading and analysis and organized into tables, where they were synthesized and discussed.

Results: after the analysis, two categories emerged: post-vaccination adverse events of mild / moderate intensity and those of severe intensity.

Conclusion: post-vaccination adverse events are often benign, local, and transient. Thus, the benefits outweigh the risks.

Descriptors: Vaccines; Adverse Effects; Immunization.

RESUMO

Objetivo: identificar, na literatura científica, evidências relacionadas aos eventos adversos pós-vacinação.
 Método: revisão integrativa com vistas a responder à questão norteadora ‘Qual a produção de evidências dos eventos adversos pós-vacinação do programa nacional de imunização?’ Para isso, realizou-se uma busca por evidências, entre 2010 a 2015, na biblioteca SciELO e nas bases de dados LILACS e PUBMED/ MEDLINE, com os descritores: vacinas; efeitos adversos e imunização, considerando os critérios de inclusão e exclusão pré-estabelecidos. Selecionaram-se 14 artigos que foram submetidos à leitura e à análise e organizados em tabelas, onde foram sintetizados e discutidos.

Resultados: após a análise, emergiram duas categorias: eventos adversos pós-vacinação de leve/moderada intensidade e os de grave intensidade.

Conclusão: os eventos adversos pós-vacinação são frequentemente benignos, locais e transitórios. Assim, os benefícios se sobrepõem aos riscos.

Descriptors: Vacinas; Efeitos Adversos; Imunização.

RESUMEN

Objetivo: identificar, en la literatura científica, evidencias relacionadas a los eventos adversos post-vacunación.
Método: revisión integrativa con miras a responder a la pregunta orientadora ‘¿Cuál es la producción de evidencia de los eventos adversos post vacunación del programa nacional de inmunización?’ Para ello, se realizó una búsqueda por evidencias, entre 2010 a 2015, en la biblioteca SciELO y en las bases de datos LILACS e PUBMED/ MEDLINE, con los descritores: vacunas; efectos adversos e inmunización, considerando los criterios de inclusión y exclusión preestablecidos. Se seleccionaron 14 artículos que fueron sometidos a lectura la análisis y organizados en tablas, sintetizados y discutidos.

Resultados: después del análisis, surgieron dos categorías: eventos adversos post-vacunación de intensidad leve / moderada y los de grave intensidad.

Conclusión: los acontecimientos adversos posteriores a la vacunación son a menudo benignos, locales y transitórios. Por lo que los beneficios se superponen a los riesgos.

Descriptors: Vacunas; Efectos Adversos; Inmunización.
The immunization program is one of the most important actions carried out in primary health care. Through immunization strategies, the control and eradication of diseases of great impact on public health have been achieved, in addition to the emphasis on reducing infant mortality.

Updates and the introduction of new vaccines in national immunization programs are constantly emerging. Innovations arise along with the improvement in the formulation of the vaccines, with multidoses being exchanged by presentations in monodoses to generate a smaller number of applications, to provide greater security and to reduce wastes. Vaccine safety data to generate confidence in its use are only possible after an active pharmacovigilance program has been conducted with the target population for several years of vaccine application.

As with medical interventions, vaccines are not entirely safe and unexpected adverse reactions may occur. There is no way to subdivide the benefits and risks of vaccination among the population and it is likely that one person will benefit more than another. Likewise, there is no way to predict who will be affected by adverse reactions, except in cases where there is previous knowledge regarding allergic manifestations, immunodeficiency or neurological deficit.

An Adverse Post-Vaccination Event (APVE) can be considered as any undesired medical occurrence that occurs after vaccination and, not necessarily, there is a causal relationship with the use of a vaccine or immunobiological.

APVEs may be associated with contamination, tampering, problems in the production process due to inadequate testing, packaging and storage. When correctly produced, there is the possibility of incorrect administration, errors in dosage, application or in relation to the contraindications of the vaccine, due to component allergy and immunodeficiency. Although produced and administered within the norms, adverse reactions generated by the antigens and/or constituents present in the composition of the vaccine may still arise.

