

Original article

An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines

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Abstract

Serious neurological disorders reported following whole-cell pertussis in comparison to acellular pertussis vaccines were evaluated. The Vaccine Adverse Events Reporting System (VAERS) was analyzed for Emergency Department (ED) visits, life-threatening reactions, hospitalizations, disabilities, deaths, seizures, infantile spasms, encephalitis/encephalopathy, autism, Sudden Infant Death Syndrome (SIDS) and speech disorders reported with an initial onset of symptoms within 3 days following whole-cell pertussis and acellular pertussis vaccines among those residing in the US from 1997 to 1999. Controls were employed to evaluate potential biases in VAERS. Evaluations as to whether whole-cell and acellular vaccines were administered to populations of similar age and sex were undertaken because these factors might influence the study's results. Statistical increases were observed for all events examined following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination, excepting cerebellar ataxia. Reporting biases were minimal in VAERS, and whole-cell and acellular pertussis vaccines were administered to populations of similar age and sex. Biologic mechanisms for the increased reactogenicity of whole-cell pertussis vaccines may stem from the fact that whole-cell pertussis vaccines contain 3000 different proteins, whereas DTaP contains two to five proteins. Whole-cell pertussis vaccine contains known neurotoxins including: endotoxin, pertussis toxin and adenylate cyclase. Our results, and conclusions by the US Institute of Medicine, suggest an association between serious neurological disorders and whole-cell pertussis immunization. In light of the presence of a safer and at least equally efficacious acellular pertussis vaccine alternative, the Japanese and US switch to using acellular pertussis vaccine seems well justified. Other countries using whole-cell pertussis-containing vaccines should consider following suite in the near future.

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1. Introduction

In 1981, Japan introduced acellular pertussis vaccination, for us a routine childhood immunization [1]. The United States made the gradual switch during the 1990s from exclusively using whole-cell pertussis vaccine to acellular pertussis vaccine manufactured primarily in Japan. The introduction of acellular pertussis vaccination began in 1992 when it was approved for use by physicians in children 18 months and 5 years old and for the entire childhood vaccination schedule (2, 4, 6, 18 months and 5 years) in 1996. By the end of 2001, whole-cell pertussis vaccines were removed from the US market

[2]. Therefore, from 1997 through 1999, both acellular pertussis and whole-cell pertussis vaccines were available for use in the same childhood vaccination schedule in the US. The purpose of this analysis was to evaluate the relative safety of whole-cell pertussis vaccination in comparison to acellular pertussis vaccination based upon an examination of vaccines administered from 1997 through 1999.

In order to evaluate the safety profile of whole-cell pertussis and acellular pertussis vaccines, the Vaccine Adverse Event Reporting System (VAERS) database was analyzed. The VAERS database is an epidemiological compilation maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse events following vaccination are required to be reported to this database as mandated by US law. The protocol for reporting

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all serious events to VAERS requires written and telephonic confirmation by the CDC. The CDC follows up on all serious events 1 year after they occur to determine whether or not the patients had fully recovered. The Food and Drug Administration (FDA) inquires into all deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA and ourselves analyze and publish epidemiologic studies based upon analyses of the VAERS database. A recent study by the VAERS Working Group of the CDC stated that VAERS is simple to use, flexible by design, and the data are available in a timely fashion [3]. The principal aim here is to use the massive size of the VAERS database to compare adverse events reported following whole-cell pertussis vaccination with those following acellular pertussis vaccination.

2. Methods

In this study, a retrospective examination of the VAERS database was undertaken using Microsoft Access. The VAERS database was analyzed for adverse events reported following whole-cell pertussis and acellular pertussis vaccines among those residing in the US from 1997 through 1999 an initial onset of symptoms within 3 days following immunization. The adverse events analyzed were: Emergency Department (ED) visits, life-threatening reactions, hospitalizations, disabilities, deaths, seizures, infantile spasms, encephalitis/encephalopathy, autism, Sudden Infant Death Syndrome (SIDS) and speech disorders. Descriptions of these adverse events were based upon those reporting them and defined fields contained within the VAERS database.

In order to calculate the incidence rates of adverse events following whole-cell-pertussis and acellular pertussis vaccinations, we examined the Biological Surveillance Summaries of the CDC from 1997 through 1999. The Biological Surveillance Summaries estimate the total number of each type of vaccine distributed/administered (this number subtracts out the number of doses returned or not distributed) per year in the US. The Biological Surveillance Summaries indicated that 10,315,270 whole-cell pertussis-containing (diphtheria–tetanus-whole-cell-pertussis and diphtheria–tetanus-whole-cell-pertussis-*Haemophilus influenzae* type b) vaccines and 52,601,190 acellular pertussis-containing (diphtheria–tetanus-acellular-pertussis and diphtheria–tetanus-acellular-pertussis-*Haemophilus influenzae* type b) vaccines were distributed/administered from 1997 through 1999.

