Surveillance for Poliovirus Vaccine Adverse Events, 1991 to 1998: Impact of a Sequential Vaccination Schedule of Inactivated Poliovirus Vaccine Followed by Oral Poliovirus Vaccine

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ABSTRACT. Background. The elimination of wild-virus–associated poliomyelitis in the Western Hemisphere in 1991 and rapid progress in global polio eradication efforts changed the risk-benefit ratio associated with the exclusive use of oral poliovirus vaccine (OPV) for routine immunization. These changes, plus the November 1987 development of an enhanced-potency inactivated poliovirus vaccine (IPV), which poses no risk of vaccine-associated paralytic poliomyelitis (VAPP), resulted in a change in polio immunization policy in the United States. In September 1996, the Centers for Disease Control and Prevention recommended that IPV replace OPV for the first 2 doses in a sequential poliovirus vaccine schedule. The Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system for adverse events after receipt of any US-licensed vaccine, is used to monitor postlicensure vaccine safety. Postlicensure surveillance of vaccines is important to identify new, rare, or delayed-onset adverse reactions not detected in prelicensure clinical trials or when new vaccine schedules are adopted. Through continual monitoring of adverse events and identification of potential vaccine risks, VAERS can serve as an important resource to ensure continued public acceptance of vaccines. We compared VAERS reports after the receipt of IPV to reports after OPV in infants from 1991 through 1998. Comparisons included reports listing IPV and OPV coadministered with other vaccines.

Methods. Annual reporting rates per 100 000 doses distributed within 3 severity categories (fatal, nonfatal serious, less serious) were examined. Distributions of severity categories by vaccine type, age, and time period (pre- and postrecommendation) were constructed. Safety profiles (distribution of 21 symptom groupings) for IPV and OPV reports were compared. Analysis was restricted to reports for infants 1 to 3 months old and 4 to 6 months old, corresponding generally to first- and second-dose recipients. Any notable increase in a severity or safety category for IPV compared with OPV was followed up by examining the frequency of specific symptoms, reporting source, and date of vaccination. An important limitation of VAERS is that reports do not necessarily represent adverse events caused by vaccines. In many cases, the events are temporal associations only.

Results. The annual rates of VAERS reports per 100 000 vaccine doses distributed by severity category, 1991 to 1998, were in general similar for reports after IPV compared with those after OPV. The reporting rates for poliovirus vaccine did not increase materially with the shift to IPV usage. The relative frequencies of symptoms in the fatal and nonfatal serious categories for 1998 vaccine administrations were similar to 1997 reports. Severity profiles for IPV and OPV reports in infants 1 to 3 months old and 4 to 6 months old, corresponding to first- and second-dose recipients, were remarkably similar. The frequency of symptoms listed on IPV reports categorized as fatal or serious was examined by age, vaccine combinations, and time period, and the distribution of symptoms was similar for ages 1 to 3 months and 4 to 6 months. In the postrecommendation period, the 10 most frequent symptoms reported with IPV were also reported with OPV in either similar or lower relative frequency. During the postrecommendation period, safety profiles for infants 4 to 6 months old showed a 2.5% higher proportion in the allergic reaction category for IPV than for OPV, but none of the allergic reaction reports indicated anaphylaxis. In general, the distribution of symptom groupings was not markedly different for IPV compared with OPV. No cases of VAPP were reported after the administration of IPV, whereas 5 VAPP cases were reported after the administration of OPV.

Conclusions. Although VAERS is subject to the limitations of most passive surveillance systems, the large number of reports and national coverage provide a unique database for monitoring vaccine safety. There was a marked increase of IPV reports in VAERS after 1996, consistent with implementation of the Advisory Committee on Immunization Practices recommendation for the sequential IPV/OPV poliovirus vaccination schedule. Given the increased use of IPV, a review of potential adverse events in VAERS compared IPV with OPV reports both before and after the introduction of the sequential vaccination schedule. Vaccine safety surveillance indicated no adverse events patterns of potential concern following the use of IPV in infants after the introduction of the sequential vaccination schedule. Ongoing surveillance is documenting a decrease in VAPP. These findings provide useful information to support the Advisory Committee on Immunization Practices recommendation, made in 1999, to shift to an all-IPV schedule. Pediatrics 2001;107(5). URL: http://www.pediatrics.org/cgi/content/full/107/5/83; inactivated poliovirus vaccine, oral poliovirus vaccine, vaccine adverse event surveillance.