The events can be classified, based on the extent, in local or systemic and according to the intensity: light, when, after the event, neither exams nor treatment are necessary; moderate, requires evaluation by a health care professional, examinations and treatment, and in the severe, hospitalization occurs for at least 24 hours, significant dysfunction or disability with sequelae.

Because the immunization service is one of the greatest demands of basic care, it is relevant to investigate the APVE, since the studies contribute to the socialization of knowledge that demystifies immunization-related myths that hinder the broad vaccine coverage and the reach of the control of the communicable diseases.

The reports of adverse events allow health professionals to monitor the most reactogenic immunobiological and thus assist in the evaluation of risks and benefits in relation to immunization. Based on this, this study is relevant because it contributes to the increase of the collection of the subject and to help in the expansion of the knowledge of the health professionals. According to the theme, this research aimed to identify, in the scientific literature, evidence related to post-vaccination adverse events.

**INTRODUCTION**

**METHOD**
Sales MCV, Araújo MCB de, Almeida CAPL et al.

with variations in Portuguese and Spanish and MeSH (Medical Subjects Headings).

The search of the indexed publications was guided by the combination of the above mentioned descriptors, used alone or in combination with the Boolean search engines (AND and OR): vaccines AND adverse effects AND immunization; vaccines OR adverse effects; immunization AND adverse effects; vaccines AND adverse effects, and its corresponding in Spanish: vaccines OR adverse effects.

In order to select the publications, the inclusion and exclusion criteria were initially applied and, afterwards, the titles and abstracts were read, with the purpose of identifying clipping that answered the guiding question, and duplicate articles were excluded in the databases. data. Afterwards, the articles were read and re-read, with the purpose of deepening the knowledge.

At the beginning of the research, 662 articles were identified and, with the application of the inclusion and exclusion criteria, 123. Therefore, 73 were excluded, after being submitted to the analysis of titles and abstracts, and 20 because they were duplicated. Thus, 16 articles were read in full and two were excluded, since the theme diverged from the objective investigated. The description of the search performed in the selected databases was presented in figure 1.

After the reading, the clippings were organized using the collection instrument validated by URSI, which contains the following variables: identification of the article by title / authors / periodical / year of publication, results / design and level of evidence.

In order to aid in the selection of the best evidence, it is recommended that the characterization be hierarchical, according to the research design, in: level I - meta-analysis of multiple controlled and randomized clinical studies; level II - individual and experimental research; level III - quasi-experimental studies; level IV - descriptive (non-experimental) or qualitative studies; level V - case or experience reports and level VI - expert opinions.

Methods should be employed in the analysis of the integrative review to ensure a thorough evaluation of the reviewed theme, providing accurate information of included studies and not just the main results. Among these methods are the observation of patterns and themes, the verification of plausibility and the making of comparisons and contrasts, to identify the variability of the data, in order to produce evidence based on a logical chain.

The results were presented in synoptic tables and the synthesis of the articles resulted in two analytical categories: post-vaccination adverse events of mild / moderate intensity and post-vaccination adverse events of severe intensity.

This study was registered in the Coordination of Research and Post-Graduation of UNINOVAFAPI University Center under process number 076/2016, on November 24, 2016. Because it was a literature review and did not involve human beings, there was no request for approval by the Research Ethics Committee (Recommendations of Resolution 466/12 of the National Health Council).
RESULTS

Of the 14 scientific papers, as shown in figure 2, half (50%) was found in international journals. Thus, seven articles are in Spanish and seven in Portuguese. As for the publication magazine, five public health, three medical, two specific nursing, one pediatrics, one epidemiology and one pharmacy were identified.

The areas that interest and act in the immunization process are comprehensive. Nursing and the pediatric medical specialty act directly in the health care of children, with the vaccination book being a tool for consultation and evaluation. Immunization is one of the main areas of public health and, with its data, it is possible to establish the epidemiological profile of the vaccinees and the vaccination coverage rates, besides the control and eradication of infectious diseases. And because they are directly related to the prevention of infectious diseases, vaccines also become a relevant topic for the pharmaceutical area.

