

# Clinical Implications of Endotoxin Concentrations in Vaccines

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**BACKGROUND:** A previous study suggested that high concentrations of endotoxin may be present in whole-cell diphtheria/tetanus/pertussis (DTP) vaccine, and the scientific literature contains many studies examining the reactivity of whole-cell DTP vaccine. The medical and scientific communities have previously reported that the presence of endotoxin in commercial vaccines may have negative effects on vaccine recipients.

**OBJECTIVE:** To determine the endotoxin concentrations in whole-cell DTP, acellular DTP (DTaP), and DT vaccines and determine the clinical experience with each vaccine.

**METHODS:** To study the endotoxin concentrations in vaccines, the *Limulus* amoebocyte lysate (LAL) assay was used. The vaccines analyzed with the LAL assay were whole-cell DTP vaccine lots manufactured by Connaught, Lederle, the Michigan and Massachusetts Departments of Health, and Wyeth; DTaP vaccine lots manufactured by Merieux and Takeda; and DT vaccine lots manufactured by Wyeth and Lederle. The incidence of adverse reactions following whole-cell DTP, DTaP, and DT vaccines were determined based on analysis of the Vaccine Adverse Events Reporting System (VAERS) database.

**RESULTS:** The results of the LAL assay showed that whole-cell DTP vaccines contained considerably more endotoxin than either DTaP or DT vaccines. The VAERS showed that statistically significantly more adverse reactions were associated with whole-cell DTP vaccine than DTaP or DT vaccines.

**CONCLUSIONS:** This analysis confirmed higher concentrations of endotoxin in whole-cell DTP vaccines compared with DTaP or DT vaccines. As high concentrations of endotoxin may be correlated with a higher incidence of adverse events, the switch from whole-cell DTP to DTaP for routine vaccinations in the US seems well justified.

**KEY WORDS:** acellular, diphtheria/tetanus, diphtheria/tetanus/pertussis, *Limulus* assay, vaccine, VAERS, whole-cell.

*Ann Pharmacother* 2002;36:776-80.

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In 1978, Geier et al.<sup>1</sup> reported on the presence of endotoxin concentrations in commercial vaccines using the *Limulus* amoebocyte lysate (LAL) assay. The vaccines they examined were smallpox, rubella, poliomyelitis, rabies, influenza, mumps, Rocky Mountain spotted fever, whole-cell diphtheria/tetanus/pertussis (DTP), typhus, and cholera. Endotoxin was shown to be detectable by the LAL assay at 10<sup>-5</sup> dilutions in whole-cell DTP vaccine. The authors concluded that the monitoring and reporting of endotoxins and other contaminants in vaccines might be useful in understanding some of the adverse effects observed in vaccine recipients. They also concluded that the selection of vaccines with the lowest endotoxin concentrations might help to avoid some of the adverse effects of vaccinations.

We recently published an in-depth review<sup>2</sup> of the history of pertussis vaccination and the social, political, scientific, and economic factors involved with its use during the 20th century. The scientific literature contains many reports of the association between whole-cell DTP vaccine and serious neurologic adverse reactions.<sup>3-15</sup> One study<sup>4</sup> described that in Sweden, as in other countries, neurologic complications after administration of whole-cell DTP vaccine have been observed. These complications occurred at a rate of 1 in 6000 injections and encephalopathies with severe lesions at a rate of 1 in 17 000 injections, based on a nationwide investigation.

The Institute of Medicine (IOM)<sup>10</sup> of the National Academy of Sciences in the US reviewed the medical literature in 1985 and reported that low-grade fever and local tenderness appeared frequently after whole-cell DTP injection. Their report went on to describe that severe adverse reac-

