The Reporting Sensitivities of Two Passive Surveillance Systems for Vaccine Adverse Events

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ABSTRACT

To evaluate reporting sensitivities for vaccine adverse events, reporting rates were estimated by dividing the number of events reported to the Monitoring System for Adverse Events Following Immunization and the Vaccine Adverse Event Reporting System in a given period by the number of doses administered or distributed during the same period. Reporting sensitivity was calculated as the ratio of the rates at which events were reported to each passive surveillance system (numerator) and occurred in controlled studies (denominator). Reporting sensitivities were generally better in the public sector than in the private sector. The significant underreporting of known outcomes, together with the nonspecific nature of most adverse event reports, highlights the limitations of passive surveillance systems in assessing the incidence of vaccine adverse events. (*Am J Public Health.* 1995;85: 1706–1709)

Introduction

Vaccines are one of the most cost-effective public health measures.[1] But while their benefits far outweigh their risks and costs, no vaccine is perfectly safe. Vaccine safety is initially assessed in prelicensure clinical trials. However, such trials usually have sample sizes that are insufficient to detect rare adverse events. In addition, vaccine trials are usually carried out in well-defined, homogeneous populations with relatively short follow-up periods, which may limit their generalizability. Postlicensure drug evaluations have relied on passive surveillance systems to monitor adverse events. Such systems are more practical and less expensive than controlled trials; however, their data are usually inadequate to determine causality.[2]

Passive surveillance systems for vaccine adverse events have been useful for evaluating contraindications to the diphtheria-tetanus-pertussis (DTP) vaccine[3] and for assessing the safety of simultaneous or combined vaccinations.[4] Reporting sensitivities allow the utility of such systems for detecting and analyzing rare adverse events to be evaluated. In this paper, we assess the reporting sensitivities of two passive vaccine adverse event reporting systems for selected adverse events.

From 1978 through 1990, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) divided the responsibility for postmarketing surveillance of vaccines in the United States. The FDA received reports of adverse events after vaccines were administered in the private sector; events occurring after the administration of vaccines purchased with public funds were reported to the Monitoring System for Adverse Events Following Immunization.[5]

The monitoring system was a stimulated passive surveillance system. In other words, when vaccines purchased with federal funds were administered in the public sector, "Important Information" forms were given to recipients or their parents or guardians instructing them to report any illnesses requiring medical attention that occurred within 4 weeks of vaccination. System coordinators at each immunization project/grantee site and at the state health department completed standardized forms that were reviewed for consistency and completeness and then forwarded to the CDC for data entry and analysis.[5]

In response to the National Childhood Vaccine Injury Act of 1988, which required health workers to report vaccine adverse events, the CDC and the FDA collaborated in 1990 to implement the Vaccine Adverse Event Reporting System to monitor the safety of vaccines in both sectors.[6] Health care professionals and parents/caretakers are encouraged to report all clinically significant vaccine ad-

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verse events. Narrative diagnostic reports are reviewed and assigned standard codes using Coding Symbols for a Thesaurus of Adverse Reaction Terms.[6] The source of the vaccines (public vs private provider) is recorded on the form.

Methods

Reports of adverse events following vaccination occurring January 1985 through October 1990 are available from the Monitoring System for Adverse Events Following Immunization; reports of such events occurring between November 1990 and the present are available from the Vaccine Adverse Event Reporting System. For seizures following the DTP vaccine, events were included if they occurred within 3 days of vaccination; this was to differentiate them from seizures caused by the measles-mumps-rubella (MMR) vaccine, which tend to occur after 6 days following vaccination.[7–9] For seizures following the MMR vaccine, events were included if they occurred between 6 and 30 days of vaccination.

For consistency with rates estimated in published studies, analyses for seizures were limited to infants less than 2 years of age; analysis for all other events included all age groups and all events occurring within 30 days of vaccination. To minimize the effect of reporting delays, this analysis was limited to reports submitted to the Vaccine Adverse Event Reporting System with vaccination dates before December 31, 1993. For this analysis, diagnoses reported to the monitoring or reporting systems were not validated. Because clinical information submitted on the reporting forms was often incomplete and unreliable, it was not possible to differentiate febrile seizures from afebrile seizures.