<table>
<thead>
<tr>
<th>Article</th>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
<th>Country</th>
<th>Qualis</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Anaphylaxis associated with measles, mumps and rubella vaccine.</td>
<td>Novadzki; Rosario Filho.</td>
<td>Journal of Public health</td>
<td>Brazil</td>
<td>A2</td>
<td>2010</td>
</tr>
<tr>
<td>A2</td>
<td>Adverse events after double adult vaccine in construction workers</td>
<td>Ferreira et al.</td>
<td>Nursing Journal of UERJ</td>
<td>Brazil</td>
<td>B1</td>
<td>2010</td>
</tr>
<tr>
<td>A4</td>
<td>Frequency of adverse reactions and associated factors after administration of influenza vaccine in health personnel during the 2009-2010 season</td>
<td>Sanchez-Paya et al.</td>
<td>Spanish Journal of Public Health</td>
<td>Spain</td>
<td>B2</td>
<td>2010</td>
</tr>
<tr>
<td>A5</td>
<td>Study of the adverse effects and protective effect of influenza vaccine in the elderly vaccinated by the public network in the city of Tubarão, State of Santa Catarina.</td>
<td>Pereira et al.</td>
<td>Journal Of the Brazilian Society of Tropical Medicine</td>
<td>Brazil</td>
<td>B1</td>
<td>2011</td>
</tr>
<tr>
<td>A6</td>
<td>Adverse events after vaccination in the municipality of Campo Grande (MS, Brazil)</td>
<td>Piacentini; Contrera-Moreno.</td>
<td>Science &amp; Collective Health</td>
<td>Brazil</td>
<td>B1</td>
<td>2011</td>
</tr>
<tr>
<td>A7</td>
<td>Adverse effects of vaccination against human papillomavirus</td>
<td>Torrecilla Rojas et al.</td>
<td>Primary Care</td>
<td>Spain</td>
<td>B2</td>
<td>2011</td>
</tr>
<tr>
<td>A8</td>
<td>Adverse events after vaccination against pandemic influenza A (H1N1) 2009 in children.</td>
<td>Andrade et al.</td>
<td>Public health Records</td>
<td>Brazil</td>
<td>A2</td>
<td>2012</td>
</tr>
<tr>
<td>A10</td>
<td>Suspected adverse reactions to the MMR reported to the Pharmacovigilance Center of the Valencian Community</td>
<td>Pérez-Vilar et al.</td>
<td>Anales de Pediatría</td>
<td>Spain</td>
<td>B3</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>Surveillance of post-</td>
<td>Moura et al.</td>
<td>Epidemiology and Health</td>
<td>Brazil</td>
<td>B2</td>
<td>2015</td>
</tr>
</tbody>
</table>
A12  |  Vaccination adverse events in the state of Ceará, in 2011.  
Costa; Leão.

A13  |  Reported cases of post-vaccination adverse events: contribution to nursing care.  
Galindo Santana; Concepcion Díaz; Galindo Sardina.

A14  |  Hypotonia and Hiperreactivity episode after the application of vaccines in Cuba during the period 2012-2013.  
Cuban Journal of Tropical Medicine

Figure 2. Distribution of selected articles according to: title, authors, journal, country, qualis and year. Teresina (PI), Brazil, 2016.

With regard to the study's host country, seven were developed in Brazil; four in Spain and three in Cuba. As for the year, the one with the greatest publication was in 2010, with four articles, and in that same year the pneumococcal 10-valent pneumococcal and the meningococcal C conjugate were included in the Brazilian vaccination schedule, and this can be pointed out as a justification for the interest do not fear The years 2011 and 2015 followed both with three articles; 2012 with two; 2013 and 2014 with only one article each year. In figure 3, for a better approach, the distribution of the studies according to the immunobiological one, more quoted as reatogenic by the investigations, the major adverse events, the type of design and the level of evidence was carried out.