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tions including shock, seizures, encephalopathy, and persistent high-pitched screaming were rare complications. They estimated that 1–2 cases per 10 million whole-cell DTP injections resulted in fatalities and that the frequency of serious neurologic disorders such as encephalopathy with persistent neurologic dysfunction 1 year later was 1 case per 110 000 injections. The US, according to the IOM report, could save millions of dollars if the acellular DTP (DTaP) replaced the whole-cell DTP as the form of vaccination in children. The IOM<sup>12</sup> reviewed the literature and reported on whole-cell DTP vaccination in 1991, and determined that the evidence was consistent with a causal relationship between whole-cell DTP vaccine and acute encephalopathy. They also found that the evidence was insufficient to indicate whether DTP vaccine caused permanent neurologic damage. In 1993, results of a 10-year follow-up<sup>14</sup> to the NCES (National Encephalopathy Study)<sup>13</sup> that had found a causal relationship between whole-cell DTP vaccine and chronic brain damage were published. The following year, the IOM conducted another extensive review<sup>15</sup> of whole-cell DTP vaccination using these findings and declared that the available data were compatible with whole-cell DTP causing permanent brain damage in otherwise healthy children.

The purpose of our study was to use the LAL endotoxin assay to determine the concentrations of endotoxin in various commercially available vaccines including whole-cell DTP, DTaP, and DT vaccines. We also examined the Vaccine Adverse Events Reporting System (VAERS) database for adverse reactions reported following the clinical use of whole-cell DTP, DTaP, and DT vaccines to determine their clinical effects on US children.

A recent publication<sup>16</sup> by the Centers for Disease Control and Prevention (CDC) described their examination of the VAERS database for adverse reactions following whole-cell DTP and DTaP vaccines and concluded that their review of the database was reassuring regarding the safety of DTaP vaccines. It was our aim in this study to use the VAERS database to ascertain differences in the incidence of serious adverse reactions following whole-cell DTP, DTaP, and DT vaccines. We and other authors have found that the massive size of the VAERS database makes it a unique and useful tool to analyze adverse reactions to vaccines. Our recent studies<sup>17–23</sup> have shown an association between hepatitis B vaccination and arthritic, immunologic, and gastrointestinal symptoms based on our analysis of the VAERS database. We have also used that database to report<sup>24–26</sup> on the incidence of adverse reactions in the state of Texas, arthritic symptoms following rubella vaccination, and joint-related adverse reactions following anthrax vaccination in light of biological warfare scenarios.

## Materials and Methods

*Limulus* E-Toxate kits were purchased from Sigma Chemical Company (St. Louis, MO). The kits contained individual test tubes of lyophilized LAL, an endotoxin-free distilled water negative control, and a 2- $\mu$ g endotoxin standard positive control. One hundred microliter samples of vaccine were withdrawn under sterile conditions by endotoxin-free syringes

and needles and injected directly into the test vials containing lysate. After mixing and 1 hour of incubation at 37 °C in a water bath, the tubes were gently inverted. Formation of a firm gel was designated as a positive result. A weak gel that could be broken was scored  $\pm$ , whereas a watery fluid result was considered negative. When it was necessary to dilute the sample because of high concentrations of endotoxin, dilutions were made using the negative control solution as diluent. Samples of the negative control were run through an identical mock dilution procedure to rule out contamination due to our manipulations. Also, assay sensitivity experiments were run using the positive controls provided. The assay sensitivity for a positive result was determined to be 0.38 endotoxin units, (EU)/mL, and a  $\pm$  result was determined to be 0.304 EU/mL. Although the LAL is a qualitative, not quantitative, test, it was made quantitative by this method. The commercially available vaccines that were purchased and analyzed in this way are summarized in Table 1.

In order to examine the clinical effects of using whole-cell DTP, DTaP, and DT vaccines, the VAERS database was analyzed using Microsoft Access. The VAERS is a passive epidemiologic database that has been maintained by the CDC in Atlanta, GA, since 1990. The database contains vaccine-associated adverse reactions that were spontaneously reported as required by US law. In this study, the VAERS was analyzed for adverse reactions reported following whole-cell DTP vaccination from 1991 to 2000, DTaP vaccination from 1997 to 2000, and DT vaccination from 1991 to 2000. We used DTaP and DT vaccine recipients as control vaccine groups.