Central to this study is the premise that in a similarly aged population an unbiased search for the incidence rate of a specific adverse event following a particular vaccine would yield similar data to the incidence rate following

another vaccine. This premise is founded on the understanding that the inherent limitations in the accuracy of reported adverse events in the VAERS database may be expected to equally affect the reports originating from both vaccines under study. Likewise, the number of administered doses of a particular vaccine, based on the Biological Surveillance Summaries of the CDC, should be unbiased since any inherent limitations of the Biological Surveillance Summaries should equally apply to each vaccine under study. In performing the statistical analyses, the premise of equal reactogenicity between vaccines forms the basis of our null hypothesis. The statistical method involved constructing 2×2 contingency tables and we employed Yate's and Fisher's Exact statistical tests to determine statistical significance. In our statistical tests we posit that the total number of adverse events following acellular pertussis vaccine and the number of doses administered (based upon the Biological Surveillance Summaries for the period examined) are the expected values, and the total number of events following whole-cell pertussis vaccine and the number of doses administered (based upon the Biological Surveillance Summaries for the period examined) are the observed values. In this analysis, the statistical package contained in Microsoft Excel and SISA was used and a P value of 0.05 was accepted as statistically significant.

The incidence rate of adverse events following whole-cell pertussis vaccine in comparison to the incidence rate of adverse events following acellular pertussis vaccine from our 2×2 contingency tables was used to determine odds ratios and attributable odds ratio percent associations for the adverse events following the vaccine under study. Attributable odds ratio percent association is obtained by subtracting one from the odds ratio, dividing this value by the odds ratio, and multiplying this computed value by 100. In addition, P values and 95% odds ratio confidence intervals (when possible) were determined.

It has been hypothesized that there may be biases present in the reporting of adverse events to the VAERS database and these biases would result in population prejudice favoring the reporting of whole-cell DTP vaccine adverse events to the VAERS database because of compelling presentations in the popular media implicating the increased neurologic reactogenicity of whole-cell DTP vaccine, therefore it would be expected that decreases in the incidence rates of adverse events following acellular DTaP vaccine would have occurred for every type of adverse event. In order to determine if there were biases present in the reporting of adverse events following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination, a cerebellar ataxia control adverse event was employed. The reason for choosing a cerebellar ataxia control adverse event is that this adverse event is a neurologic event and because it has been recently reported to occur at a similar incidence following whole-cell and acellular pertussis immunizations by Kuno-Sakai and Kimura [4]. We also evaluated, as additional controls,

the overall mean age and the male/female ratios of those reporting adverse events following whole-cell and acellular pertussis vaccines to the VAERS database. We hypothesize that differences in the mean ages and male/female ratios of vaccine recipients may influence the incidence rate of adverse events reported to the VAERS database.

3. Results

There were a total of 1533 adverse event reports reported to the VAERS database following whole-cell pertussis vaccination. There were 767 classified as occurring in males, 746 classified as occurring in females and 20 that did not specify a sex (male/female ratio = 1.0). The overall mean age of event reports reported to the VAERS database following whole-cell pertussis vaccination was 1.4 years old. There were a total of 3772 adverse event reports reported to the VAERS database following acellular pertussis vaccination. There were 1949 classified as occurring in males, 1725 classified as occurring in females and 98 that did not specify a sex (male/female ratio = 1.1). The overall mean age of event reports reported to the VAERS database following acellular pertussis vaccination was 2.0 years old. Table 1 summarizes adverse events reported following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination. It was determined that there were statistical increases for each type of adverse event examined following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination, with the exception of cerebellar ataxia. It was found that cerebellar ataxia occurred similarly following whole-cell and acellular pertussis vaccinations.

4. Discussion

The results of this analysis showed that whole-cell pertussis vaccination was more reactogenic than acellular pertussis vaccination based upon tens of millions of each type of vaccine administered to US children, as part of the same childhood vaccination schedule during the same years. These results are similar to ones obtained by other authors over several decades [2].

Our results are also similar to previous studies conducted by the CDC based upon analysis of the VAERS database. Braun et al. reported on an assessment of the first 2 years' data from the VAERS database following infant immunization with acellular pertussis vaccines [5]. The authors found declines in deaths, non-fatal serious events, and less serious events reported to the VAERS database following pertussis-containing vaccines as the United States switched from using whole-cell pertussis-containing vaccines to acellular pertussis-containing vaccines. Similarly, DuVernoy and Braun showed, based upon analysis of the VAERS database, a decrease in the number of reports of hypotonic–hyporesponsive episodes from 1996 (99 cases) to 1998 (38 cases), when the predominant pertussis vaccine administered to infants changed from whole-cell to acellular [6]. A VAERS database study by Rosenthal et al. showed that there were statistically significant decreases in the incidence rate of total reports, fever, seizures, and hospitalizations following DTaP vaccine in comparison to DTP vaccine [7].

