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Fabiana Ramos Martin de Freitas[I]

Helena Keico Sato[II]

Clélia Maria Sarmento de Souza Aranda[II]

Benedito Antonio Figueiredo Arantes[II]

Maria Aparecida Pacheco[II]

Eliseu Alves Waldman[III]

Adverse events following diphtheria, pertussis and tetanus vaccinations and factors associated with severity

ABSTRACT

OBJECTIVE: To analyze adverse events following vaccinations against diphtheria, pertussis and tetanus (AEFV-DPT) and to investigate factors associated with event severity.

METHODS: A cross-sectional study was carried out with a descriptive and analytical component covering AEFV-DPT that were notified in the State of São Paulo, Brazil, between 1984 and 2001, among children less than seven years old. Cases were defined as used in AEFV-DPT surveillance; the data source was AEFV-DPT passive surveillance. In calculating the rates, the numerator was the number of AEFV-DPT and as denominator was the number of doses applied. The association between severity of AEFV-DPT and the exposures of interest was investigated by means of non-adjusted and adjusted estimates of odds ratios, with their respective 95% confidence intervals, using non-conditional logistic regression.

RESULTS: A total of 10,059 AEFV-DPT were identified, corresponding to 6,266 children who presented one or more AEFV-DPT, 29.5% were hospitalized and 68.2% presented contraindications for subsequent DPT doses. Around 75% of the events occurred during the first six hours after vaccination. The most frequent AEFV-DPT were: fever < 39.5°C, local reactions, hypotonic-hyporesponsive episodes and convulsion. Time interval of less than one hour between vaccination and the event (OR = 2.1), first dose applied (OR=5.8) and previous personal (OR=2.2) and family (OR=5.3) neurological histories were independently associated with severe events.

CONCLUSIONS: Passive surveillance of AEFV-DPT was shown to be useful for monitoring the safety of the DPT vaccine, through describing the characteristics and magnitude of these events, and also enabling identification of possible factors associated with severe forms.

KEY WORDS: Diphtheria-tetanus-pertussis vaccine, adverse effects. Vaccines, Adverse events following vaccine. Epidemiologic surveillance. Cross-sectional studies.

INTRODUCTION

Because of the high effectiveness of vaccination, this activity forms a mandatory component of public health programs. Evaluation of vaccination programs requires continuous monitoring of the vaccination coverage, equity of access, incidence and severity of the diseases targeted in the program and also the safety of the vaccination.[4]

[I] Programa de Pós-Graduação. Faculdade de Saúde Pública (FSP). Universidade de São Paulo (USP). São Paulo, SP, Brasil

[II] Centro de Vigilância Epidemiológica "Alexandre Vranjac". Secretaria de Estado da Saúde de São Paulo. São Paulo, SP, Brasil

[III] Departamento de Epidemiologia. FSP-USP. São Paulo, SP, Brasil

Correspondence:
Eliseu Alves Waldman
Faculdade de Saúde Pública
Universidade de São Paulo
Av. Dr. Arnaldo, 715
01246-904 São Paulo, SP, Brasil
E-mail: eawaldma@usp.br

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Just like other pharmaceutical products, vaccines are not entirely free from risks. While most side effects are not serious, some vaccines have been associated with rare but serious adverse events[12] that, because they are very infrequent, are identified only after widespread use among the population.[4]

Rigorous monitoring of vaccine safety is the main instrument for maintaining confidence in and adherence to immunization programs and thereby avoiding the resurgence of diseases that have already been brought under control. This has occurred in the past, in several countries, in relation to pertussis[14] and more recently with diphtheria,[13] thus justifying the need for surveillance of adverse events following vaccination (AEFV). This surveillance has the aim of promptly identifying reactogenic batches and unknown adverse events, and also to provide backing for identifying predictive factors and at-risk groups.[23]

The combined vaccine against diphtheria, pertussis and tetanus (DPT) is the one that is most frequently associated with adverse events among the vaccines in routine use.[17] Thus, the present study had the objective of assessing AEFV-DPT and the factors associated with event severity.

METHODS

This was a cross-sectional study with descriptive and analytical component that was carried out in the State of São Paulo. There, since the mid-1980s, the coverage of the course of three doses of DPT vaccine has reached a proportion of more than 85% of the population less than one year of age. This has made it possible to bring DPT under control.*

The study population was made up of children under the age of seven years who had received at least one dose of the DPT vaccine in the State of São Paulo between 1984 and 2001. The basic scheme for this vaccination consists of applications at the ages of two, four, six and 15 months, and again at the age of five or six years.

