Adverse Events Temporally Associated with Immunizing Agents

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SUMMARY

In Canada during 1990, a total of 2832 reports of adverse events temporally associated with the administration of immunizing agents were received by the Childhood Immunization Division of the Laboratory Centre for Disease Control. This paper summarizes the data collected, describes the surveillance system, and demonstrates that, with more than 12 000 000 doses of vaccines distributed during 1990, the incidence of adverse events reported is very low.

RÉSUMÉ

Le laboratoire canadien de lutte contre les maladies et sa Division de l'immunisation infantile ont reçu, pendant l'année 1990, un total de 2 832 rapports d'effets indésirables temporaires reliés à l'administration des agents d'immunisation. Cet article résume les données colligées, décrit le système de surveillance et démontre, avec plus de 12 000 000 de doses de vaccin distribuées, que l'incidence des effets indésirables rapportés est très faible.

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THE GOAL OF IMMUNIZATION programs is to provide safe and effective vaccines to all eligible persons in order to decrease the morbidity and mortality associated with vaccine-preventable illnesses in Canada. However, just as no vaccine is perfectly effective, none is entirely without risk; therefore, adverse events following immunization are expected at times.

The purpose of monitoring the occurrence of these reactions is to ensure that vaccines remain as safe as they can be. Monitoring permits researchers to estimate rates of occurrence of illnesses and untoward reactions that could follow immunization, to monitor unusually high rates of adverse events by vaccine lot in order to detect a possible bad lot and take action, and to raise awareness of the proper handling and administration of vaccines (when improper handling leads to an adverse event).

In Canada, surveillance for such adverse events associated with immunizing agents is the responsibility of the Bureau of Communicable Disease Epidemiology (BCDE) of the Laboratory Centre for Disease Control in Ottawa. The main source of information is spontaneous reporting by physicians and nurses to local health authorities of events thought to be due to vaccine administration (*Figure 1*). This information is then forwarded to BCDE through provincial and territorial epidemiologists. As well, BCDE receives reports directly from vaccine manufacturers and other agencies. This surveillance is separate from the surveillance of adverse events following the use of prescription drugs, which is the responsibility of the Drugs Directorate of Health and Welfare Canada.

The following is an abridged version of the fourth annual national summary on adverse events temporally associated with vaccine administration. The summary includes events resulting from immunizations between January 1 and December 31, 1990, that were reported to BCDE by December 31, 1991. It also compares

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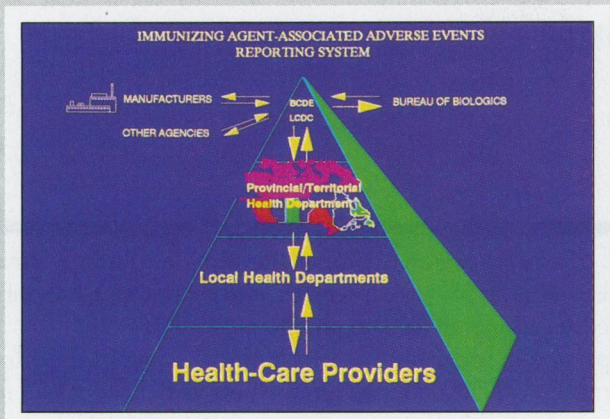
some of the 1990 figures with those published for 1988[1] and 1989.[2]

METHODS

A standard reporting form is now used, with local modifications, by most jurisdictions across Canada. Reports are received either by mail or via electronic file. Reports are accepted only from health care providers and not from the general public. A computer database contains epidemiologic and medical data on reported adverse events related to patients vaccinated since January 1, 1987.

Figure 1. **Reporting system for adverse effects associated with immunizing agents**



To be included in the database, the adverse event has to meet specific criteria[2] and must not be attributable to any coexisting condition. These eligibility criteria are based on both surveillance and clinical studies with vaccines carried out internationally and define a range of adverse events and their temporal relationship with vaccine administration. Reports not meeting these eligibility criteria are entered in the database but flagged as to be excluded from reports. They can still be retrieved as needed.