The adverse reactions analyzed were total reaction reports, emergency department (ED) visits, life-threatening reactions, hospitalizations, disabilities, deaths, seizures, fevers, and permanent brain damage. These

**Table 1.** Measured Concentration of Endotoxin Present in Each Lot of Vaccine Analyzed

Manufacturer/Lot	Type of Vaccine	Concentration of Endotoxin (EU/mL)
Connaught		
6E81056	whole-cell DTP	49 400
6K71139	whole-cell DTP	44 080
8M91039	whole-cell DTP	181 640
8A01100	whole-cell DTP	42 560
Wyeth		
142-529	whole-cell DTP	110 960
181-657	whole-cell DTP	90 440
193-656	whole-cell DTP	97 280
Lederle		
163-454	whole-cell DTP	58 520
193-657	whole-cell DTP	69 920
187-664	whole-cell DTP	28 880
187-665	whole-cell DTP	38 000
Massachusetts State		
DPT256	whole-cell DTP	10 640
DPT259	whole-cell DTP	11 400
DPT260	whole-cell DTP	11 400
DPT261	whole-cell DTP	11 400
Michigan State		
1204A	whole-cell DTP	7600
Takeda	DTaP	37.77
Merieux		
1972	DTaP	509.2
1917	DTaP	1390.8
1974	DTaP	433.2
Wyeth		
4868175	DT	0.288
Lederle		
184655	DT	14.4

DT = diphtheria/tetanus; DTaP = diphtheria/tetanus/acellular pertussis; DTP = whole-cell diphtheria/tetanus/pertussis.

categories of adverse reactions, with the exception of permanent brain damage, were based on descriptions of adverse reactions by those reporting them and by defined reporting fields contained in the VAERS database. We defined a case of permanent brain damage as an encephalopathy or encephalitis adverse reaction that was also classified as a case in which the patient was unable to recover based on the information reported to the VAERS database.

The incidence rates calculated in this study were based on the estimates of the CDC for the number of doses administered during each respective study period examined. The CDC estimates indicate that 73 316 439 doses of whole-cell DTP were administered from 1991 to 2000, 50 824 579 doses of DTaP were administered from 1997 to 2000, and 9 335 142 doses of DT were administered from 1991 to 2000. The relative risk for adverse reactions was determined. We used  $\chi^2$  statistical analysis to ascertain whether there were any statistically significant differences in the incidence of adverse reactions following whole-cell DTP, DTaP, or DT vaccines. We used the statistical package contained in Corel's Quattro Pro for our  $\chi^2$  analysis and accepted a p value of <0.05 as statistically significant.

### Results

Table 1 summarizes the measured concentration of endotoxin present in each lot of whole-cell DTP, DTaP, and DT vaccine tested. Table 2 summarizes the mean measured concentration of endotoxin present in each vaccine tested. In Tables 1 and 2, we show that whole-cell DTP vaccine contained the highest concentrations of endotoxin in comparison with DTaP or DT vaccine. Table 3 summarizes the incidence per 10 million vaccinations of total reac-

tions reported, ED visits, life-threatening reactions, hospitalizations, disabilities, and deaths attributed to each vaccine studied in our analysis of the VAERS database. We found that the incidence rates per 10 million doses of whole-cell DTP ( $p < 0.01$ ) were higher in comparison with DTaP vaccine. Table 4 summarizes the incidence of seizures and fevers attributed to each vaccine studied in our analysis of the VAERS database. When compared with the incidence rates per million doses of DT ( $p < 0.01$ ) and DTaP vaccines ( $p < 0.01$ ), whole-cell DTP vaccine was higher for fevers and seizures. A total of 40 cases of permanent brain damage (5.5 cases/10 million vaccinations) were reported to the VAERS database following whole-cell DTP vaccination in comparison with only 14 cases of permanent brain damage (2.75 cases/10 million vaccinations) following DTaP vaccination and 2 cases (2.15 cases/10 million vaccinations) following DT vaccination. The observed incidence of permanent brain damage was increased ( $p < 0.05$ ) following whole-cell DTP vaccine in comparison with both DTaP (RR 2.0) and DT vaccine (RR 2.6).

### Discussion

We believe the high concentrations of endotoxin we found in whole-cell DTP vaccines are a potential cause for concern. Our results demonstrated that these high concentrations were due almost solely to the pertussis component of the vaccine. The average endotoxin concentrations between companies tested varied up to 13-fold, while the lot-to-lot variation tested within different lots from a single company was observed to vary up to 4.2-fold. The DTaP vaccines contained reduced endotoxin concentrations ranging from a tenfold to a 2900-fold reduction compared with whole-cell DTP vaccines.