Two case definitions were followed: one in force from 1984 to 1996 and the other from 1997 to 2001. Both of them covered children less than seven years old who were vaccinated in the State of São Paulo. The first of these was more sensitive and included AEFV-DPT identified during the first 72 hours after vaccination, independent of the severity; cases presenting the clinical syndrome of encephalopathy were considered possible for up to seven days after the vaccination. The second definition, which has been in force since 1997, excludes the mildest AEFV-DPT while keeping the severe and medium-intensity events, such as manifestations of somnolence, irritability, vomiting and anorexia.

Considering that hypotonic-hyporesponsive episodes (HHE) can be confounded with several other events, among which syncope and convulsions,[5] whenever a notified case of AEFV-DPT showed HHE and convulsions simultaneously, only convulsions were recorded as an adverse event.

Cases in which the forms giving notification of the AEFV to the surveillance body did not contain information on the vaccine received, type of adverse event presented, identification of the notification source and unit, or date when the vaccine under suspicion was applied were excluded from the study. Cases that did not present time consistency between the application of the vaccine and the start of the first manifestations were also excluded, in accordance with the Ministry of Health norms.

The data analyzed related to surveillance of AEFV for the DPT vaccine in the State of São Paulo. All the data relating to notifications of the events of interest, results from case investigations, batch identification and total numbers of doses of DPT vaccine applied were obtained from the AEFV surveillance body, which was coordinated by the Immunization Division of the "Professor Alexandre Vranjac" Epidemiological Surveillance Center, of the São Paulo State Health Department. AEFV surveillance was started in the State of São Paulo in 1984 and gained national coverage in 1992, under the coordination of the Ministry of Health. It is a passive surveillance system that receives notifications from the primary network and hospitals of both the public and private health services, with predominance of the public network. The main objectives of AEFV surveillance include discovering, quantifying, investigating and analyzing AEFV; drawing up recommendations regarding indications and contraindications for vaccines; identifying reactogenic batches and maintaining the safety of the national immunization program (NIP).

The following variables were analyzed: sex, age, date when the vaccine was applied, year when the adverse event occurred, interval between vaccine application and adverse event occurrence, types of adverse event notified, severity of the event, approach adopted, evolution, personal and family neurological antecedents and vaccine batch number.

The data for the period from 1984 to 1998 were subdivided into five different databases (using EpiInfo), covering 1984 to 1991, 1993 to 1995, 1996, 1997 and

* Centro de Vigilância Epidemiológica "Prof Alexandre Vranjac". Casos, incidência, óbitos e letalidade de tétano, coqueluche e difteria. 1979 – 2005 — Estado de S. Paulo. 2005 [accessed on Jun 4, 2005]. Available at: http://www.cve.saude.sp.gov.br/htm/zoo/tetac_7905.htm

1998. The data for 1992 were excluded because they were incomplete. The data for 1999 to 2001 were stored in software exclusive to the Ministry of Health, named the Information System for Adverse Events Following Vaccination.

All the original databases were then converted into the format of SPSS version 8. Since the variables present in the original databases did not follow the same criteria regarding name, type and classification, all the variables that entered the final analysis were standardized so that all the data could then be integrated in a single database. Before this last stage, consistency analysis was performed on all the variables, in order to eliminate double-entry of cases and the patients who did not meet the case definition criteria.

Some data relating to the two performance indicators for surveillance (acceptability and opportunity) were presented first. Following descriptive analysis, the notification rates for AEFV-DPT were then calculated by taking the total number of cases of AEFV-DPT was the numerator and the number of doses applied as the denominator.

In accordance with criteria adopted by the Centers for Disease Control and Prevention[8] and the World Health Organization (WHO),* the events classified as severe were those that resulted in hospitalization for more than 12 hours (independent of the type of event presented) and also the following events: HHE, convulsions, encephalopathy and purpura and/or hypersensitivity reactions starting within two hours of vaccine application. The other events were considered to be non-severe.