A range of possible events has been associated with vaccine administration. Still, the volume of reports makes it impossible to verify the accuracy of each one, except for the most serious reactions, such as a fatality, paralysis, or encephalopathy, which are followed up if further information is required. Other than the eligibility criteria, no other judgments are made to include or exclude a report.

The system, therefore, relies on judgment "in the field" by the reporting health care providers with screening only for eligibility criteria. It is, thus, important to be aware that acceptance of a report does not imply a causal relationship between the administration of the immunizing agent and the medical outcome, and this summary report can only give an impression of the frequency of events that follow the routine use of immunizing agents.

To calculate rates of events following the use of immunizing agents, we used the number of doses of each vaccine distributed across Canada. This information is provided by the manufacturers on a monthly basis, by province and lot number.

RESULTS

For 1990, 4109 reports were received from across Canada. The Ontario Ministry of Health was unable to send any reports because of technical reasons arising from a new computer reporting system. Of the total, 2832 (69%) met the eligibility criteria, compared with 79% and 58% of all reports received for 1989 and 1988, respectively. Some reports that were accepted contained information on more than one immunizing agent or more than one adverse event for a given patient. For this reason, the number of individual reports analyzed (2832) is less than the number of adverse events reported (4301) and the number of immunizing agents implicated (4498).

Reporting rates vary between provinces, from less than one to nearly 50 per 100 000 population.

Not surprisingly, given the frequency with which this group receives vaccines, most reactions (51.1%) occurred among children younger than 1 year of age. Overall, children younger than 2 years accounted for 68.9% of all reports. There was no significant difference in adverse events between the sexes; male patients accounted for 50.1% while female patients accounted for 49.9%.

Table 1. **Adverse event reports temporally associated with immunization:** *Rate is frequency of adverse events for every 100 000 doses distributed.*

	1988		1989		1990	
IMMUNIZING AGENT	**NO.**	**RATE**	**NO.**	**RATE**	**NO.**	**RATE**
DTP	1546	77.7	1591	104.8	2137	120.6
OPV (Sabin)	916	56.0	1025	45.0	1402	49.2
DPTP	365	43.1	291	29.2	162	189.3
Haemophilus influenzae type B	126	22.6	171	32.0	220	70.5
Measles, mumps, and rubella	323	40.6	168	27.3	196	28.1
Hepatitis B	48	18.7	72	22.2	53	15.5
Influenza	40	1.9	62	2.4	75	2.6
Tetanus-diphtheria (adult)	30	6.1	52	6.4	91	9.7
Diphtheria-tetanus (child)	25	5.7	39	34.3	38	34.9
Typhoid	17	12.3	21	19.5	30	41.1

Table 1 presents the distribution of adverse event reports for the most common immunizing agents during 1990 as well as 1988 and 1989. Diphtheria, pertussis, and tetanus (DPT) and DPT with polio (DPTP) vaccines were cited most often. Although many reports cited oral polio (Sabin) (OPV), only one indicated an adverse event after OPV was given alone; thus, it is more likely that another antigen was responsible for the adverse events mentioned. Moreover, no reports pertained to contact cases of immunized children.

The number of events reported in each adverse event category is presented in *Table 2*. The most commonly reported adverse event was fever, which was cited in 1556 reports (36.2%); 328 (7.6%) of these indicated a temperature greater than or equal to 40.5°C. The second most frequently reported events were screaming episodes (18.8%) followed by severe local reactions (11.8%).

When several immunizing agents are given at once, it is difficult to attribute an adverse reaction to only one (*Table 3*). We tabulated adverse events for each agent as long as it was among those administered to the patient; thus, we do not imply a direct relationship with that agent but only that it was identified as one of a possible combination of agents.

The delay between administration of the immunizing agent and onset of its initial adverse event ranged from 1 minute to 76 days. A total of 303 reactions (10.7%) occurred less than 2 hours after the immunizing agent was administered; 2091 (73.8%) occurred after less than 1 day, and 2522 (89.1%) occurred after less than 7 days. The median delay was approximately 6 hours.