It has been demonstrated in several studies<sup>27-32</sup> that endotoxin can cause leakiness of the blood-brain barrier, which could potentially be a cause for neurologic adverse reactions following whole-cell DTP vaccination. In 1958, Eckman<sup>27</sup> reported that, in rabbits, a 50- $\mu$ g intraarterial injection of endotoxin altered the permeability of the blood-brain barrier to allow circulating colloids normally excluded from the brain to enter it. Another important development

Manufacturer	Type of Vaccine	Mean Concentration $\pm$ SD of Endotoxin (EU/mL)
Connaught	whole-cell DTP	79 400 $\pm$ 53 300
Wyeth	whole-cell DTP	99 600 $\pm$ 43 700
Lederle	whole-cell DTP	48 800 $\pm$ 24 300
Massachusetts State	whole-cell DTP	11 200 $\pm$ 4500
Michigan State	whole-cell DTP	7600
Takeda	DTaP	38
Merieux	DTaP	780 $\pm$ 500
Wyeth	DT	0.3
Lederle	DT	14

DT = diphtheria/tetanus; DTaP = diphtheria/tetanus/acellular pertussis; DTP = whole-cell diphtheria/tetanus/pertussis.

Vaccine	Total Reaction Reports (n)	ED Visits (n)	Life-Threatening Reactions (n)	Hospitalizations (n)	Disabilities (n)	Deaths (n)
Whole-cell DTP <sup>b</sup>	2370	1124	46	320	30	78
DTaP	1073	466	29	37	13	34
RR <sup>c</sup>	2.2	2.4	1.6	8.6	2.3	2.3
DT	1193	538	21	89	18	6.4
RR <sup>c</sup>	2.0	2.1	2.2	3.6	1.7	12.2

DT = diphtheria/tetanus; DTaP = diphtheria/tetanus/acellular pertussis; DTP = whole-cell diphtheria/tetanus/pertussis; ED = emergency department; VAERS = Vaccine Adverse Events Reporting System.

<sup>a</sup>Incidence per 10 million vaccines.

<sup>b</sup>Statistically significantly more total reaction reports, ED visits, life-threatening reactions, hospitalizations, disabilities, and deaths ( $p < 0.01$ ) by  $\chi^2$  analysis than DTaP or DT vaccines.

<sup>c</sup>Relative risk in comparison with whole-cell DTP.

in the understanding of the effects of endotoxin contained in whole-cell DTP vaccination has been reported<sup>28</sup> in a study showing that intracerebral injection of whole-cell pertussis vaccine into mice caused swelling of the brain. Sidey et al.<sup>32</sup> extended this work by developing a mouse model system of pertussis vaccine encephalopathy that correlated the amount of neurologic damage observed to the amount of endotoxin present in the vaccine used.

The most reactogenic childhood vaccination examined, based on our analysis of the VAERS database, was whole-cell DTP vaccine. There was a greater incidence of total reaction reports, ED visits, hospitalizations, disabilities, deaths, seizures, permanent brain damage, and fevers attributed to this vaccine than any other vaccine examined. It is very interesting to compare the reactivity of whole-cell DTP with that of DTaP vaccine. If whole-cell DTP and DTaP vaccines had similar reactogenicities, it would be expected that a fairly similar incidence rate of adverse reactions would be attributed to whole-cell DTP and DTaP vaccines reported to the VAERS database, considering they were both administered to children in the US in the same childhood vaccination schedule. This similarity in vaccine schedule was reflected by the mean ages in which fevers (DTP 1.7 y old, DTaP 1.8 y old) and seizures (DTP 1.3 y old, DTaP 1.1 y old) were reported to the VAERS database following vaccination. This analysis showed that DTaP vaccine had a statistically significantly lower incidence rate of attributed total reaction reports, ED visits, hospitalizations, deaths, seizures, disabilities, and fevers ( $p < 0.01$ ) and of permanent brain damage ( $p < 0.05$ ) by  $\chi^2$  analysis than did whole-cell DTP vaccine.