The numbers of vaccine doses administered during the periods covered by the monitoring and reporting systems were estimated (1) from doses purchased with public sector funds from January 1985 through October 1990 (the monitoring system) and from January 1, 1991, to December 31, 1993 (the reporting system—public sector), compiled by the National Immunization Program from all state and local recipients of grant funds; and (2) from CDC Biologics Surveillance of doses distributed by manufacturers less those returned by providers, 1991 to 1993 (CDC Biologics Surveillance).[10] The National Health Interview Survey was used to estimate the proportion of DTP and measles-containing vaccines that was ad-

TABLE 1—Frequency of Selected Vaccine Adverse Event Reports and Estimated Doses Administered, MSAEFI and VAERS, 1985 to 1993

Adverse Events	Vaccine	Interval (Days)	Doses (millions)		Adverse Event Frequency	
			MSAEFI	VAERS	MSAEFI 1985–1990[a]	VAERS 1990[b]–1993
Vaccine-associated poliomyelitis	OPV	0–30	43.8	53.8	6	7
Seizures	DTP	0–3	39.8	45.1	1323	861
	MMR + MR	4–30	18.2	10.1	626	567
Hypotonic–hyporesponsive episodes	DTP	0–30	39.8	45.1	824	641
Rash	MMR	0–30	18.2	31.8	1115	1284
Thrombocytopenia	MMR	0–30	18.2	31.8	3	36

Note. MSAEFI = Monitoring System for Adverse Events Following Immunization; VAERS = Vaccine Adverse Event Reporting System; OPV = oral poliovirus vaccine; DTP = diphtheria-tetanus-pertussis vaccine; MMR = measles-mumps-rubella vaccine; and MR = measles-rubella vaccine.
[a]To October 1990.
[b]From November 1990.

TABLE 2—Reporting Efficiencies for Selected Outcomes in MSAEFI and VAERS

Adverse Events	Reporting Efficiency, %		
	MSAEFI	VAERS (Overall)	VAERS (Public)
Vaccine-associated polio (OPV)	72	68	. . .[a]
Seizures (DTP)	42	24	36
Seizures (MMR + MR)	23	37	49
Hypotonic–hyporesponsive episodes (DTP)	4	3	4
Rash (MMR)	<1	<1	5
Thrombocytopenia (MMR)	<1	4	1

Note. MSAEFI = Monitoring System for Adverse Events Following Immunization; VAERS = Vaccine Adverse Event Reporting System; DTP = diphtheria-tetanus-pertussis vaccine; MMR = measles-mumps-rubella vaccine; MR = measles-rubella vaccine.
[a]Public and private sector information is missing on these cases.

ministered to children less than 2 years of age.[11,12] Rates of adverse events were estimated as vaccine adverse event reports in the monitoring system, in the reporting system overall, and in the reporting system—public sector only, divided by the estimated number of doses administered.

Incidence rates for selected adverse events after vaccinations—rash following MMR,[13] thrombocytopenia following MMR,[14] seizures following DTP,[15–18] seizures following MMR,[8] hypotonic–hyporesponsive episodes following DTP,[16] and vaccine-associated paralytic poliomyelitis in recipients of the oral poliovirus vaccine[19]—were estimated based on a review of published studies. For seizures, multiple studies were available; a weighted

average was therefore calculated using the sample sizes of the individual studies. Reporting sensitivities were calculated as the ratio of the rates at which events were reported to each passive surveillance system (numerator) and occurred in controlled studies (denominator). Reporting sensitivities in the reporting system were calculated for vaccine administered in the public and private sectors combined (overall) and in the public sector only.

Results

A total of 11 848 reports was submitted to the Monitoring System for Adverse Events Following Immunization January 1985 through October 1990, and 26 010 reports were submitted to the Vaccine

Adverse Event Reporting System from November 1990 to December 1993. The number of reports for selected outcomes and the estimated number of vaccine doses administered are shown in Table 1.

