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Incidence of hypotonic-hyporesponsive episodes associated to the combined DTP/Hib vaccine used in Brazilian National Immunizations Program

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Abstract

Objective: To evaluate the safety of a combined diphtheria-tetanus-whole cell pertussis-*Haemophilus influenzae* type b vaccine used on the Brazilian National Immunizations Program, chiefly the incidence of hypotonic-hyporesponsive episodes.

Method: Follow-up of a cohort of 21,064 infants (20,925 or 99.7% adhered to the study protocol), within 48 hours of vaccination with diphtheria-tetanus-whole cell pertussis-*Haemophilus influenzae* type b vaccine in health care units in the City of Rio de Janeiro, to ascertain and investigate spontaneous and solicited severe adverse events. Each child was followed-up for one dose only.

Results: The rate of hypotonic-hyporesponsive episodes was 1/1,744 doses (confirmed cases) and 1/1,495 doses (confirmed plus suspect cases). The rate of convulsions was 1/5,231 doses. No cases of apnea were detected. These results are comparable to those found in the literature with diphtheria-tetanus-whole cell pertussis vaccine.

Conclusion: The diphtheria-tetanus-whole cell pertussis-*Haemophilus influenzae* type b vaccine under study can be safely used in the National Immunizations Program, according to the current precautions and contraindications.

J Pediatr (Rio J). 2007;83(6):523-528: Active surveillance, hypotonic-hyporesponsive episodes, DTwP/Hib vaccine, safety.

Introduction

DTwP vaccine (diphtheria-tetanus toxoids and whole-cell pertussis vaccine) produced by Instituto Butantan has been distributed in Brazil since 1992, and in large scale since 1996. In 1999, Haemophilus influenzae type b (Hib) vaccine was introduced for use in infants, simultaneously with DTwP, but at a different site. In 2002, DTwP and Hib vaccines began to

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be administered as a single injection mixed at the time of administration and at the end of this year the National Immunizations Program (NIP) received from some Brazilian states reports of increased frequency of adverse events temporally related to the DTwP/Hib vaccine, chiefly hypotonic-hyporesponsive episodes (HHE).

The pathogenesis and predisposing factors of HHE are unknown and it has been referred to by various terms, such as "shock" or "collapse" and diverse case descriptions. Most cases occur within the first 12 h after immunization, and virtually all within 48 h.[1-3] The diagnosis is based on clinical description and there are no further investigations (laboratory or other) for establishing the diagnosis. HHE has been documented to occur after immunization with diphtheria, tetanus, Hib and hepatitis B vaccines, but most cases have been associated to vaccines with a pertussis component, most frequently after the primary series, and more often after pertussis whole-cell vaccines than acellular (DTaP).[1,4] In fact, use of vaccines with acellular pertussis component has been followed by decrease in rates of HHE and other adverse events.[5] However, although controversial,[6] there are strong evidences indicating that DTPw/Hib provides more lasting protection than DTaP/Hib against clinical Hib disease.[7] It is noteworthy that the DTwP/Hib vaccine has controlled all diseases intended by the vaccine in Brazil.

Since 1998, the Ministry of Health has a National System for Surveillance of Adverse Events, a passive system of reporting based on information from 22,000 Public Health Centers all over Brazil.

As available data generated from the above system were inconclusive and contradictory, a study sponsored by the Ministry of Health was conducted to estimate more precisely the incidence of HHE and other severe adverse events, such as convulsions, apnea, high fever and others. This study was conceived as the best and feasible approach to address the great concern with the safety of that vaccine among health professionals.

Methods

We followed up a cohort of infants immunized with DTwP/Hib, to ascertain and investigate spontaneous and induced severe adverse events occurring within the first 48 hours following immunization. This time window was considered appropriate to detect HHE. The study was conducted in 16 health care units of Rio de Janeiro City, and covering all programmatic areas of the municipality. They were believed to provide a reasonable representation of the target population for the purpose of this study, given the high vaccination coverage achieved in Rio de Janeiro. Parents and guardians of infants eligible for DTwP/Hib vaccine, who agreed to participate and signed the informed consent, were interviewed at the health care unit on the day of immunization. Parents were asked to return to the health care unit for follow-up interview 2-3 days after immunization. Those who did not return were interviewed by phone or at home.

All infants in their first year of life, who were given a dose of DTwP/Hib in one of the selected health care units, were invited to participate in the study. The following comprised exclusion criteria: DTwP/Hib vaccine administered out of the public health care network, parents/guardians not available for post-vaccination interview or lack of signed informed consent.