Another interesting examination is comparing the relative reactivity of DT vaccine with that of whole-cell DTP vaccine. These vaccines are interesting to compare because

they were both childhood vaccinations and DT vaccine lacks the pertussis component, allowing analysis to determine, specifically, whether it is the pertussis component of the vaccine that causes adverse reactions. A statistically significant decrease, determined by  $\chi^2$  analysis, in the incidence of reaction reports, ED visits, hospitalizations, fevers, life-threatening reactions, seizures and deaths, and of permanent brain damage following DT vaccination when compared with whole-cell DTP vaccination was observed. A comparison of reactions reported following DT vaccination with reactions reported following DTaP vaccination showed the DT vaccine was consistently associated with a slight increase in adverse reactions over those reported following DTaP vaccination. Since DTaP vaccine is made by adding aP vaccine to DT vaccine, it might at first seem implausible that DT alone was more reactogenic than DTaP. However, it must be kept in mind that children who had a developing neurologic condition were generally given DT rather than DTaP vaccine or whole-cell DTP vaccine. This tends to elevate the background rate of neurologic reactions following the DT vaccination and probably accounts for the apparent discrepancy.

## Summary

Our analysis clearly demonstrates that the temporal association between whole-cell DTP vaccination and a myriad of serious adverse reactions is not due to coincidence. This analysis confirmed higher concentrations of endotoxin in whole-cell DTP vaccines compared with DTaP or DT vaccines. The results of this study suggest that the high concentrations of endotoxin present in whole-cell DTP vaccine may be correlated with a higher incidence of adverse events. The recommendation by the American Academy of Pediatrics to use DTaP vaccine for the entire childhood vaccination schedule beginning in 1996 and the unavailability of whole-cell DTP in the US beginning in 2001 seems well justified based on the results of this study.

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## References

1. Geier MR, Stanbro H, Merrill CR. Endotoxins in commercial vaccines. *Appl Environ Bio* 1978;36:445-9.
2. Geier DA, Geier MR. The history of pertussis vaccination: a sordid legacy? *J Hist Med Allied Sciences* (in press 2002).
3. Felton HM, Verwey WF. The epidemiological value of a non-cellular pertussis antigen. *Pediatrics* 1953;16:637-50.
4. Strom J. Is universal vaccination against pertussis always justified? *BMJ* 1960;2:1184-6.

**Table 4.** Seizures and Fevers Following Vaccination Based on Analysis of the VAERS Database

Reaction	Gender (n)		Age <sup>a</sup> (y)	Onset <sup>a</sup> (d)	Incidence per Million Vaccinations
	Female	Male			
<b>Seizures</b>					
whole-cell DTP <sup>b</sup>	810	960	1.3 ± 1.5	2.1 ± 4.1	25
DTaP	145	183	1.1 ± 1.4	3.2 ± 5.0	6.5
RR <sup>c</sup>					3.9
DT	32	42	6.0 ± 8.0	2.8 ± 4.0	8.4
RR <sup>c</sup>					2.9
<b>Fever</b>					
whole-cell DTP	3926	4477	1.7 ± 2.6	1.3 ± 3.0	116
DTaP	675	741	1.8 ± 2.7	2.6 ± 4.0	29
RR <sup>c</sup>					4.0
DT	150	146	13.7 ± 17.5	2.2 ± 3.7	35
RR <sup>c</sup>					3.3

DT = diphtheria/tetanus; DTaP = diphtheria/tetanus/acellular pertussis; DTP = whole-cell diphtheria/tetanus/pertussis; VAERS = Vaccine Adverse Events Reporting System.

<sup>a</sup>Mean ± SD.

<sup>b</sup>Significantly more fevers and seizures ( $p < 0.01$ ) by  $\chi^2$  analysis than DTaP or DT vaccines.

<sup>c</sup>Relative risk in comparison with whole-cell DTP.