<table>
<thead>
<tr>
<th>Article</th>
<th>Immunobiological</th>
<th>Adverse Events</th>
<th>Outlining</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Triple Viral</td>
<td>Anaphylaxis</td>
<td>Control case</td>
<td>III</td>
</tr>
<tr>
<td>A2</td>
<td>dT</td>
<td>Pain or inflammation in the axillary region</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A3</td>
<td>Pentavalent</td>
<td>Fever, inflammation at the site of application</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A4</td>
<td>Seasonal Influenza Vs. A (H1N1)</td>
<td>Pain, malaise and myalgias</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A5</td>
<td>Seasonal Influenza</td>
<td>Malaise, runny nose, headache, fever and pain at the site of application</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A6</td>
<td>dT</td>
<td>Pain, erythema, heat, induration, fever, and hypotonic-hyporesponsive episode</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A7</td>
<td>HPV</td>
<td>Pain, edema and fever</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A8</td>
<td>Influenza A (H1N1)</td>
<td>Pain on hand, erythema at the injection site, fever, irritability</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A9</td>
<td>DTP</td>
<td>Fever, injection site reaction</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A10</td>
<td>Triple Viral</td>
<td>Edema, erythema at the site of injection, fever and rash</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A11</td>
<td>Rotavirus</td>
<td>Fever, diarrhea, vomiting, intestinal invagination</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A12</td>
<td>Tetravalent</td>
<td>Hypotonic-hyporesponsive episode and fever</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A13</td>
<td>Tetravalent</td>
<td>Pain, flushing and heat, induration, edema and erythema at the site of injection</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
<tr>
<td>A14</td>
<td>Pentavalent</td>
<td>Hypotonic-hyporesponsive episode</td>
<td>Quantitative descriptive approach</td>
<td>IV</td>
</tr>
</tbody>
</table>

Figure 3. Distribution of selected articles according to: immunobiological, adverse events, design and level of evidence. Teresina (PI), Brazil, 2016.
DISCUSSION

Influenza is a recurring theme addressed by surveys. Thus, three articles were selected that deal with the reactions of the vaccine. The triple bacterial diphtheria, tetanus and pertussis (dT) and their combinations were the most cited as causing adverse events. Evidence shows that local manifestations are the most frequent. Of these, pain was reported by seven studies, erythema in four and edema reported by three articles. Among the systemic events, the fever was the most cited, in nine studies, followed by the hypotonic-hyporesponsive episode, evidenced in three. According to the system of classification of evidence, which depend on the methodological approach adopted, the sample of this review is composed of an item with level III, which is a quasi-experimental study, and the others of level IV, which are non-experimental descriptive studies.

The studies presented mixed results regarding the post-vaccination adverse events and the indices of immunobiological reactions. Through the thematic analysis, two categories were identified to discuss the main aspects found. For a better approach, the events were divided into intensity, mild / moderate, and severe.

♦ Adverse events post-vaccination of mild / moderate intensity

The occurrence of reactions at the site of application of diphtheria and tetanus (dT) vaccine without prior antisepsis at the site of application was evaluated. Adverse reactions were evaluated 48 hours after the procedure, with evidence of only two cases of pain or tongue in the axillary region (lymphadenopathy) present only during the first day after vaccination, an expected reaction in this type of vaccine. The study concluded that there is no increase in the incidence of infections by dispensing with alcohol in skin antisepsis prior to the administration of the vaccine. However, there is no way to state that the absence of infectious signs at the site of application of the dT vaccine is related to the non-performance of antisepsis and it is necessary that randomized clinical trials be performed.

As asepsis of the user’s skin is not recommended when administering vaccines. Only water and soap or 70% alcohol should be used in cases of noticeable soiling. The use of common alcohol is not the best option for asepsis due to its low volatility and low antiseptic power. Therefore, its use should be restricted to exceptional situations, such as in the rural area and in the hospital environment.11

From January 2006 to December 2007, in Cuba, 852 post-vaccination adverse events were reported. The diphtheria, tetanus, pertussis (DTP), hepatitis B (recombinant) and Haemophilus influenzae type b (Hib) vaccine, called pentavalent, were associated with the highest number of events (252 cases). The most frequent systemic event was fever, with 511 reports, being a common manifestation for practically all the vaccines included in the study. Swelling, pain and redness at the injection site were the most commonly reported local manifestations. Errors such as vaccine preparation and storage and site-of-application error are not directly related to immunobiological composition, but can also be identified as responsible for local adverse events.12