The unit of analysis was the child, regardless of the dose of the vaccine. There was only one interview per child. Their guardians signed an informed consent approved (together with the study protocol) by the Ethics Committee from Fundação Oswaldo Cruz. The study was conducted with the collaboration of the Health Secretary of Rio de Janeiro City.

The DTwP/Hib vaccine has been manufactured through a partnership of Bio-Manguinhos (Hib component) and Butantan Institute (DTP component). It has been routinely used at 2, 4 and 6 months of age, 0.5 mL IM. Each dose has diphtheria and tetanus antigen (enough for induction of 2 IU of antitoxin in guinea pigs), pertussis antigen (equivalent to 4 IU of individual human dose), PRP conjugated to tetanus toxoid (10 µg), aluminum hydroxide (1.25 mg in aluminum) and thimerosal (0.01%).

Based on the rate of 1 per 1,400 infants (considering only one of the three first doses of the primary series) of hypotonic-hyporesponsive episodes obtained with active surveillance by Cody et al.,[8] a sample of 21,000 infants was expected to generate 15 episodes (95% confidence interval: 8-25). The field work aimed at a balanced distribution of study subjects per dose: 7,000 infants in the first, second and third doses of the vaccine. Estimation of rates for each dose in the first year of life was justified on biological grounds, and on the lack of conclusive evidence from previous research on the subject.

Personnel from health care units were trained to use a questionnaire designed to collect demographic and clinical data, and to detect signs or symptoms comprising the syndromes of interest. The vaccine lot number was also recorded. Items of the questionnaire written in easily understandable words were asked about signs of hypotonic or hyporesponsive episodes and other relevant health events regardless of the perceived link with the vaccine. Physicians or nurses from the health care unit, who collected a thorough report of the event and conducted appropriate clinical investigation to obtain a precise diagnosis, further interviewed subjects who reported any of those events. A pediatrician from the study coordinating center revised those records. All deaths, hospital admissions and other reports of severe health conditions were also investigated. Later, an adjudicating committee that included the study coordinators (physicians and nurses with clinical and programmatic expertise in adverse events following immunization) analyzed cases. This committee discussed all the data gathered from records and interviews to classify

the cases according to data elements adapted from Braun et al.,[9] namely, sudden onset of hypotonia and/or reduced response to verbal and other sensorial stimuli, and/or pallor or cyanosis. In the analysis of possible cases, other conditions that could be related to the signs and symptoms were considered, such as, postictal states, manifestations of immediate hypersensitivity, vomiting/gastroesophageal reflux, or simple sleepiness. Cases with the all three aforementioned components, and none of the alternative conditions were labeled "confirmed". Cases with incomplete clinical data that led to uncertainty about alternative conditions were categorized as "suspect". Cases were considered "indeterminate" if available data suggested hypotonic or hyporesponsive states but lacked the elements to permit a conclusion about their nature.

Finally, cases that could not be discarded based on available clinical data were openly discussed by an external data monitoring committee comprised of three senior physicians with expertise in adverse events following immunization, with no professional link to the vaccine manufacturer, who gave the last word on the classification of cases.

All collected data were obtained through answers to questions, without any direct measurement by study personnel, including fever.

An ancillary study was conducted to verify the precision of the data, with independent re-interview of parents/guardians by five selected interviewers and a supervisor, and comparison to the data collected with routine study procedures. A subsample of 820 subjects was re-interviewed, based on assumed 5% rate of discrepancy. Twenty records for each of the 41 interviewers were selected randomly, to provide a representation of study personnel. Re-interviews were conducted preferentially by telephone, or in home or hospital visits, if appropriate.

The rates of adverse events by category (HHE, convulsion, apnea, axillary temperature ≥ 39 ºC and other severe adverse events) were estimated with 95% confidence intervals (95%CI). Children included more than once by mistake had only the first observation considered for data analysis. Comparisons were made with rates reported in the literature. Descriptive analysis of adverse events included sociodemographic features, diagnosis, and time of onset, severity, outcome, immunization status and pathological history.

Data management and analysis were performed with Epi-Info® version 2000 (Centers for Disease Control, Atlanta, Georgia) and SPSS®, version 13 (SPSS Inc., Chicago, Illinois).

Results

A total of 21,064 infants immunized with DTwP/Hib from March 2004 to December 2004, were followed up, and 99.3% (20,925) of them had complete questionnaires. Parents/guardians were re-interviewed on average 4.5 days (standard deviation: 4.2) after immunization. These follow-up interviews were conducted in the health care unit for 70.5% of the volunteers, by telephone for 26.1%, and at the volunteer's home for 2.6%. Follow-up disclosed 14 cases of HHE (1/1,495 or 6.7 per 10,000; 95%CI 3.7-11.2 per 10,000), 4 of convulsions (1/5,231 or 1.9 per 10,000; 95%CI 0.5-4.9 per 10,000), 436 of high fever – axillary temperature ≥ 39 ºC – (2.1%; 95%CI 1.9-2.3%) and no cases of apnea (0.0 per 10,000; 95%CI 0-2.0 per 10,000). Fever of any degree after vaccination was found in 35.4% of children.