For exploratory analysis of the factors associated with the severity of AEFV, the data relating to the period when the first case definition was in force (1984 to 1996), since some of the variables of interest were unavailable from the second period. Furthermore, with the changes in case definition, the proportion of severe events became around 85% of the notified event, i.e. much above what is seen in the literature for populations exposed to vaccines.[17,20]

For bivariate and multivariate analysis, the dependent variable was taken to be the one that expressed the severity of the event. The existence of an association between severe forms of AEFV-DPT and the exposures of interest was investigated through unadjusted and adjusted estimates of odds ratios, with the respective 95% confidence intervals, using unconditional logistic regression. The statistical significance of the variables in the models was assessed by means of the likelihood ratio test.[10]

The study was submitted to and approved by the Ethics Committee of the School of Public Health of the University of São Paulo.

RESULTS

Between 1984 and 2001, around 54 million doses of DPT vaccine were applied in the State of São Paulo and 10,051 cases of AEFV-DPT were notified, corresponding to 6,266 children vaccinated, i.e. a mean of 1.6 events per case. Out of this total, 55.6% were male and the median and mean ages were, respectively, 5.0 and 11.9 months.

The mean annual number of adverse events notified over the whole period was 369, and over the last five years it was 476. Between 1997 and 2001, 367/645 (57%) of the municipalities in the State of São Paulo made at least one notification, and 33 of them (9%) did so at least once a year. Only 39 municipalities in the state had more than 15,000 inhabitant aged less than five years, thus diminishing the likelihood of identifying rare events like AEFV in the smaller municipalities.

Information regarding age, sex, date when applied, start of symptoms, main symptoms and vaccine batch number was present on more than 90% of the notification forms. The proportion was lower in relation to evolution, approach adopted and hospitalization: information on these was present on 48%, 27% and 65% of the forms. The interval between the date when the vaccine was applied and the time of notification was one day in 24% of the cases and within tem days in 74%.

Analyzing the information available for the period, 29.5% (1,661/5,632) of the cases were hospitalized. Among these, 42.2% (467/1,106) remained hospitalized for more than 12 hours, 68.2% (1,154/1,691) presented contraindications for the subsequent doses of DPT vaccine, with possible replacement by DPaT (DPT with the acellular pertussis component), and 97.4% (3,166/3,250) evolved to cure without sequelae. There were no confirmed deaths among the cases.

While the first case definition was in force, 32.0% of the notifications (1,246/3,899) were severe cases, 21.6% (767/3,547) were hospitalized and 67.9% (1,136/1,673) did not complete the subsequent doses of the vaccine. While the second definition was in force, 88.0% of the cases (2,094/2,379) were severe and 42.9% (894/2,085) were hospitalized. For the second period there were no records of the approach adopted and evolution.

* World Health Organization. Uppsala Monitoring Centre. Definitions: Serious Adverse Event or Reaction. Uppsala, Sweden; 2004 [accessed on March 30, 2005]. Available at: http://www.who-umc.org/index2.html

Table 1. Distribution of adverse events following vaccination against diphtheria, pertussis and tetanus, according to the interval between the time when the vaccine was applied and the onset of symptoms. State of São Paulo, Southeasterm Brazil 1984-2001.

Type of event	Interval (in hours)											
	< 1		1-6		7-12		13 - 24		25 - 72		> 72		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HHE*	645	35.0	1,076	58.3	71	3.8	41	2.2	12	0.7	0	0	1,845	100.0
Convulsions	262	23.6	538	48.4	185	16.6	100	9.0	27	2.4	0	0.0	1,112	100.0
Fever > 39.5°C	273	25.6	501	47.0	128	12.0	126	11.8	38	3.6	0	0.0	1,066	100.0
Fever < 39.5°C	560	23.3	1,235	51.5	308	12.8	244	10.2	53	2.2	0	0.0	2,400	100.0
Local reaction	227	16.4	632	45.7	186	13.4	232	16.8	82	5.9	24	1.7	1,383	100.0
Hypersensitivity < 2 hours	102	85.0	18	15.0	0	0.0	0	0.0	0	0.0	0	0.0	120	100.0
Hypersensitivity > 2 hours	0	0.0	97	46.6	42	20.2	54	26.0	13	6.3	2	1.0	208	100.0
Others	496	25.8	961	49.9	168	8.7	209	10.8	54	2.8	41	2.1	1,925	100.0
Total	2,565	25.5	5,058	50.2	1,088	10.8	1,006	10.0	279	2.8	67	0.7	10,059**	100.0

Source: Immunization Division of the "Professor Alexandre Vranjac" Epidemiological Surveillance Center, São Paulo State Health Department
*HHE: hypotonic-hyporesponsive episodes
** Total value corresponds to the number of events, which can be more than one per patient

For 92.4% (5,789/6,266) of the AEFV, the corresponding batches of vaccine were identified, totaling 752 batches. The mean and median numbers of events notified per batch were, respectively, 7.6 and 2. For 1.9% (11/752) of the batches, more than 50 notifications were recorded.