The vaccine storage chamber should maintain the temperature between 2 °C and 8 °C until the vaccine is used, 5 °C being safest against oscillations of energy. In case of exposure to high temperatures, bacterial antigens are disrupted and release endotoxins. The aluminum hydroxide adjuvant, if preserved at 0 °C, may cause local reactions such as nodule, pain and edema. It is necessary to guarantee the quality in the conservation, since the temperature influences in the effectiveness of the immunobiológico.13

Regarding the distribution of events by intensity, the majority were mild events, 567 of the 852 events reported, with the symptomatology manifesting in the first 48 hours after vaccination and spontaneous resolution. The physicians were pointed out, by the study, as the main professionals who made the notification (36%). One possible explanation is that most of the adverse events reported, such as fever, pain, edema, among others, did not occur immediately and, therefore, motivated the population to seek medical attention, probably because they did not relate such manifestations with the vaccine, but rather with diseases that commonly affect children.12

In a survey of health workers during the 2009 vaccination campaign, in which two vaccines, seasonal influenza and influenza A (H1N1), were applied, the frequency of adverse events ranged from 24.5%, for those who received only the seasonal, to 82.6%, for H1N1. One justification is the fact that the H1N1 vaccine contains adjuvant and is responsible for the reactions. The most cited events were pain in the area of application, malaise and myalgia, with few cases of fever.
There were no reports of immediate allergic reaction after the vaccine and no serious events. Thus, both vaccines were considered safe.\textsuperscript{14}

A final sample of 129 children aged six months to two years for pandemic influenza A (H1N1) vaccination in 2009 had an incidence of adverse events after the first larger dose than after the second dose of vaccine (40.3\% vs. 35.5\%). The most common local events were pain and erythema at the site of injection, and systemic irritability, fever and vomiting, being systemic more reported than local and most classified as mild (89.7\%). The moderates were reported by (9.8\%). The incidence of systemic events is related to the age of the study participants, since these manifestations occur more frequently in those who did not have previous contact with the vaccine antigens, in this case, the children.\textsuperscript{15}

Regarding the adverse events of the influenza vaccine in the elderly over 60 years, 22.5\% had at least one adverse event. Among local reactions, pain at the site of application was the most frequent, with 3.8\%, and among the systemic reactions, malaise was the main complaint, with 11.8\%. Among the other events mentioned are: nasal discharge (8.7\%), headache (7.6\%) and fever (6.9\%). However, it was a small group of vaccinees who reported these reactions.\textsuperscript{16}

As discussed in the studies reported above, the occurrence of adverse events after influenza vaccination is infrequent and those reported without severity. Due to the mutations of the virus and its risks of causing pandemics, such as 2009, it is reaffirmed that the prospect for the future is the expansion of vaccination. Therefore, research on vaccine production should be invested as it is the most efficient way to minimize the complications of the disease and avoid cases of death.

Of the 41 reports of vaccine reactions in the city of Campo Grande (MS) in Brazil, 53.6\% occurred between the ages of zero and ten years and the majority was in children under one year old (31.7\%). One reason for this age group to be more affected is due to the immaturity of the immune system and the large number of vaccines indicated in the first year of life. The isolated vaccine that caused the most reactions was dT, with 26.8\%, indicated for those under seven years of age. When analyzing the set of immunobiologicals, the tetravalent had a predominance of reactions, with 19.5\%. Most of the manifestations came in the first 24 hours. The most commonly reported adverse events were pain, erythema and heat (22.4\%), followed by induration (18.4\%), and in 75.6\% of cases, the vaccination schedule was maintained.\textsuperscript{17}

The human papillomavirus vaccine (HPV) is the first vaccine for the prevention of cancer induced by a virus. There are many associated oncogenic genotypes, two (16 and 18) produce 60 to 80\% of cancer cases and make up the bivalent vaccine reported in the research, in which the authors report that of the 2,124 investigations that had some type of event, 467 (22\%), the main reactions were: pain (72.4\%), edema (49.5\%), fever (6.6\%) and redness (6\%), claiming to be a safe vaccine, as only about a quarter of respondents reported adverse events and none of them were considered severe.\textsuperscript{18}