Seven cases of adverse events of moderate to high severity occurred 20 minutes to 24 hours after administration of DTwP/Hib and led to hospitalization (5 cases) and death (two cases). A two-month-old infant who died 23 hours after vaccination, without hospital admission, had a post-mortem diagnosis of bronchopneumonia. Another two-months-old infant was hospitalized with bronchiolitis 24 hours after vaccination, and died 5 days after. Non-fatal cases had the following diagnoses: convulsion from hyperinsulinism, aspiration pneumonia (child had bronchodisplasia), bronchiolitis, tuberculous meningitis and febrile convulsion. The latter was the only one considered to be causally related to the vaccine.

In 323 cases at least one of the items of the questionnaire indicated signs or symptoms with the potential for the adverse events of interest, namely, HHE, convulsions, apnea, high fever or other severe events and were revised by the local study coordinators (physicians or nurses) at the health care unit. Forty-six of those cases had at least one of the signs of HHE. Based on their assessment, 25 cases of HHE were identified at the local level. Further review of those cases by the medical supervisor, the coordinating committee and the external data monitoring committee led to 14 confirmed or suspect cases. (Table 1). Three cases were classified as Indeterminate and disregarded in the other analyses.

Among the 14 confirmed or suspect cases time of onset of signs ranged from 30 minutes to 24 hours (median of 2 hours). Episodes lasted from 10 minutes to 4 hours (median of 45 minutes). The rate of HHE related to the third dose of the vaccine was 2.2 and 2.6 times higher than those reported after the first and second doses, respectively, but the difference was not statistically significant. Likewise, the rate of HHE was 2.6 times higher among female infants without statistical significance ($p = 0.134$). Low birth weight (< 2,500 grams) appeared to be associated to HHE (relative risk = 1.8) but the data were not conclusive ($p = 0.332$).

Among 12 confirmed cases of HHE, 10 had fever, 3 of them being high fever (reported axillary temperature: 39.5 ºC) in the first 48 hours after vaccination. HHE was 9 times higher and 16 times higher in children whose mothers/guardians informed fever or high fever, respectively, compared to those who did not measure temperature nor reported fever. Only one case had high fever, and two others had around 38.5 ºC at the time of HHE or soon after. In the other cases fever was

Table 1 - Frequency of hypotonic-hyporesponsive episodes by DTP/Hib dose and level of certainty

Dose of vaccine	Subjects vaccinated	Confirmed HHE, n	Suspect HHE, n	Confirmed + suspect, n	Indeterminate, n	Total, n	Rate	
							Confirmed*	Confirmed + suspect†
Dose 1	9,259	4	1	5	1	6	1/2,315	1/1,852
Dose 2	6,582	3	0	3	0	3	1/2,194	1/2,194
Dose 3	5,084	5	1	6	2	8	1/1,017	1/847
Total	20,925	12	2	14	3	17	1/1,744	1/1,495

HHE = hypotonic-hyporesponsive episodes.
* p = 0.37.
† p = 0.26 (chi-squared test of the comparison across doses).

low, absent, or was not perceived at the time of HHE, appearing or rising later.

No association was found between HHE and Apgar at 5 minutes, personal or familial history of convulsive disorders, severe adverse event in previous immunization, use of medication on the day or before immunization, vaccines other than those in the basic immunization schedule, and technical problems with immunization. Convulsions were also found to be unrelated to those factors, except the use of medication which showed a marginally significant association (p = 0.053; Fisher's exact test).

In the ancillary study, interviewers had 90% of the questionnaires consistent with reinterviews and 41% of all interviewers had 100% concordance. No significant difference was found regarding the events of interest among them.

Ongoing follow-up of confirmed and suspect cases of HHE has not disclosed any signs of neurological impairment up to the moment this manuscript was submitted.

Discussion

Reactogenicity for common adverse events of the DTwP/Hib vaccine currently used by Brazilian NIP has already been found to be similar to a reference DTwP/Hib vaccine (Clemens).[10]

Passive surveillance, although useful, has serious limitations (Chen),[11] and the safety concerns they raise often require confirmation by laboratory and epidemiological studies (Zhou),[5] such as this one.