5. Haire M, Dane DS, Dick G. Reactions to combined vaccines containing killed *Bordetella pertussis*. The Medical Officer 1967;117:55-8.
6. Kulenkamff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. Arch Dis Child 1974;49:46-9.
7. Bajc OTS. Convulsions after pertussis vaccination. Schweiz Med Wschr 1971;110:1965-71.
8. Torch WC. Diphtheria-pertussis-tetanus (DPT) immunization: a potential cause of sudden infant death syndrome (SIDS) (abstract). Neurology 1982;32:A169-70.
9. Pittman M. The concept of pertussis as a toxin-mediated disease. Pediatr Infect Dis 1984;3:467-86.
10. US Institute of Medicine. New vaccine development: establishing priorities. Washington, DC: National Academy Press, 1985.
11. Ibsen P, Moller S, Heron I. Lipopolysaccharides in a traditional pertussis vaccine. J Biol Stand 1988;16:299-309.
12. US Institute of Medicine. Adverse effects of pertussis and rubella vaccines. Washington, DC: National Academy Press, 1991.
13. Alderslade R, Bellman MH, Rawson NSB, Ross EM. Whooping cough. London: HM Stationary Office, 1981:79-169.
14. Miller D, Madge N, Diamond J, Wadsworth J, Ross EM. Pertussis immunization and serious acute neurological illnesses in children. BMJ 1993;307:1171-6.
15. US Institute of Medicine. DPT vaccine and chronic nervous system dysfunction: a new analysis. Washington, DC: National Academy Press, 1994.
16. Braun MM, Mootrey GT, Salive ME, Chen RT, Ellenberg SS. Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS) (abstract). Pediatrics 2000;106:E51.
17. Geier MR, Geier DA. Hepatitis B vaccine and gastroenterologic adverse reactions (letter). Hepatogastroenterology 2001;48:37.
18. Geier MR, Geier DA. Arthritic reactions and hepatitis B vaccination: an analysis of the vaccine adverse events reporting system (VAERS) from 1990 through 1997 (letter). Clin Exp Rheumatol 2000;18:789-90.
19. Geier MR, Geier DA. Immunological reactions and hepatitis B vaccine (letter). Ann Intern Med 2001;134:1155.
20. Geier DA, Geier MR. Hepatitis B vaccination and adult associated gastrointestinal reactions: a followup analysis. Hepatogastroenterology (in press 2002).
21. Geier DA, Geier MR. Hepatitis B vaccination and arthritic adverse reactions: a followup analysis of the vaccine adverse events reporting system (VAERS) database (letter). Clin Exp Rheumatol 2002;20:119.
22. Geier MR, Geier DA. Immunological reactions and hepatitis B vaccine (letter). Ann Intern Med (in press).
23. Geier MR, Geier DA. Hepatitis B vaccination safety. Ann Pharmacother 2002;36:370-4.
24. Geier DA, Geier MR. An analysis of the reactivity of vaccines administered in the state of Texas from 1991 through 1999: based upon the vaccine adverse events reporting system (VAERS) database. Texas Med (in press 2002).
25. Geier DA, Geier MR. Rubella vaccine and arthritic adverse reactions: an analysis of the vaccine adverse events reporting system (VAERS) database from 1991 through 1998. Clin Exp Rheumatol 2001;19:724-6.
26. Geier DA, Geier MR. Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios. Clin Exp Rheumatol 2002;20(in press).
27. Eckman PL. Studies on the blood brain barrier. Am J Pathol 1958;34:631-43.
28. Iwasa S, Ishida K, Akuma K. Swelling in the brain in mice caused by pertussis vaccine — its quantitative determination and the responsible factors in the vaccine. Jpn J Med Sci Biol 1985;38:53-65.
29. Homma R, Kuratsuka K, Shimazaki Y, Funasaka I. The partial purification and some biological activities of histamine sensitizing factor from *Bordetella pertussis*. Jpn J Med Sci Biol 1970;23:277-81.
30. Bergman RK, Munoz JJ. Effect of *Bordetella pertussis* extract and vasoactive amines on vascular permeability. J Allergy Clin Immunol 1975;55:378-85.
31. Linthicum DS, Munoz JJ, Blaskett A. Acute experimental autoimmune encephalomyelitis in mice. Cell Immunol 1982;73:299-310.
32. Sidey FM, Furman BL, Wardlaw AC. Effect of hyperreactivity to endotoxin on the toxicity of pertussis vaccine and pertussis toxins in mice. Vaccine 1989;7:237-41.