ABBREVIATIONS. IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; VAPP, vaccine-associated paralytic poliomyelitis; CDC, Centers for Disease Control and Prevention; ACIP,
Polio vaccination reached a peak in the United States in 1952, with over 20,000 paralytic cases. Subsequently, inactivated poliovirus vaccine (IPV) was licensed in 1955 and used extensively until the early 1960s. In 1963, trivalent oral poliovirus vaccine (OPV) was licensed. Because of the ease of administration, greater immunogenicity, and mucosal immunity, OPV primarily replaced IPV use in the United States for all except adults and immunocompromised persons. With the onset of widespread polio vaccination, the incidence of poliomyelitis dramatically declined. The last reported case of paralytic poliomyelitis caused by endemic transmission of wild virus in the United States was in 1979. Between 1980 and 1996, a total of 142 confirmed cases of paralytic poliomyelitis were reported; 134 (94%) were likely attributable to the administration of OPV. The risk of vaccine (OPV)-associated paralytic poliomyelitis (VAPP) was estimated to be 1 case per 2.4 million doses distributed, with the majority of VAPP cases occurring after the administration of the first dose (1 case per 750,000 first doses).

The elimination of wild-virus–associated poliomyelitis in the Western Hemisphere in 1991 and rapid progress in global polio eradication efforts changed the risk-benefit ratio associated with the exclusive use of OPV for routine immunization. These changes, plus the November 1987 development of an enhanced-potency IPV, which poses no risk of VAPP, resulted in a change in polio immunization policy in the United States. In September 1996, the Centers for Disease Control and Prevention (CDC) accepted the Advisory Committee on Immunization Practices’ (ACIP) recommendation for a sequential IPV/OPV schedule to reduce the risk of VAPP. The recommended schedule consisted of 4 doses, with the primary series administered at ages 2 months (IPV), 4 months (IPV), 12 to 18 months (OPV), and 4 to 6 years (OPV). On June 17, 1999, to eliminate the risk of VAPP, the ACIP recommended an additional change to an all-IPV schedule for routine childhood polio vaccination in the United States.

Manufacturers’ reports and data on adverse events from countries that have either relied exclusively on enhanced-potency IPV for routine poliovirus vaccination or sequential IPV/OPV vaccination have not documented any serious side effects. This sequential IPV/OPV schedule, however, has only been used before 1996 in Denmark, Hungary, Lithuania, and Canada’s Prince Edward Island. The adoption by the United States, with its birth cohort of 3.9 million, represented a major increase in the number of children exposed to this polio vaccination regimen.

The Vaccine Adverse Event Reporting System (VAERS), a passive reporting system for adverse events after the receipt of any US-licensed vaccine, is one of the tools used to monitor postmarketing vaccine safety. Postmarketing surveillance of vaccines is important to identify new, rare, or delayed-onset adverse reactions not detected in prelicensure clinical trials or when new vaccine schedules are adopted. Through continual monitoring of adverse events and identification of potential vaccine risks, VAERS can serve as an important resource to ensure continued public acceptance of vaccines. Potential risks identified in VAERS generate hypothesized associations for subsequent scientific evaluation of attribution of causality to the vaccine. This was demonstrated in the recent studies of intussusception after rotavirus vaccination. We evaluated VAERS reports after the receipt of IPV compared with OPV from 1991 through 1998, with particular attention to events reported after implementation of the sequential polio vaccine schedule.

METHODS

VAERS was established through a collaborative effort by the CDC and Food and Drug Administration in 1990. Approximately 10,000 reports to VAERS are received annually. VAERS reports after IPV or OPV with vaccination date between January 1, 1991, and December 31, 1998, were examined. VAERS reports include data on age, sex, reporting source, a description of the adverse event(s), dates of vaccination and onset of adverse event, all vaccines given on the date listed, and a checklist for event severity. Adverse-event signs and symptoms are recorded in free text and coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). Each report can contain multiple COSTARTs and typically contains 3 to 4.

Reporting rates for VAERS (number of reports per 100,000 doses of vaccine administered) were calculated by dividing the number of vaccine-specific reports by the net doses distributed in the United States, according to CDC Biologies Surveillance (preliminary unpublished data, 1996–1998). These net distribution figures are only approximations and serve as a denominator for incidence estimates of adverse events in the absence of doses administered data. Net distribution equals total doses distributed by vaccine type during the period, less returned doses. The approximate number of doses administered for age-specific comparisons or comparisons for specific coadministered vaccines are not available. Reporting rates must not be interpreted as incidence rates because of substantial underreporting. Moreover, there is no certainty that the vaccine caused the adverse event; the event may have occurred by chance after the vaccine administration. Relative reporting rates provide a data source for exploratory analysis that may suggest risk. An evaluation of risk would require a well-defined vaccinated population and complete adverse-event reporting for the groups evaluated.

