Prevalence and factors associated with the occurrence of adverse events following immunization in children

Prevalência e fatores associados à ocorrência de eventos adversos pós-vacinação em crianças

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Abstract

Objective: To characterize adverse events following immunization in children under one year old.
Methods: Cross-sectional study conducted with data from the Brazilian Notification System on Adverse Events Following Immunization between 2009 and 2013.
Results: A total of 810 cases were analyzed, with a rate of 6.76 adverse events per 100,000 doses. Adverse events were related to the tetravalent (45.1%) and pentavalent (37.4%) vaccines, and associated with age, dosage, time elapsed from immunization, and adopted course. Hypotonic-hyporesponsive episode (27.0%) was the most prevalent event ($p<0.001$).
Conclusion: Adverse events were more frequent in children younger than three months that received the first dose of the tetravalent and pentavalent vaccines; they occurred within the first twenty-four hours following immunization, and the prevalent course consisted in changing the immunization schedule.

Resumo

Objetivo: Caracterizar os eventos adversos pós-vacinação ocorridos em crianças menores de um ano.
Métodos: Estudo transversal, realizado com dados do Sistema de Informação de Eventos Adversos Pós-vacinação, no período de 2009 a 2013.
Resultados: Foram analisados 810 casos, com uma taxa de 6,76 eventos adversos por 100.000 doses. Os eventos adversos foram mais relacionados com as vacinas tetravalente (45,1%) e pentavalente (37,4%) e associados com a idade, dose, tempo decorrido da vacinação e a conduta adotada. O episódio hipotônico hiporresponsivo (27,0%) foi o evento mais prevalente ($p<0,001$).
Conclusão: Os eventos adversos foram mais frequentes em crianças menores de três meses, que tomaram a primeira dose das vacinas tetravalente e pentavalente, ocorreram nas primeiras vinte e quatro horas pós-vacinação e a conduta mais prevalente foi a troca do esquema vacinal.

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Introduction

Vaccines are considered safe products, effective in disease prevention, and cost-effective. In their historic context, it is possible to identify important advances in the reduction of morbidity and mortality rates and in the control of communicable diseases, such as the global eradication of smallpox and the eradication of urban yellow fever in Brazil.[1-6]

Expanding and keeping high and homogeneous immunization coverage is necessary to achieve and maintain these achievements. It is important to mention that the expansion of vaccination coverage leads to the probability of occurrence of adverse events following immunization (AEFI), as vaccines are pharmacological products and are not exempt from causing adverse events in certain individuals.[1-3, 7,8]

Adverse events following immunization consist in any undesirable effect following immunization, not necessarily having a causal relation with the use of a vaccine or other immunobiological preparation. Most AEFIs are mild, local and systemic, thus, surveillance actions are focused on moderate and severe events. These events are related to several factors, such as the type of vaccine, conditions of administration, storage, and characteristics of the vaccinees. Their intensity, however, may vary from mild and expected effects such as local manifestation to moderate and severe events and rare cases, classified as unexpected.[1,3,7]

Considering the characteristics of the vaccinees, children under one year old represent the most AEFI-affected group. The highest concentration of vaccines offered and doses applied take place in this age group. Studies conducted in São Paulo and Teresina showed that the distribution of AEFI in this age group represented approximately 80% in relation to the other population segments.[7-9] In this sense, it is important to perform screening and monitoring following immunization so that AEFI are identified and intervention measures are adopted in a timely manner, enabling the maintenance of quality, safety of the vaccinees, and preservation of the reliability of the immunization.[1,9]

AEFI should be carefully investigated aiming at avoiding a mismatch of cause and effect with the immunization, especially in cases presenting the occurrence of transitory association of the complication with the immunization. On the other hand, confirmed cases of AEFI should be disclosed in order to enable health professionals to become aware of them and consequently adopt specific preventive measures, as well as prescribe immunizations with a higher level of safety.[1,3,6]

Considering the relevance of information on AEFI for public health, safe immunization, and maintenance of the advances in the control of immunopreventable diseases, the objective of the present study was to characterize AEFI in children under one year old.