EXTRACTO

**TRASFONDO:** Un estudio previamente publicado sugirió que niveles altos de endotoxina pueden estar presentes en las vacunas de DTP de células completas, y la literatura científica contiene muchos estudios que examinan la reactividad de la vacuna de DTP de célula completa. Las comunidades médicas y científicas han informado que la presencia de endotoxinas en vacunas comerciales puede tener efectos negativos en los que son inoculados.

**OBJETIVO:** El propósito de este estudio era determinar los niveles de endotoxina en las vacunas de DTP de célula completa, de DTaP acelular, y de DT y determinar la experiencia clínica de cada vacuna.

**MÉTODOS:** Para estudiar los niveles de endotoxina en las vacunas, se usó el ensayo de lisato de amebocito *Limulus* (LAL). Las vacunas analizadas con LAL fueron lotes de la vacuna de DTP de célula completa fabricadas por Connaught, Lederle y los departamentos de salud de Michigan y Massachusetts y Wyeth; lotes de la vacuna de DTaP acelular fabricadas por Merieux y Takeda; y lotes de la vacuna DT fabricadas por Wyeth y Lederle. La incidencia de efectos adversos que ocurrieron después de administrarse las vacunas se determinó mediante un análisis de la base de datos del Sistema de Reporte de Eventos Adversos a Vacunas (VAERS).

**RESULTADOS:** Los resultados del ensayo de LAL demostraron que las vacunas de DTP de célula completa contienen considerablemente más endotoxina que las vacunas de DTaP acelular o de DT. El análisis de la base de datos de VAERS reveló que la vacuna de DTP de célula completa causó significativamente más reacciones adversas que las vacunas de DTaP acelular y DT.

**CONCLUSIONES:** Este análisis confirma que existen más endotoxinas en la vacuna de DTP de célula completa que en las vacunas de DT. Dado que altos niveles de endotoxina pueden estar relacionados con una mayor incidencia de eventos adversos, un cambio de la vacuna de DTP de célula completa a la vacuna de DTaP para las vacunaciones rutinarias en los Estados Unidos parece estar justificada.

Homero A Monsanto

RÉSUMÉ

**OBJECTIF:** Le but de cette étude était de documenter les niveaux d'endotoxines dans 3 types de vaccins et de résumer l'expérience clinique cumulée avec chacun d'entre eux. Les vaccins étudiés étaient les vaccins antidiphtérique, antitétanique, et anticoquelucheux (DTC) préparés sur cellules entières, les vaccins DTC non préparés sur cellules (DTaC), et les vaccins antidiphtérique et antitétanique (DT).

**MÉTHODOLOGIE:** La technique de gélification en présence d'un lysat de *Limulus polyphemus* (LAL) a été utilisée pour déterminer les taux d'endotoxines de tous les vaccins. Les vaccins DTP évalués étaient ceux manufacturés par les compagnies Connaught, Lederle, et Wyeth ainsi que ceux des départements de santé publique du Massachusetts. Les vaccins DTaC provenaient de Merieux et de Takeda, tandis que les vaccins DT étaient de Lederle et de Wyeth. La fréquence des réactions indésirables sérieuses associées à l'administration de chacun des 3 types de vaccins a été déterminée suite à une analyse détaillée de la banque de données VAERS (Vaccine Adverse Events Reporting System).

**RÉSULTATS:** Les résultats de la technique LAL ont documenté un taux considérablement supérieur d'endotoxines contenues dans les vaccins DTC par rapport aux 2 autres types de vaccins. De même, une fréquence significativement plus élevée de réactions indésirables était aussi associée avec l'utilisation de ces vaccins.

**CONCLUSIONS:** Cette analyse suggère que l'administration de vaccins contenant un taux plus élevé d'endotoxines semble entraîner une plus grande fréquence d'événements indésirables. D'ailleurs, l'Académie Américaine de Pédiatrie recommande maintenant, pour son programme de vaccination de la jeune enfance, l'utilisation des vaccins DTaC.

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