VAERS includes reports of adverse events among vaccine recipients but no information about the population at risk of experiencing an adverse event. Consequently, proportional distributions were used in qualitative comparisons of different vaccinated groups as follows. VAERS reports were classified by severity: death, nonfatal serious (defined as life-threatening illness, hospitalization or prolongation of preexisting hospitalization, permanent disability), and less serious. Severity profiles were constructed as the percentage distribution of severity category by vaccine type. In addition, COSTART terms were divided into 21 symptom groupings to construct safety profiles. The proportional distributions examined used VAERS terms as denominators.

Age-specific severity profiles and safety profiles of OPV and IPV were compared for reports with vaccination date within pre- and postrecommendation periods, January 1991 to September 1996, and October 1996 to December 1998, respectively. Comparisons included reports listing IPV or OPV in combination with any other vaccine(s). Analysis was restricted to reports for infants ages 1 to 3 months and 4 to 6 months, corresponding generally to first- and second-dose recipients. Any notable increase in a severity or safety category for IPV compared with OPV was followed up by examining the frequency of specific symptoms, reporting source, and date of vaccination. Duplicate and foreign reports were ex-
RESULTS

The annual frequency of VAERS reports associated with IPV and OPV by vaccine combinations, ie, vaccines administered simultaneously, is shown in Table 1. In recent years, both are most often coadministered with other routine childhood vaccines. For example, in our data (recent years), IPV was most often coadministered with diphtheria and tetanus toxoids and acellular pertussis (DTaP) and *Haemophilus influenzae* type b or DTaP, *H influenzae* type b, and hepatitis B; OPV was coadministered with diphtheria and tetanus toxoids and pertussis with *H influenzae* type b (DTPH) or DTPH and hepatitis B.

The annual reporting rates per 100,000 doses distributed associated with IPV or OPV by severity category are shown in Fig 1. In general, the annual reporting rates of events were similar for IPV and OPV, except for a somewhat higher rate of death after IPV than OPV (0.83 vs 0.17 per 100,000) doses and of nonfatal serious events (1.6 vs 0.9 per 100,000 doses) in 1998. The number of fatalities reported in 1997 for IPV was 24 given 5,228,097 net doses distributed and 48 for OPV given 12,595,000 net doses distributed. In contrast, 50 reports of death after IPV administration were reported in 1998 with 6,048,082 net IPV doses distributed, compared with 20 reports of death after receipt of OPV with 11,740,830 net doses distributed. A good possibility for the observation of a greater number of IPV than OPV deaths is that IPV is more likely than OPV to be given at ages 2 to 4 months when there is a higher risk of sudden infant death syndrome (SIDS) and death. The number of fatalities reported to VAERS for either IPV or OPV was 72 in 1997 and 70 in 1998. Overall, the data indicate that the reporting rate of poliovirus vaccine-associated adverse events has not increased with the increased use of IPV in infants. The relative frequency of symptoms in the fatal and nonfatal serious categories for 1998 vaccine administrations was similar to 1997 reports (data not shown).

Severity profiles for IPV and OPV reports were examined according to whether they preceded or followed the September 1996 recommendation. Data were also stratified by age and vaccine combinations. Because the CDC recommendation targeted infants <1 year old, the data presented focus on this age group. The percentage of reports by age, time period, and severity category for IPV or OPV in combination with any other vaccine(s) is shown in Fig 2. Severity profiles were remarkably similar, particularly in infants 4 to 6 months old. For IPV-associated reports on infants 1 to 3 months old, a slightly greater percentage was classified as nonfatal serious (20% vs 15.7%) in the prerecommendation period; a slightly greater percentage of deaths (9.8% vs 6.8%) were reported in the postrecommendation period. The absolute number of deaths reported in the postrecommendation interval was 47 for IPV versus 34 for OPV in infants 1 to 3 months old, and 27 for IPV versus 33 for OPV in infants 4 to 6 months old.