Around 75.0% of the cases notified began within the first six hours after vaccination. The distribution of the time intervals between the vaccine and each of the AEFV-DPT is presented in Table 1.

While the first case definition was in force, the mild reactions that were most notified were fever of less than 39.5ºC (52.6%) and local reaction (39.5%). Prominent among the severe reactions were HHE (15.4%) and convulsions (12.8%) (Table 2). Overall, the greatest proportion of AEFV occurred during the first year of life.

The notification rates for cases of local reaction, HHE and convulsions were one episode for every 35,714, 62,500 and 76,923 doses, respectively. In an investigation carried out in 1996 on a more reactogenic batch, the estimated rates of HHE and convulsions were one episode for every 3,047 and 6,095 doses applied, respectively.

Between 1997 and 2001, when mild reactions ceased to be notified, the most frequent AEFV-DPT were HHE (57.0%), convulsions (28.5%) and fever greater than 39.5ºC (34.1%). Over this period, there were also greater absolute numbers of notified cases of HHE and convulsions, such that the notification rates for these two AEFV went up to one episode for every 12,658 and 25,000 doses, respectively.

Among the AEFV with systemic manifestations, the ones that were most notified over the period of interest were HHE and convulsions; their main characteristics are presented in Table 3. In comparison with convulsions, HHE occurred in younger children, were earlier reactions and more frequently occurred following the first dose ($p<0.001$), whereas there was a higher proportion of neurological antecedents in the family among those who presented convulsions ($p<0.001$).

The bivariate and multivariate analyses for predictors of severe forms of AEFV-DPT are presented in Tables 4 and 5. The final model from the analysis, using unconditional multivariate logistic regression, showed that the following exposures were associated with event severity, independent of the others: time interval of less than one hour between vaccine application and the event (OR=2.1 and 95% CI: 1.6;2.9), first dose applied (OR=5.8 and 95% CI: 1.6;20.8), personal neurological antecedents (OR=2.2 and 95% CI: 1.1;4.8) and family neurological antecedents (OR=5.3 and 95% CI: 2.9;9.7).

Table 2. Distribution of the most frequent adverse events following vaccination against diphtheria, pertussis and tetanus, according to age group. State of São Paulo, Southeastern Brazil 1984-1996.