The Institute of Medicine (IOM), of the United States' National Academy of Sciences, in 1985 reviewed the medical literature and reported that low grade fever and local tenderness appeared frequently after whole-cell DTP

Table 1

A summary of adverse events reported with an initial onset of symptoms within 3 days following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination to VAERS database from 1997 through 1999

Type of reaction	Incidence per million whole-cell pertussis vaccines	Incidence per million acellular pertussis vaccines	Odds ratio	Attributable odds ratio percent association	Statistical significance	95% Odds ratio confidence interval
Emergency department visits	72	32	2.3	56	$P < 0.0001$	2.10–2.4
Life-threatening reactions	2.5	1.0	2.5	60	$P = 0.0001$	1.60–4.0
Hospitalizations	16	6.2	2.6	60	$P < 0.0001$	2.10–3.1
Disabilities	1.4	0.38	3.6	72	$P = 0.0002$	1.80–7.1
Deaths	2.7	1.5	1.8	44	$P = 0.009$	1.20–2.8
Seizures	13.4	3.6	3.7	73	$P < 0.0001$	3.00–4.6
Infantile spasms	0.39	0.11	3.4	71	$P = 0.04^*$	–
Encephalitis/encephalopathy	0.78	0.095	8.2	88	$P < 0.0001$	2.70–25
Autism	0.49	0.11	4.4	77	$P = 0.03$	1.30–14
Sudden infant death syndrome (SIDS)	1.5	0.87	1.7	41	$P = 0.03^*$	–
Speech disorders	0.78	0.23	3.4	70	$P = 0.01$	1.40–8.3
Cerebellar ataxia	0.29	0.27	1.1	9	$P = 0.85$	0.31–3.8

P value determined using Fisher's exact test statistic.

injection. Their report went on to describe that severe disturbing untoward reactions, including shock, seizures, encephalopathy, and persistent high pitched screaming, were rare complications. They estimated one to two cases per 10 million whole-cell DTP injections resulted in fatalities and the frequency of serious neurological disorders such as encephalopathy were one case per 110,000 injections with persistent neurological dysfunction 1 year later. The United States, according to the IOM report, could save millions of dollars if the acellular DTaP replaced the whole-cell DTP as the form of vaccination in children [8]. The IOM, again, 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 neurological damage [9]. In 1994, after a 10-year follow-up to the British National Encephalopathy Study (NCES) was published in 1993 that showed an increased risk between whole-cell DTP vaccine and chronic brain damage within 7 days of immunization in comparison to matched-controls, the IOM conducted another extensive review of whole-cell DTP vaccination and declared the available data were compatible with whole-cell DTP causing permanent brain damage in otherwise healthy children within 7 days of immunization [10–12].

In evaluating our controls, we observed that cerebellar ataxia was reported similarly following whole-cell and acellular pertussis vaccines to the VAERS database, as predicted based upon Kuno-Sakai and Kimura's report. These observations help to mutually validate the observations we made in the United States and the observations made in Japan following the switch from whole-cell DTP vaccine to acellular DTaP vaccine, in both countries. In addition, Kuno-Sakai and Kimura found that based upon tens of millions of doses of both acellular and whole-cell pertussis vaccines administered in Japan, whole-cell pertussis vaccine was statistically significantly increased in comparison to acellular pertussis vaccine, comparable to the observations made in this analysis of the VAERS database, for such adverse reactions as encephalopathy, SIDS, seizures and infantile spasms within 7 days of immunization. Therefore, this mutually validating data suggests that statistically significant increases in the incidence rate of adverse reactions were only observed following whole-cell pertussis vaccine, when the higher toxicity of whole-cell pertussis vaccine was indeed responsible for the adverse reactions. In addition, our examination of the overall mean ages and male/female ratios among whole-cell and acellular pertussis vaccines, indicates that they were administered to similar populations with regard to age and sex and age-related and sex-related phenomena may have had a limited impact on our results.