Methods

Cross-sectional, retrospective study with quantitative approach. The database consisted of secondary data from the Brazilian Notification System on Adverse Events Following Immunization (SI-EAPV, as per its acronym in Portuguese) of the State Immunization Program of Pernambuco, located in the Northeastern region of Brazil, with an estimated population of 9,208,50 inhabitants, being 137,885 (1.5%) under one year old.[10]

The study sample consisted in the total of cases of AEFI occurred in children under one year old (11 months and 29 days) between 2009 and 2013. This period was chosen because in 2009 the AEFI notification flow was organized and the network professionals were trained, and 2013 was the last year of consolidation of the database within the data collection period. Three cases were excluded due to lack of information considered necessary for the study analysis; one related to the type of adverse event and two related to the type of vaccine. Data collection occurred between September 2014 and February 2015.

Adverse event following immunization was elected as the dependent variable, classified according to the options contained in the notification sheet. In this context, the ten most recurrent events were considered in the present study. The others were classified as others and represented 27 (3.3%) of the total of AEFI.

The independent variables consisted of those related to the vaccinee (sex, age - based on the interval and number of vaccines of the national immunization schedule); time (interval between the immunization and occurrence of the adverse event - time elapsed); immunobiological (vaccine associated with the adverse event, vaccine dose); and outcome of the case related to the intensity of the event, adopted course, and progress of the case. The variable intensity of the AEFI was classified as severe (consisting in cases that required hospitalization for at least 24 hours according to the Manual of Epidemiological Surveillance of Adverse Events Following Immunization) or non-severe.[1] The categorizations of the independent variables are described in chart 1.

Descriptive data analysis was conducted based on the relative and absolute frequency distributions for all the variables. The coefficient of incidence of AEFI was calculated taking into account the number of events notified by the quantitative doses of vaccines applied within the period of the study, multiplied by 100,000 doses. The association between the dependent and the independent variables was conducted through the use of Pearson's chi-squared test. The differences between all the vaccines and a comparison between the vaccines presenting higher frequency of AEFI in the population of the study were considered for the associations. Statistical significance of 5% ($p < 0.05$) was adopted; the software STATA version 12.0 was used for the analysis.

The study complied with Resolution 466/12 of the National Health Council and was approved by the Research Ethics Committee of the University Hospital Oswaldo Cruz/Cardiologic Emergency of Pernambuco, under protocol nº 741,975/2014.

Results

A total of 1,167 cases of AEFI were notified to the State Program of Immunization of Pernambuco between 2009 and 2013; of these, 810 (69.4%) occurred in children under one year old. The highest frequencies of notification occurred in 2012 (33.9%) and 2013 (30.2%), whereas the lowest frequency was reported in 2009 (3.2%). The years of 2010 and 2011 accounted for 10.9% and 21.7% of the cases, respectively. The mean incidence of AEFI per dose within the period of the study was 6.76 per 100,000 doses.

It was observed that 711 (87.9%) of the cases of adverse events were related to the first two doses of vaccine. The occurrence of events prevailed in the first 24 hours (Table 1), with 515 (82.7%) having occurred in the first six hours following immunization.

Table 1. Distribution of the cases of adverse events following immunization in children under one year old (n=810)

Variables	n(%)
Age	
Under 3 months	166(20.5)
Between 3 months and 6 months	399(49.2)
Between 6 months and 9 months	187(23.1)
Between 9 months and 12 months	58(7.2)
Sex	
Female	392(48.4)
Male	418(51.6)
Dose	
1st dose	476(58.9)
2nd dose	235(29.0)
3rd dose	80(9.8)
Others	19(2.3)
Time elapsed*	
Less than 24 hours	623(80.2)
Between 1 and 7 days	124(16.0)
Above 7 days	30(3.8)

*33 cases had no information on the time of the event

Chart 1. Categorization of the independent variables related to the vaccinee, time, immunobiological agent, and outcome of the case