In a study carried out in Cuba, 26,159 adverse events associated with vaccinations were reported in the years 1999 to 2008. The triple bacterial, DTP, and combinations thereof had the highest rate of events and the oral polio vaccine (OPV) had the lowest rates. Among the events are fever (67\%) and reactions at the injection site (17.1\%). The triple acellular bacterium (dTPa), known to be less reatogenic, is available for commercialization, however, because of its high value, it becomes unfeasible to be added to the vaccination schedule, especially for developing countries.\textsuperscript{19}

After 545,830 doses of measles, mumps and rubella vaccine (threefold virus) in five years, 96 cases of adverse events were reported, involving a total of 181 events in children under 15 years of age. The local manifestations (35.4\%) reported, more frequently, were swelling and redness at the injection site, being, respectively, 36.5\% and 22.9\%. When the systemic ones were treated (49\%), the most reported were fever (42.7\%) and rash (21.9\%).\textsuperscript{20}

A study of 402 records of EAPV, from the year 2011, was observed in the State of Ceará. The tetravalent resulted in the largest number of events, with 80.1\%. The bacterial vaccines were the majority, with 82.6\%, when compared with the viral ones, with 17.4\% of the registries. Fever greater than 39.5 ° C (12.7\%) occurred mainly due to DTP and tetravalent vaccines. As for viral vaccines, the generalized exanthema (19.5\%) had the greatest prominence.\textsuperscript{21}

Benign and / or local events such as rash, fever, headache, vomiting, pain, flushing and heat, myalgia, and others, however, such as induration and warm local abscess, have been reported for both bacterial and viral vaccines.\textsuperscript{21}
In Rio de Janeiro, 214 records of post-vaccination reports were analyzed in the period from 2010 to 2013. Data show that children under one year were the most affected (64%). Local reactions were the most significant and frequent in almost all vaccines. Pain, redness and heat were observed in 19.1%, induration (10.7%), edema (8.9%) and erythema (2.8%). The tetravalent group had the highest percentage (24.2%). The authors argue that the main reason for the reactions is the fact that the vaccine has the adjuvant aluminum hydroxide.17,21,22

Substances used in vaccines, such as the aluminum hydroxide adjuvant, have the purpose of stimulating the body’s defense system, promoting a local reaction of inflammation that assists in the immune response.3

To avoid local reactions, it is necessary to perform rotational movements of the vaccine vial for homogenization of the solution prior to dose aspiration and slow administration of the administered liquid.22

**Post-vaccination adverse events of severe intensity**

Any vaccine component has the potential to cause anaphylaxis, which is a clinical condition, sudden onset and emergency, with risk of fatality. Among the symptomatology, there are manifestations such as urticaria and erythema, associated or not with dyspnea, bronchospasm, hoarseness, cough, hypotension, cyanosis, syncope and vomiting.23

For the study sample, children aged between one and five years, who received the second dose of the triple viral vaccine, were selected. In all, 61,319 doses of the vaccine were administered and 42 reports of suspected adverse events occurred during the National Vaccination Campaign in 2004. Of these, 22 children fall into the definition of anaphylaxis. The onset of clinical manifestations ranged from zero to two hours after the vaccine, which lasted, on average, three hours. All children needed medical attention. The majority had a favorable evolution of the condition, however, two of them required the use of adrenaline.23

In another study, among all reports of triple viral events, 8.3% were classified as severe, with two cases of febrile seizure, but no anaphylaxis was reported.20

The hypotonic-hyporesponsive episode was more reported due to bacterial vaccines, with 16.3%, especially due to DTP and tetravalent. Regarding viral infections, it was reported in 9.3% of cases.21

The hypotonic-hyporesponsive episode (HHE) is considered to be of unknown and probably multifactorial pathogenesis and may result from idiosyncratic factors in the child or inherent in the vaccines. It is characterized by the sudden onset of the triad: decreased muscle tone, less responsiveness than usual to verbal stimuli or other sensory stimuli (hyporesponsiveness) and altered skin color (pallor or cyanosis). Most of the episodes appear after the administration of vaccines with the pertussis component, mainly, after the first dose, being the majority of the cases in the less than two years. The time for the onset of the signs varies from three to four hours to up to 48 hours after immunization and the duration of the signs is generally six to thirty minutes.3