The biologic mechanisms for the increased reactivity of whole-cell pertussis vaccine in comparison to acellular pertussis vaccine may stem from the fact that

whole-cell pertussis vaccines contain 3000 different proteins, whereas DTaP contains two to five proteins. Whole-cell pertussis vaccine contains endotoxin, pertussis toxin (PT) and adenylate cyclase, known neurotoxins. In DTaP, PT is deactivated by formaldehyde and adenylate cyclase and endotoxin levels are vastly reduced by purification steps. PT has been shown to sensitize vaccines to histamine, causes a rise in insulin secretion (this can cause brain damage since the brain is dependent on sugar for its energy), elevates white-blood cell counts and lowers the blood–brain barrier, potentially allowing toxins and viruses to enter the brain. Adenylate cyclase has been shown to adversely effect neurotransmitters [13]. In addition, recent studies suggest that whole-cell pertussis vaccine contains a 10- to 2900-fold increase in endotoxin concentration in comparison to acellular pertussis vaccine and that endotoxin can cause leakiness of the blood–brain barrier, which could potentially be a cause for the neurological adverse reactions following whole-cell pertussis vaccination [14]. The three active neurotoxins, probably, work synergistically to produce serious adverse reactions in susceptible whole-cell pertussis vaccine recipients.

Recently, Donnelly et al. developed a novel murine model wherein seizure-like behavioral changes were induced following parenteral administration of whole-cell pertussis vaccine [15]. The authors observed that the proinflammatory cytokine interleukin- β (IL-1 β), production of which has been associated with many neurodegenerative conditions, was significantly increased in the hippocampus and hypothalamus of vaccinated animals. Accompanying this change was a decrease in the release of the inhibitory neurotransmitters γ -aminobutyric acid and adenosine in the hippocampus. The authors concluded that their results suggest a causal relationship between IL-1 β induction and convulsive behavior following whole-cell pertussis vaccination, whereas acellular pertussis vaccine neither increased IL-1 β induction nor induced behavior changes in mice.

In conclusion, the results of this analysis, in combination with the conclusions of the US IOM, and a number of studies published throughout the many decades suggest that whole-cell pertussis immunization is associated with an increased risk of serious neurological adverse reactions. In light of the existence of a safer and at least equally efficacious [16] acellular pertussis vaccine alternative, the complete switch to using acellular pertussis vaccine in the US and Japan seems well justified. It would seem prudent that the countries that are still in the process of administering whole-cell pertussis-containing immunization should consider following the US and Japanese examples by following suite in the near future.

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Dr. Mark R. Geier and David A. Geier have served as expert witnesses and as consultants involving vaccine

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References

- [1] Kimura M, Kuno-Sakai H. Current epidemiology of pertussis in Japan. *Pediatr Infect Dis J* 1990;9:705–9.
- [2] Geier D, Geier M. The true story of pertussis vaccination: A sordid legacy? *J Hist Med Allied Sci* 2002;57:249–84.
- [3] Singleton JA, Lloyd JC, Mootrey GT, Salive ME, Chen RT. An overview of the vaccine adverse events reporting system (VAERS) as a surveillance system. VAERS Working Group. *Vaccine* 1999;17:2908–17.
- [4] Kuno-Saki H, Kimura M. Epidemiology of pertussis and use of acellular pertussis vaccines in Japan. *Dev Biol Stand* 1997;89:331–2.
- [5] 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). *Pediatrics* 2000;106:E51.
- [6] DuVernoy TS, Braun MM. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998. *Pediatrics* 2000;106:E52.
- [7] Rosenthal S, Chen R, Hadler S. The safety of acellular pertussis vaccines vs whole-cell pertussis vaccine. A postmarketing assessment. *Arch Pediatr Adolesc Med* 1996;150:457–60.
- [8] Institute of Medicine (U.S.). *New vaccine development: establishing priorities*. Washington, DC: National Academy Press; 1985.
- [9] Institute of Medicine (U.S.). *Adverse effects of pertussis and rubella vaccines*. Washington, DC: National Academy Press; 1991.
- [10] Alderslade R, Bellman MH, Rawson NSB, Ross EM. *Whooping Cough*. London H.M. Stationary Office 1981;79–169.
- [11] Miller D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunization and serious acute neurological illnesses in children. *Br Med J* 1993;307:1171–6.
- [12] Institute of Medicine (U.S.). *DPT vaccine and chronic nervous system dysfunction: a new analysis*. Washington, DC: National Academy Press; 1994.
- [13] Wardlaw AC, Parton R. Bordetella pertussis toxins. *Pharmacol Ther* 1982;19:1–53.
- [14] Geier DA, Geier MR. Clinical implications of endotoxin concentrations in vaccines. *Ann Pharmacother* 2002;36:776–80.
- [15] Donnelly S, Loscher CE, Lynch MA, Mills KHG. Whole-cell but not acellular pertussis vaccines induce convulsive activity in mice: Evidence of a role for toxin-induced interleukin-1 in a new murine model for analysis of neuronal side effects of vaccination. *Infect Immunol* 2001;69:4217–23.
- [16] Greco D, Salmaso S, Mastrantonio P, Giuliano M, Tozzi AE, Anemona A, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996;334:341–8.