Characteristic	Age group			Total* (N=3,814)	p value
	< 7 months (N=2,153)	7 – 12 months (N=374)	> 12 months (N=1,287)		
HHE					<0.0001
No	1,732 (80.4%)	323 (86.4%)	1,170 (90.9%)	3,225 (84.6%)	
Yes	421 (19.6%)	51 (13.6%)	117 (9.1%)	589 (15.4%)	
Total	2,153 (100.0%)	374 (100.0%)	1,287(100.0%)	3,814 (100.0%)	
Convulsions					>0.05
No	1,863 (86.6%)	319 (85.5%)	1,141 (88.8%)	3,323 (87.2%)	
Yes	289 (13.4%)	54 (14.5%)	144 (11.2%)	487 (12.8%)	
Total	2,152 (100.0%)	373 (100.0%)	1,285 (100.0%)	3,810 (100.0%)	
Fever					>0.05
No	526 (25.8%)	101 (28.0%)	358 (36.6%)	985 (27.0%)	
Yes <39,5°C	1,101 (54.0%)	197 (54.6%)	620 (32.3%)	1,918 (52.6%)	
Yes >39,5°C	413 (20.2%)	63 (17.4%)	269 (36.1%)	745 (20.4%)	
Total	2,040 (100.0%)	361 (100.0%)	1,247 (100.0%)	3,652 (100.0%)	
Persistent crying					<0.0001
No	1,545 (83.7%)	310 (95.4%)	1,120 (97.2%)	2,975 (89.5%)	
Yes	301 (16.3%)	15 (4.6%)	32 (2.8%)	348 (10.5%)	
Total	1,846 (100.0%)	325 (100.0%)	1,152 (100.0%)	3,323 (100.0%)	
Local reaction					<0.0001
No	1,431 (66.5%)	238 (63.8%)	634 (49.3%)	2.303 (60.5%)	
Yes	720 (33.5%)	135 (36.2%)	651 (50.7%)	1,506 (39.5%)	
Total	2,151 (100.0%)	373 (100.0%)	1,285 (100.0%)	3,814 (100.0%)	
Hypersensitivity					<0.05
No	2,028 (94.2%)	348 (93.0%)	1,187 (92.2%)	3,563 (93.4%)	
Yes < 2 hours	33 (1.5%)	9 (2.4%)	42 (3.3%)	84 (2.2%)	
Yes > 2 hours	85 (3.9%)	16 (4.3%)	51 (4.0%)	152 (4.0%)	
Yes, interval ignored	6 (0.3%)	1 (0.3%)	7 (0.5%)	14 (0.4%)	
Total	2,152 (100.0%)	374 (100.0%)	1,287 (100.0%)	3,813 (100.0%)	
Local abscess					<0.005
No	2,055 (95.4%)	345 (92.2%)	1,196 (92.9%)	3,596 (94.3%)	
Yes	98 (4.6%)	29 (7.8%)	91 (7.1%)	218 (5.7%)	
Total	2,153 (100.0%)	374 (9.8%)	1,287 (100.0%)	3,814 (100.0%)	
Vomiting					<0.0001
No	1,679 (90.9%)	269 (82.82%)	983 (85.4%)	2,931 (88.2%)	
Yes	168 (17.2%)	56 (17.2%)	168 (14.6%)	392 (11.8%)	
Total	1,847 (100.0%)	325 (100.0%)	1,151 (100.0%)	3,323 (100.0%)	
Somnolence					>0.05
No	1,709 (92.6%)	306 (94.4%)	1,083 (94.1%)	3,098 (93.3%)	
Yes	137 (7.4%)	18 (5.6%)	68 (5.9%)	223 (6.7%)	
Total	1,846 (100.0%)	324 (100.0%)	1,151 (100.0%)	3,323 (100.0%)	

*Information on the child's age was not available on 84 notification forms for AEFV-DPT

Table 3. Characteristics of the hypotonic-hyporesponsive episodes and convulsions following vaccination against diphtheria, pertussis and tetanus. State of São Paulo, Southeastern Brazil 1984-2001.

Characteristic	HHE (N=1,959) N (%)	Convulsions (N=1,181) N (%)	p value
Sex			>0.05
Female	908 (46.3%)	546 (46.2%)	
Male	1,051 (53.7%)	635 (53.8%)	
Total	1,959 (100%)	1,181 (100.0%)	
Age			
Median	4 months	6 months	<0.001*
Interval between application and event			<0.001
< 1 hour	645 (34.3%)	262 (23.6%)	
1 – 6 hours	1,076 (57.3%)	538 (48.4%)	
> 6 hours	124 (6.6%)	312 (28.0%)	
Total	1,878 (100.0%)	1,112 (100.0%)	
Hospitalized			<0.001
Yes	656 (37.2%)	624 (58.8%)	
No	1,107 (62.8%)	437 (41.8%)	
Total	1,763 (100.0%)	1,061 (100.0%)	
Dose applied			<0.001
1st dose	984 (50.4%)	393 (33.5%)	
2nd dose	407 (20.8%)	248 (21.2%)	
3rd dose	266 (13.6%)	215 (18.3%)	
1st booster	228 (11.7%)	290 (24.7%)	
2nd booster	67 (3.4%)	27 (2.3%)	
Total	1,952 (100.0%)	1,173 (100.0%)	
Personal neurological antecedents			>0.05
No	456 (90.1%)	390 (92.8%)	
Yes	50 (9.9%)	30 (7.2%)	
Total	506 (100.0%)	420 (100.0%)	
Family neurological antecedents**			<0.001
No	300 (95.2%)	261 (83.9%)	
Yes	15 (2.7%)	50 (16.1%)	
Total	315 (100%)	311 (100.0%)	
Approach adopted**			>0.05
Scheme maintained	16 (4.5%)	9 (3.8%)	
Scheme suspended	341 (95.5%)	228 (96.2%)	
Total	357 (100.0%)	237 (100.0%)	

* Kruskal-Wallis test
** Information available only for the period from 1984 to 1996

DISCUSSION

The low incidences of diphtheria, pertussis and tetanus seen in the State of São Paulo over the last 20 years* indicate the favorable impact of the high coverage rates achieved with the DPT vaccine. The results presented here consistently indicate the magnitude, characteristics and factors associated with the severity of AEFV-DPT and the importance of surveillance over these events.