Estimation of rates of adverse events by uncontrolled follow-up studies assumed that the vaccine explained all the observed events. Although other causes are also plausible, the scientific evidence, the close temporal link with vaccination and the clinical data available for the study cases allowed to select those events thought to be causally linked to the DTP vaccine. Nevertheless, it is possible, albeit unlikely, that the estimated rates were inflated by coincidental cases unrelated to vaccination. Also, other vaccines administered simultaneous to DTwP/Hib as recommended by the Brazilian NIP, namely, oral vaccine against poliomyelitis and hepatitis B (third dose), might induce adverse events. Assessment of other vaccines was not feasible in this setting but the well known reactogenicity profile of those vaccines, make it rather unlikely that one vaccine will be blamed for the adverse events caused by another.

The rates of HHE and convulsions observed in the present study are consistent with the results obtained elsewhere with comparable methods,[2,4,8,12-16] except that in the present study, DTP was combined to the Hib component, and the number of infants equals the number of doses. As far as we know, there are no published studies with adequate sampling and active surveillance methodology for ascertaining the incidence of HHE after DTwP/Hib vaccination (Table 2).

Large variation in the rates of HHE among different studies may represent genuine variation in the occurrence of adverse events, due to vaccine composition or manufacturing processes, but may also reflect other factors, such as different vaccination schedules, intensity and duration of surveillance, increased awareness for adverse events due to the introduction of a new vaccine[11] and different definitions of adverse events or methods of evaluation. The difficulty in the diagnosis of HHE may be a relevant source of variation, as characterization of this syndrome often relies on a few signs reported by parents, without anatomical or laboratory correlates. Moreover, in the Brazilian program, HHE implies vaccination free of charge with acellular pertussis component in subsequent doses,[17] which could be an incentive for the diagnosis and reporting of HHE.

The items of the questionnaire related to HHE were conceived to maximize sensitivity, with exclusion criteria to improve specificity. The need for training and guidelines for health professionals reporting adverse events was indicated by cases detected at the local level but not confirmed by further review. The present study showed that a final diagnosis

Table 2 - Frequency per dose of HHE and convulsions in large active follow-up studies of adverse events following immunization with DTwP

Author, year	Doses per child	Doses of DTwP	HHE	Convulsions
Stehr, 1998[12]	4	16,424	1/16,667	1/5,556
Stehr, 1998[12]	3	11,962	1/11,962	1/5,981
Greco, 1996[13]	3	13,520	1/1,492	1/4,545
Gustafsson, 1996[14]	3	6,143	1/1,234	1/6,250
Olin, 1997[15]	3	60,792	1/1,786	1/4,762
Simondon, 1997[16]	3	6,595	0	1/2,564
Cody, 1981[1]	5	15,752	1/1,750	1/1,750
Cody, 1981[1]	3	12,685	1/1,409	1/2,114
Vigat, 2004*	1†	20,925	1/1,495	1/5,231

Modified from Edwards & Decker.[2]
DTwP = diphtheria-tetanus toxoids and whole-cell pertussis; HHE = hypotonic-hyporesponsive episodes.
* Acronym for the present study.
† Assessment of three doses, with each child contributing observation of one dose.

of HHE should only be given after careful clinical investigation and differential diagnosis of those individuals presenting one of the signs.

As in the study by Cody et al., but differently from others,[1] the association of HHE with vaccine dose did not appear significant, nor related to simultaneous administration of other vaccines. The strong association with fever may be a clue to the pathogenesis of the syndrome.

Although frightening and often requiring emergency care, the syndrome has almost always very short duration, leaving no sequelae,[18] and the risk of recurrence is extremely low.[19] HHE is of benign nature, and all our cases had good recovery, similar to other studies.[18-20]

The main strengths of this study were (1) follow-up (rather than passive surveillance) of a sample large enough to estimate the rates of infrequent events, (2) observations conducted in the average conditions of immunization services in accordance to the Brazilian immunization program (3) systematic screening with objective and easily understandable questions to maximize detection of events of interest, and (4) thorough review of selected cases by *ad hoc* committees. As limitations of the study, we acknowledge that, by design, only short-term events after one of the primary three doses were detected. The estimates of HHE rates did not appear to be affected as the distribution of time of onset of HHE was consistent with previous findings. Short-term follow-up made it feasible to interview 20,925 subjects twice, with minimum losses. Conflicting information in a subset of questionnaires did not seem to impact on the estimates, as there was no significant difference in the events of interest among the different interviewers.

In summary, with approval of the independent Data Monitoring Committee, we concluded that (1) the DTP/Hib vaccine used by the Brazilian NIP has a reactogenicity profile similar to other whole-cell pertussis vaccines previously assessed; (2) reports of localized increase in frequency of HHEmight be partly explained by inaccurate characterization of the syndrome, as were the rates of HHE in our study group based on initial assessment of health professionals.

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