Assessed items	Variable	Categorization
Related to the vaccinee	Sex	Male; Female
	Age in months	Under 3; between 3 and 6; between 6 and 9; between 9 and 12
Related to time	Time elapsed	Less than 24 hours; between 1 and 7 days; more than 7 days
Related to the immunobiological agent	Vaccine associated with the event	Tetravalent; Pentavalent; Human Rotavirus Oral Vaccine (VORH); BCG; 10-valent pneumococcal (Pn10); Meningococcal C (MnC); Hepatitis B (HB); Influenza (INF); Others (DTP, Triple viral, VIP/VOP) *
	Vaccine dose	1st; 2nd; 3rd; others (1st booster shot and campaign)
Outcome of the case	Intensity	Severe; non-severe
	Course	Maintenance of immunization schedule; contraindication with and without change of immunization schedule; without course
	Progress	With sequelae; without sequelae

*Vaccine nomenclature in accordance with the National Immunization Schedule of the Ministry of Health

Of the total of adverse events, 668 (82.5%) were related to the tetravalent and pentavalent vaccines, whereas 142 (17.5%) were related to the following vaccines: VORH 27 (3.3%), BCG 26 (3.1%), Pn10 17 (2.1%), MnC 17 (2.1%), HB 14 (1.8%), INF 14 (1.8%) and other vaccines (VIP/VOP, human rabies and yellow fever) 27 (3.3%). The cases of adverse effects related to the tetravalent vaccine (diphtheria, tetanus and pertussis combined with *Haemophilus influenzae* type b vaccine) corresponded to 365 (45.1%) and the events related to the pentavalent vaccine (diphtheria, tetanus, pertussis, hepatitis B (recombinant) and *Haemophilus influenzae* type b) 303 (37.4%). The associations of the cases of AEFI according to the applied vaccines are shown in table 2.

The association of the vaccines with the types of AEFI showed that hypotonic-hyporesponsive episodes (HHE) were the most frequent event among the cases of AEFI. A statistically significant difference in the HHE was observed in relation to the tetravalent in comparison with the pentavalent and the other vaccines (Table 3).

The progress of the cases of AEFI consisted of cure without sequelae in 807 (99.6%) cases. One case, classified as severe and/or unusual event, evolved to cure with sequelae; two cases, classified as fever higher than 39.5ºC and local cold abscess, had not recorded the progress. Regarding the course adopted by the health staff, 457 (56.4%) considered the immunization as contraindicated and consequent change of schedule, 267 (32.9%) maintained the schedule, 54 (6.7%) did not adopt any course, and 32 (3.9%) considered as contraindicated, but without change of schedule. In relation to the intensity of the event, 776 (95.8%) of the notified events were classified as non-severe and 34 (4.2%) as severe.

Table 2. Association of adverse events following immunization in children under one year old according to the immunobiological agent administered and the variables analyzed

Variables	Immunobiological agent			p-value	p-value Tetra versus Penta
	Tetravalent (n=365)	Pentavalent (n=303)	Others (n = 142)		
Age					
Under 3 months	51(14.0)	71(23.5)	44(31.0)	< 0.001†	< 0.001†
Between 3 months and 6 months	188(51.5)	167(55.1)	44(31.0)		
Between 6 months and 9 months	105(28.8)	51(16.8)	31(21.8)		
Between 9 months and 12 months	21(5.7)	14(4.6)	23(16.2)		
Sex					
Female	169(46.3)	148(48.8)	75(52.8)	0.411	0.512
Male	196(53.7)	155(51.2)	67(47.2)		
Dose					
1st dose	183(50.1)	207(68.3)	86(60.6)	< 0.001†	< 0.001†
2nd dose	129(35.3)	73(24.1)	33(23.2)		
3rd dose	53(14.6)	23(7.6)	4(2.8)		
Others		0(-)	19(2.3)		
Time elapsed	0(-)				
Less than 24 hours	306(86.9)	246(84.8)	71(52.6)	< 0.001†	0.145
Between 1 and 7 days	46(13.1)	41(14.2)	37(27.4)		
Above 7 days	0(-)	3(1.0)	27(20.0)		
Course					
Contraindication with schedule change		191(63.1)	20(14.2)	< 0.001†	0.003†
Contraindication without schedule change		1(0.3)	28(19.8)		
Schedule maintained		110(36.3)	54(38.3)		
No course		1(0.3)	39(27.7)		