The analysis of these results needs to take into consideration the limitations of passive surveillance of AEFV. Among these is its low sensitivity, such that the rates of these events are underestimated because of

* Centro de Vigilância Epidemiológica "Prof Alexandre Vranjac". Casos, incidência, óbitos e letalidade de tétano, coqueluche e difteria. 1979 – 2005 – Estado de S. Paulo. 2005 [accessed on Jun 4, 2005]. Available at: http://www.cve.saude.sp.gov.br/htm/zoo/tetac_7905.htm

Table 4. Bivariate analysis for factors associated with the severity of adverse events following vaccination against diphtheria, pertussis and tetanus. State of São Paulo, Southeastern Brazil 1984-1996.

Characteristic	Clinical manifestation (N=3,899)			Unadjusted OR (95% CI)
	Non-severe	Severe	Total	
Sex				
Female	1,111	576	1687	1.0
Male	1,541	671	2,212	0.84 (0.73;0.96)
Total	2,652	1,247	3,899	
Age group				
> 12 months	970	321	1,291	1.0
Up to 6 months	1,381	772	2,153	1.7 (1.4;2.0)
7 to 12 months	255	119	374	1.4 (1.1;1.8)
Total	2,606	1,212	3,818	
Interval between application and event				
> 6 hours	783	204	987	1.0
< 1 hour	447	378	825	3.2 (2.6;4.0)
1 – 6 hours	1,206	608	1,814	2.9 (2.6;3.3)
Total	2,436	1,190	3,626	
Dose applied				
2nd booster	378	62	440	1.0
1st dose	749	497	1,246	4.0 (3.0;5.4)
2nd dose	545	243	788	2.7 (2.0;3.7)
3rd dose	416	193	609	2.8 (2.1;3.9)
1st booster	517	241	758	2.8 (2.1;3.9)
Total	2,605	1,236	3,841	
Notifications per batch				
1 to 2	90	49	139	1.0
3 to 5	72	29	101	0.7 (0.4;1.3)
6 to 10	164	58	222	0.6 (0.4;1.0)
11 to 20	485	229	714	0.9 (0.6;1.3)
21 to 34	700	333	1,033	0.9 (0.6;1.3)
35 or more	972	454	1,426	0.9 (0.6;1.2)
Total	2,483	1,152	3,635	
Personal neurological antecedents				
No	915	680	1,595	1.0
Yes	13	33	46	3.4 (1.8;6.5)
Total	928	713	1,641	
Family neurological antecedents				
No	878	603	1,481	1.0
Yes	19	67	86	5.1 (3.0;8.6)
Total	897	670	1,567	

the impossibility of having adequate numerators and denominators. Moreover, there are the difficulties in standardizing case definitions and obtaining information on re-exposure among individuals who present reactions following vaccination.[9,17,24]

The use in the present study of a denominator consisting of the number of doses applied, and not the number distributed (which has been done in other countries), have provided greater internal validity for the estimates obtained. The consistency and biological plausibility

Table 5. Final model from the multivariate analysis for factors associated with the severity of adverse events following vaccination against diphtheria, pertussis and tetanus. State of São Paulo, Southeastern Brazil 1984 -1996.

Characteristic	Adjusted OR	95% CI	p value*
Sex			
Female	1.0		> 0.05
Male	1.0	0.8;1.2	
Age group			> 0.05
> 12 months	1.0		
Up to 6 months	0.6	0.2;1.9	
7 to 12 months	0.6	0.2;2.1	
Interval between application and event			<0.0001
> 6 hours	1.0		
< 1 hour	2.1	1.6;2.9	
1 – 6 hours	1.6	1.2;2.1	
Dose applied			<0.0001
2nd booster	1.0		
1st dose	5.8	1.6;20.8	
2nd dose	4.2	1.2;15.1	
3rd dose	4.8	1.3;17.4	
1st booster	3.5	2.1;5.8	
Personal neurological antecedents			<0.0001
No	1.0		
Yes	2.2	1.1;4.8	
Family neurological antecedents			<0.0001
No	1.0		
Yes	5.3	2.9;9.7	