Reporting sensitivities of various outcomes are shown in Table 2. Sensitivities ranged from 72% for poliomyelitis after the oral poliovirus vaccine to less than 1% for rash and thrombocytopenia after the MMR vaccine. Reporting sensitivity of the reporting system overall was lower than that of the monitoring system for all vaccine-outcome combinations except seizures after MMR and thrombocytopenia after MMR, but reporting sensitivity of the reporting system when analyzed by vaccines administered in the public sector only was greater than that of the system overall for all outcomes except thrombocytopenia.

Discussion

The utility of passive surveillance has several potential limitations. For example, underreporting is often a problem, limiting the system's ability to detect new or rare events.[20] Clinical information obtained on report forms is often inadequate for assessment, and reports may be biased to prevailing concepts of adverse events and changing publicity.[2,21] An increase in reported events may be owing to an increase in the number of doses of vaccine administered, information that may not be readily available.

Reporting of adverse events appears to depend on a number of factors, such as clinical seriousness, temporal proximity to vaccination, and health care workers' awareness of and obligation to report particular adverse events.[22] In our study, reporting sensitivities for adverse events surveillance in the United States varied widely, ranging from 72% for vaccine-associated poliomyelitis to less than 1% for acute thrombocytopenic purpura following the MMR vaccine and hypotonic–hyporesponsive episodes following the DTP vaccine. This underreporting of known outcomes highlights the limitations of passive surveillance in measuring the incidence of vaccine adverse events.

Despite underreporting, the reporting sensitivities of the reporting and monitoring systems for certain serious events appear to be higher than those of other passive surveillance systems that monitor adverse drug reactions. Such systems in Britain, for example, receive reports on from only 1% to 10% of events estimated to have occurred.[20] Reporting

sensitivities of the two US systems for serious events are comparable to estimated reporting sensitivities of vaccine-preventable diseases in the United States: 33% for pertussis deaths,[23] 40% for tetanus deaths,[24] and 22% for congenital rubella syndrome.[25] Disease surveillance systems are generally more straightforward than drug adverse event monitoring systems in the United States since they focus on one disease, have a defined clinical syndrome, and generally can be confirmed by laboratory diagnostics.

Outcomes with delayed onset after vaccination or outcomes not generally recognized to be associated with vaccination often have significantly lower reporting sensitivities. Narrative report forms and reporting by parents/caretakers decrease diagnostic accuracy. Unlike diseases for which distinct case definitions exist, many adverse events are poorly defined clinical syndromes. Clinical information reported is often difficult to categorize and encode.

Total reporting sensitivities for the Vaccine Adverse Event Reporting Systems were consistently lower (except for seizures [MMR] and thrombocytopenia) than those for the Monitoring System for Adverse Events Following Immunization. The latter system depends on the cooperation of private physicians and manufacturers for reports, and reporting rates are believed to be lower in the private sector.[22] Similarly, in the reporting system, estimated reporting sensitivity in the public sector was higher than that in the private sector, confirming the difficulty of obtaining private sector participation in surveillance.[26] On the other hand, state and city immunization programs have responsibility for ensuring the timeliness and completeness of adverse events reporting for vaccines administered in the public sector. Interestingly, the monitoring system had a better reporting sensitivity for seizures following the DTP vaccine but had a lower sensitivity for seizures following the measles vaccine. This is most likely owing to a reporting artifact resulting from the limitations of adverse event reporting systems.

Nevertheless, if reporting is reasonably consistent, it may be possible to detect changes in trends of known common adverse events. In addition, passive surveillance remains a potentially cost-effective way to monitor rare adverse events that cannot be detected in relatively small prelicensure clinical trials. Case reports received by the Vaccine Adverse Event Reporting System can be

used to generate hypotheses that can be evaluated in controlled studies, such as large-linked databases in which exposure and outcome variables are computerized.[6] □

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