The frequency of symptoms listed on IPV reports categorized as fatal or serious was examined by age, vaccine combinations, and time period. The distribution of symptoms was similar for ages 1 to 3 months and 4 to 6 months, and Table 2 presents the percentage of symptoms for ages 1 to 6 months by poliovirus vaccine and time period. In the postrecommendation period, symptoms reported with IPV were also reported with OPV in either similar or lower relative frequency. OPV reports had a somewhat greater percentage of fever and agitation. From January 1991 to September 1996, the relative frequency of apnea, stupor, and cyanosis was higher for IPV than for OPV.

Safety profiles are shown in Fig 3 by vaccine type for infants 1 to 3 months old in the postrecommendation period. Slightly higher proportions (<2 per-

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**TABLE 1. Annual Frequency of Poliovirus Vaccine Combination Reports: VAERS, 1991 to 1998**

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**IPV Reports**

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**OPV Reports**

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HIB indicates *Haemophilus influenzae* type b; HEP B, hepatitis B; DTP, diphtheria-tetanus-pertussis; MMR, measles-mumps-rubella.

* Aggregated less frequent combinations.
centage points) were noted for IPV primarily in the behavioral (agitation, somnolence), other systemic, gastrointestinal, and infection symptom groupings. Unexpectedly, a higher proportion of local reactions was seen for OPV than IPV. No symptoms in the rheumatologic grouping were reported in association with either vaccine. The safety profiles presented in Fig 4 for infants 4 to 6 months old show a somewhat higher percentage for IPV than OPV in the allergic reactions category, other neurologic, and dermatologic symptom groupings, (difference of 2.5%, 1.5%, and 2%, respectively). In general, however, the distribution of symptom groupings was not remarkably different for IPV compared with OPV. No cases of VAPP were reported after the administration of IPV, whereas 5 VAPP cases were reported after the administration of OPV in infants 1 to 6 months old during this period. A frequency of symptoms in the allergic reaction category showed that 88% of the 26 IPV reports listed urticaria compared with 67% of the 21 OPV reports (Table 3). None of the

**TABLE 2.** Fatal and Nonfatal Serious Report Symptoms by Poliovirus Vaccine and Pre-Postrecommendation Period, Ages 1 to 6 Months: VAERS

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<td><strong>OPV</strong></td>
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<tr>
<td>Fatal</td>
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<td>Number of symptoms</td>
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<tr>
<td>Symptoms†‡</td>
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<tr>
<td>Fever</td>
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<td>SIDS</td>
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<tr>
<td>Convulsions</td>
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<td>Agitation</td>
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<td>Apnea</td>
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<td>Stupor</td>
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<td>Infection</td>
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<td>Hypotonia</td>
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* In combination with any other vaccine(s).
† Symptoms are the 10 COSTARTs most frequently reported after IPV in the postrecommendation period.
‡ Percentage of reports.
IPV reports of allergic-reactions were reported as anaphylaxis.

**DISCUSSION**

In recent years, the tolerance of risk for poliomyelitis caused by OPV has decreased in the United States because of the diminished risk for wild-virus-associated disease. Consequently, in October 1996, ACIP recommended a new poliovirus vaccination policy that increased reliance on IPV. This review of reports to VAERS from 1991 through 1998 after the administration of IPV or OPV provides a unique assessment of the relative safety of IPV and OPV for the US population. These data indicate that the reporting rate of poliovirus vaccine-associated adverse events has not increased with the increased use of IPV in infants. In general the annual rates of events were similar for IPV and OPV, except for a somewhat higher rate of death after IPV than after OPV (0.83 vs 0.17 per 100,000 doses) and of nonfatal serious events (1.6 vs 0.9 per 100,000 doses) in 1998. Most reports of a fatal event for either poliovirus vaccine indicated SIDS; 44 cases in 1997 and 45 in 1998. The relative frequencies of symptoms in the fatal and nonfatal serious categories for 1998 vaccine administrations were similar to 1997 reports. Ongoing surveillance is documenting a decrease in VAPP. Current data show that 1 VAPP case was reported to VAERS in 1996, 4 in 1997, and none in 1998. Annual adverse-event reporting rates, severity profiles, and the proportional distribution of adverse-event groupings were generally similar for infants vaccinated with IPV compared with OPV.