In a study conducted in Cuba from January 1999 to December 2008, there were three cases of hypotonic-hyporesponsive episodes (0.01%). Other events include persistent crying (10.2%), febrile convulsions (0.4%), two cases of encephalopathy (0.008%) and two cases of anaphylaxis (0.007%).19

In a more recent study conducted in Cuba on HHE, 27 episodes were reported within a year, and 92.6% of them were caused by pentavalent, manifesting in the first 12 hours after the application of the vaccine (74%). Therefore, it is necessary to reinforce the orientation of the observation of the child in the first hours after vaccination. Most events occurred after the first dose, with those under six months being the most affected (85.4%). The hypotonic-hyporesponsive episode is an adverse event that is difficult to diagnose, since the characterization of the episode is based on signs reported, mostly by the parents, in the absence of laboratory evidence, and it is essential that health professionals are trained to the recognition of symptomatology.24

It is a difficult task to assess whether an adverse event is actually due to or coincided with vaccination, since most vaccines are given in the first few years of life, when problems such as hearing loss or developmental disorders become more visible. If the event is due to the vaccine, it is still necessary to differentiate between the reaction of the immunobiological itself and possible errors of administration, storage or handling.19

The adverse events of Calmette-Guérin bacillus (CGB), an immunobiological agent formed by live attenuated bacteria against tuberculosis, are usually related to technical errors, dosage above indicated volume and inadequate application, which can lead to
spontaneous drainage abscess, as occurred in three cases reported in the study conducted in Rio de Janeiro, at a three-year interval. Among other events, there are seven cases of hypotonic-hyporesponsive episode, five cases of febrile seizure and one case of Guillain-Barré syndrome caused by the influenza vaccine.22

Guillain-Barré syndrome - GBS is based on demyelinating inflammation of the peripheral nerves and nerve roots. Its manifestations are stages of muscle weakness with changes in sensitivity, respiratory failure, hemodynamic instability and cardiac disorders. This syndrome has little etiology and it is believed that immune stimulation has a role in its pathogenesis. In rare situations, some live attenuated virus vaccines may precede GBS.1

During the period 2007-2011, at least 185,654 rotavirus doses were administered and 37 adverse events were reported, with a reporting rate equivalent to 20 per 100,000 doses administered. Nine of the 34 reports (26%) were classified as severe. The most frequent events reported in this vaccine are fever, diarrhea and vomiting, with manifestation around three days after vaccination. Two cases of intestinal invagination occurred within the first seven days and both cases with resolution of the condition. The authors state that the vaccine has a good safety profile and the risk of invagination should be investigated in more in-depth studies.25

One of the most common causes of acute abdomen in childhood is invagination, being the most common reason for intestinal obstruction in infants. It is based on an invagination of the proximal intestine into the distal intestinal lumen. Sixty percent of cases are during the first year of life and 90% occur through the end of the second year. During the first two weeks after the rotavirus vaccine dose, episodes of abdominal pain in colic characterized by crying and flexing of the legs toward the abdomen, as well as episodes of vomiting, blood in the stool, and severe irritability should be considered. The child with suspected intussusception should be taken to the health service immediately.3

**CONCLUSION**

Evidence related to post-vaccination adverse events reports that pain, erythema and edema are the most frequent local manifestations, and among the systemic events, fever and the hypotonic-hyporesponsive episode were the most cited. Although this episode generates fear and requires emergency care, it can be characterized as short-term, does not leave sequels and most cases have a full recovery of the picture. It can thus be stated that post-vaccination adverse events are often benign, local and transient, which leads to the conclusion that the benefits of vaccination overlap with the risks.

Research proving the low reactogenicity and safety of vaccines may encourage the vaccination of individuals who avoid it because they are apprehensive of manifesting adverse events. Therefore, frequent reactions studies should be conducted to increase confidence and to publicize the benefits of vaccines, since homogeneous vaccination coverage is critical to disease control and, in some cases, eradication.

Professionals need to be refined for the notification of such events, as they are important sources of study for future research, preferably those with a high delineation level, such as the meta-analysis of multiple randomized controlled clinical studies that guarantee more credibility to results.

**REFERENCES**


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