†Statistically significant association (p < 0.05)

Table 3. Association of cases of adverse events following immunization in children under one year old according to the immunobiological agent administered and the adverse reaction

Adverse event	Immunobiological agent			p-value	p-value Tetra versus Penta
	Tetravalent (n = 365)	Pentavalent (n = 303)	Others (n = 142)		
Hypotonic-Hyporesponsive Episode	142(38.9)	69(22.8)	8(5.6)	< 0.001†	0.001†
Fever > 39.5ºC	14(3.8)	20(6.6)	1(0.7)		
Pain, flushing, and heat	6(1.7)	5(1.6)	12(8.5)		
Fever < 39.5ºC	31(8.5)	26(8.6)	5(3.5)		
Persistent crying	34(9.3)	30(9.9)	18(12.7)		
Other severe and/or unusual events	56(15.3)	41(13.5)	10(7.0)		
Febrile seizure	7(1.9)	6(1.9)	7(4.9)		
Local warm abscess	9(2.5)	16(5.3)	19(13.4)		
Generalized rash	30(8.2)	39(12.9)	10(7.0)		
Generalized urticaria	6(1.7)	12(4.0)	6(4.3)		
Other events	30(8.2)	39(12.9)	46(32.4)		

†Statistically significant association ($p < 0.05$)

Discussion

The present study has common limitations related to the use of secondary data. Underreporting of occurrences of AEFI may exist, as well as inadequate filling of the investigation sheet, thus interfering in the quality of the collected information. Nevertheless, considering the size of the sample, the results of the study provide important information for AEFI monitoring actions and contribute to update health professionals and service managers that work in the area of immunization. It is also important to mention the scarcity of published articles that analyze the occurrence of AEFI in the first year of life.

Furthermore, this study emphasizes the fact that the increased percentage of AEFI during the studied period is probably due to the training conducted with professionals of the network and the organization of the notification flow in the state, in 2009, which may have contributed to improve the recording and detection of new cases. However, it is important to mention that since 2005 the notification of any suspected or confirmed cases of AEFI was already considered mandatory throughout the national territory.

Discussions on the risks of immunization should be balanced by the recognition of the already well established benefits in the prevention of diseases and in the disabilities and deaths caused by infectious diseases. In this sense, the identification of AEFI enables the improvement of healthcare routines for children and contributes to interventions aiming at the safety of vaccines as the passive surveillance of AEFI may be considered useful in the monitoring of vaccine-related safety.[2,6,7]

The nursing team plays a prominent role as vaccinators and vaccine room supervisors, monitoring technical and operational aspects, and in the screening and monitoring of the vaccine status of users, especially in primary health care. Therefore, studies on AEFI may contribute to the identification of opportunities to improve the actions developed in immunization rooms. Also, they may contribute to reduce the losses of opportunities for immunization, as the decisions at the moment of the vaccination screening and post-vaccination follow-up will be made more safely.[3,11,12]

Specific measures to prevent AEFI, including proper screening to verify possible contraindications or the need to postpone vaccines, continuous training for vaccinators, and education in health may contribute to the quality and safety of immunization, thus ensuring the advances verified in the eradication and control of diseases preventable by immunization. It is important to mention that the evidence on the safety and effectiveness of vaccines in the routine of immunization in children and adults are significantly favorable.[1,2,12,13]

Immunization coverage rates in Brazil are considered high, especially in relation to children, granting the country global recognition regarding immunization actions, considered an important

measure of social coverage.[1,14] The high frequency of AEFI in children under one year old found in this study was also evidenced in other studies.[7,8,15] This study points out that in this age group there is a higher concentration of vaccines applied and the immune system is still immature, increasing the probability of infectious processes, allergies, and clinical alterations that may be associated with immunization.[13,14,16,17]

The present study evidenced the predominance of AEFI in children aged between 3 and 6 months. Six of the fifteen vaccine doses are recommended for children under one year old. There were also notifications of AEFI in children between 9 and 12 months, a period in which there are no specifically recommended vaccine doses, suggesting the immunization of children with a delayed or late vaccine schedule.