* Likelihood ratio test

of the present study have also strengthened its results. The acceptability and opportuneness indicators of the surveillance were close to the performance of similar systems in industrialized countries.[7,8,20]

The first case definition used was more sensitive and provided data that was more representative of the spectrum of such events. Thus, the results from this first period show that the proportion of severe cases was greater than what has been found by the passive surveillance systems for AEFV in Australia and the United States,[7,17] (10.0% and 15.0%, respectively). This suggests that the rates in the present study may have been overestimated because of notification bias, giving preference to cases of greater severity.[16]

The proportions of hospitalized cases (29.5%), cases with sequelae (2.6%) and contra-indications for subsequent doses of the whole-cell DPT vaccine (68.2%) indicate the potential impact of these events on the perception of risk among the population, and its cost to medical care. This also indicates the importance of surveillance for rapid identification of batches that are more reactogenic and groups and risk factors that should be considered in drawing up strategies aimed at making vaccination safer.

The high proportion of reactions during the first six hours after vaccination (75%) shows the importance of alerting the population regarding this, especially when dealing with groups at higher risk. Nonetheless, it also indicates the possibility that the frequency of AEFV starting later on might be underestimated.[20]

While the first case definition was in force, local reactions stood out among the mild events, although the rate found here was less than the 40% reported by Cody et al[11] (1981) and Baraff et al[1] (1984). However, such manifestations may also have been associated with other factors, such as incorrect application procedures.[22] The lower estimate in the present study is expected also to be related to notification bias, as mentioned earlier.[16]

HHE predominated among the AEFV-DPT with systemic manifestations, throughout the period of interest. The intensity of its clinical condition, even knowing that all the patients affected achieved recovery, makes it possible to infer that this has an impact on adherence to DPT vaccination.[6,15]

HHE is considered to be an AEFV that is typically associated with the DPT vaccine, even though it has been associated with other vaccines.[6,15] In Brazil, its occurrence is a contraindication for subsequent doses of the whole-cell DPT vaccine and its replacement by the acellular type. Although there have been reports of cases of HHE following application of the acellular (DPaT) and double child (DC) types of DPT vaccine, the frequency of this event under these circumstances has been found to be lower.[11,19]

The notification rate for HHE cases in the present study can be considered low when compared with the literature, in which there is a range from 36 to 250 cases per 100,000 doses applied.[6] Likewise, the rate for convulsion cases was lower than what has been observed by other authors.[3,11] The lower estimate in the present study is possibly due to the low sensitivity of passive surveillance already mentioned. Nonetheless, the relative importance of these two events in relation to the others is consistent with the literature.[5]

In analyzing the factors predicting the severity of AEFV-DPT, it was not possible to differentiate between convulsions that were or were not accompanied by fever, thus making it impossible to investigate any association between fever and convulsions following DPT vaccination.[3,5]

Bivariate analysis did not show any association between event severity and the number of cases notified per vaccine batch. This is concordant with the findings of Baraff et al,[2] (1989), who did not find that any single batch was consistently associated with higher rates, for most of the adverse events. Because of lack of information in the present study, the number of doses applied per batch was not taken into account, although this may be very variable. Nevertheless, considering that the risk was not analyzed and the number of batches giving rise to AEFV was large, while accepting that both of these are randomly distributed, it is plausible to think that the number of doses applied might not have significantly influenced the measurement of this association.

Among the factors that were shown to be associated with severity, independent of the others, the early appearance of manifestations of the event within the first hour after vaccination indicates the need for special guidance for the period immediately following the vaccination, particularly among groups at higher risk.

The first dose was another factor that was shown to be independently associated with severity, and this result was consistent with what was found by Cody et al[11] (1981). Finally, personal and family neurological antecedents were also found to be factors strongly associated with the severity of AEFV, as already described in the literature.[18,21] The biological plausibility of this result in relation to HHE cannot easily be discussed, since its physiopathogenesis has not been perfectly established.[6,15]

Since the comparison group for analyzing factors associated with the severity of AEFV was children presenting mild forms of AEFV and not children without these events, the associations may have been underestimated.

Despite its limitations, passive surveillance of AEFV has been shown to be useful, enabling better knowledge of these events through indicating the characteristics and magnitude of such events and also the factors that may be associated with severity. These information are important for continual updating of the norms in order to ensure the safety and reliability of the national immunization program.

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