A slightly higher percentage of allergic reactions was observed for IPV than for OPV in the proportional distribution of adverse-event groupings for
infants 4 to 6 months old between 1996 and 1998. Because IPV contains trace amounts of streptomycin and neomycin, hypersensitivity reactions are possible in individuals sensitive to these antibiotics. Also, it is important to note that IPV was most frequently coadministered with DTaP in this age group. Studies in Japan have attributed allergic reactions, particularly systemic urticaria, to the gelatin stabilizer in some brands of DTaP. OPV, on the other hand, was most frequently coadministered with DTPH. The impact of differential coadministration of vaccine (DTaP with IPV and DTPH with OPV) may explain the result of local reactions for infants 1 to 3 months old being more common after OPV than after IPV.

A published analysis of VAERS reports concerning infant immunization against pertussis between January 1, 1995 (when whole-cell vaccine was in exclusive use), and June 30, 1998 (when acellular vaccine was in predominant use), indicated the relative safety of DTaP. The annual number of reported events categorized as nonfatal serious for all pertussis-containing vaccines declined (from 334 in 1995 to 93 in the first half of 1998); the annual number of less serious reports declined (from 1652 in 1995 to 357 in the first half of 1998); while ~80 deaths were consistently reported each year.

Qualitative approaches (proportional distributions) were used to determine comparative safety attributable primarily to the lack of information on age-specific vaccine usage. The proportionate distributions examined use VAERS reports as denominators. The major difficulty in interpretation is that the relative frequency of other symptom categories may affect the proportional morbidity for the category of interest. As a result, an observed excess of one category in a particular exposure group may represent a true increase, but may also merely represent a deficit of events in some other category(s).

One of the major difficulties in interpreting VAERS data are that when vaccines are coadministered, as is common with pediatric vaccines, it is often impossible to disentangle their separate and joint effects. Another difficulty interpreting VAERS data arises from confounding by indication. IPV has been recommended in lieu of OPV in adults and immunocompromised persons. This may explain the slightly higher reporting rates of IPV-associated events.

The other limitations of VAERS have been well-documented and are similar to spontaneous reporting systems for other adverse drug events. A common phenomenon is a higher rate of reports after a change in immunization policy, which perhaps is reflected in the increased reporting rate of serious and fatal IPV reports in 1998. To encourage reporting of any possibly vaccine-induced adverse event, VAERS solicits reports from health professionals, vaccine manufacturers, patients, and parents. VAERS includes any report submitted, no matter how tenuous the connection with vaccination might seem. Many adverse events reported are only coincidentally associated with vaccination because childhood vaccines are administered to nearly all infants. Some of these health problems will, by chance, occur in recently vaccinated children. The leading symptoms listed on reports of fatality after the administration of either IPV or OPV in infants are SIDS and apnea. SIDS being the leading cause of postneonatal mortality is consistent with observed temporal association with vaccination. Controlled studies have failed to show a causal association between SIDS and the diphtheria-tetanus-pertussis vaccine; furthermore, research findings suggest an important mechanism for SIDS related to prone sleeping position. Apnea is not listed as a cause of death by itself but is listed along with SIDS or other underlying conditions, such as lung disorders and cardiovascular conditions. Despite efforts to increase reporting, VAERS also suffers from underreporting (not all vaccine-induced events are reported). Furthermore, underreporting varies according to the type of adverse event. On the other hand, one might expect a fairly complete reporting of certain categories of serious outcomes occurring within a short period of time after specified childhood vaccinations, which physicians are required to report either directly to VAERS or to the manufacturer. In addition, VAERS is limited by the lack of consistent diagnostic criteria and the difficulty in determining causal relationships between vaccines and adverse events.

Although VAERS is subject to the limitations noted previously, the large number of reports and national coverage provide a unique database for monitoring vaccine safety. The collection and processing of VAERS data are considerably more timely and of lower cost than the more sophisticated Vaccine Safety Datalink, a large computerized record linkage system designed to permit more rigorous evaluation of adverse events after vaccination. VAERS serves as a sentinel for the detection of either previously unreported vaccine adverse events or unusual increases in reported events as evidenced by the recent intussusception and rotavirus vaccine experience. There was a marked increase of IPV reports in VAERS after 1996, consistent with implementation of the ACIP recommendation for the sequential IPV/OPV poliovirus vaccination schedule. Given the increased use of IPV, a review of potential adverse events in VAERS compared IPV with OPV reports both before and after the introduction of the sequential vaccination schedule. Overall, no new adverse event patterns of potential concern were identified. Thus, the relative safety of IPV has been affirmed. These findings provide useful information to support the ACIP’s recommendation to shift to an all-IPV schedule.

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