Despite the slight predominance of males, no statistically significant difference of AEFI was observed between genders. A study of the CDC[12] with children evidenced the same proportion of notifications between genders. A study conducted in Uruguay[16] found a higher frequency for males between 2 months and 17 years old, and a study conducted in Brazil evidenced a predominance of female children.[15]

Tetravalent and pentavalent vaccines presented the highest frequency of AEFI. Other studies associated AEFI with DTP[15] and BCG.[8] The tetravalent vaccine was implemented in the routine of immunization of the Unified Health System in 2002 and the pentavalent vaccine in 2012. The combination of vaccines enables a reduction of operational and logistic costs and provides a higher level of comfort to users (displacements to health units, number of injections applied, and reduction in the occurrence of local manifestations associated with less exposure).[1,18] These aspects may contribute to increase adherence to immunization.

The vaccine component related to the pertussis toxin, used in the prevention of pertussis, is considered highly immunogenic. However, it may cause several changes in the immune response, such as hypersensitivity and development of autoimmune diseases. The association of AEFI with the DPT, tetravalent, and pentavalent vaccines containing this toxin may not be confirmed unless specific tests are performed to prove the causal relation considering all the components present in these immunological agents.[7,17,19]

However, after the implementation of the tetravalent vaccine, some states registered increase in the number of cases of AEFI, especially HHE.[19] In this study, HHE were the most prevalent event, and other severe and unusual events associated with the tetravalent and pentavalent vaccines were registered. Studies conducted in Teresina and Campo Grande verified HHE as the second and fourth[8,15] most prevalent event, and fever > 39.5º, pain, flushing, and heat as the most prevalent events.

There are few specific studies on the frequency of HHE associated with the pentavalent vaccine. HHE is characterized by the triad: decreased muscle tone, absence of response to stimuli, and altered skin color. The pathogenesis of HHE is still unknown, representing a rare condition that results in transitory signs. Most cases are reported in children under two years old.[1,20]

Regarding the outcome of the AEFI, the course in most cases was the contraindication with change in the vaccine schedule, especially related to the tetravalent and pentavalent vaccines. In most cases the intensity of the AEFI was considered non-severe and the progress consisted in cure without sequelae. Other authors also reported similar outcomes.[8,12,13]

Information on vaccine safety, contraindications, and the possible occurrences of AEFI are necessary for the control of immunopreventable diseases. Ignorance of the population may undermine reliability on the product and immunization coverage, as observed in relation to the influenza vaccine in 2012.[20,21]

In view of the above, the present study suggests the improvement of surveillance actions in relation to AEFI, accuracy in completing the notification form, and continuous education in health services in order to update professionals working in immunization rooms and guide the population on the theme to increase the reliability, quality, and safety of immunization.[1,2,22]

Conclusion

AEFI were more frequent for the tetravalent and pentavalent vaccines, and in these cases they were associated with the age (younger children) and dose (first dose). HHE was the most prevalent event. The identification of AEFI may contribute to the improvement of surveillance, children healthcare routines, and new interventions aimed at the safety of the vaccinees. The study suggests that further research be conducted to broaden knowledge on the causal relationships of AEFI with the vaccine components of the most reatogenic immunobiological agents.

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Collaborations

Santos MCS contributed with the design of the research project, analysis and interpretation of data, and writing of the article. Andrade MS collaborated in the conception and design of the article, data analysis, and critical review of its content. Pontes Netto VB collaborated in the data analysis and critical review of the study content. All the authors participated in the approval of the final version of the manuscript.

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