The overall number of DPT- and DPTP-associated adverse event reports is similar regardless of the dose number within the series (first, second, third...). However, severe local reactions do increase with later doses.

Nearly all patients recover fully from a vaccine-associated adverse event. At the time physicians made their original report, 2509 patients (88.6%) were already fully recovered and 34 patients (1.2%) still had residual effects. These 34 patients were followed up approximately 1 year after that initial report was received and 13 had recovered, two still had residual effects (one reported having hearing loss and the other had brachial neuritis with arthritis), and 19 remained unknown. One death (an 84-year-old man tentatively diagnosed with Guillain-Barré syndrome) was reported 3 weeks after influenza vaccine was administered. One hundred sixty-four patients were hospitalized for periods ranging from 1 to 32 days (average length of stay was 3 days). The leading causes for hospitalization were high fever and convulsions.

Table 2. **Citations of 10 most frequent adverse events temporally associated with immunizing agents:** *Rate is frequency of adverse events for every 100 000 doses distributed.*

ADVERSE EVENT*	1988		1989		1990	
	NO.	RATE	NO.	RATE	NO.	RATE
Fever	1366	12.8	1217	9.7	1556	12.9
Screaming episode	584	5.5	720	5.7	809	6.7
Allergic reaction	151	1.4	167	1.3	156	1.3
Severe vomiting	115	1.1	150	1.2	257	2.1
Severe pain	125	1.2	149	1.2	506	4.2
Other severe or unusual event	75	0.7	148	1.2	296	2.5
Hypotonic or hyporesponsive episode	96	0.9	132	1.0	231	1.9
Rash	153	1.4	114	0.9	118	1.0
Convulsion or seizure	142	1.3	99	0.8	129	1.1
Sterile abscess, nodule, or necrosis	73	0.7	72	0.6	85	0.7

* *Estimated number of doses distributed used for calculation = 12 056 000.*

DISCUSSION

Despite its voluntary basis in all provinces except Ontario (where reporting is mandatory in the same way as certain communicable diseases), reporting of vaccine-associated adverse events is extremely useful. Periodic reports are sent to the Ministries of Health of all provinces and territories and as feedback to manufacturers about their products. The system has helped investigate and resolve concerns that occasionally arise about vaccines. These include reports of clusters of adverse events, suspected increases in the number of adverse event reports for a particular vaccine, and questions or concerns from health care providers about adverse events to vaccines. In some cases, information in the database is used collaboratively by the Bureau of Biologics (the licensing authority for vaccines), the provincial and territorial authorities, the manufacturers, and the Laboratory Centre for Disease Control.

A passive system nevertheless has two important shortcomings: underreporting and a temporal reporting bias. Further, it is often difficult to attribute a reaction to a particular antigen, as many childhood vaccines are given simultaneously. Data are lacking also on the baseline rates of certain illnesses that become associated with vaccine administration, such as encephalopathies, seizures, or high fevers, which occur regularly in the population being immunized, and which could then be coincident to the recent administration of a vaccine. We also lack accurate data on the number of doses actually given to patients. We must rely on manufacturer data on the number of doses distributed to provincial immunization programs instead, without any knowledge of the potential amount wasted. All of these factors can artificially increase or decrease the rate of adverse events and make it difficult to obtain a true estimate.

For rate calculations we rely on manufacturer data for the number of doses distributed. We must accept these data because we have no accurate evaluation of the vaccine coverage in Canada.

Reporting systems

The sensitivity, specificity, and timeliness of the reporting of vaccine adverse events vary greatly across the country, as highlighted by the distribution of rates of adverse events. Both within and between

Table 3. **Adverse events temporally associated with vaccines**

ADVERSE EVENT	DPT		OPV (SABIN)		DPTP		DIPHTHERIA-TETANUS (CHILD)		INFLUENZA		HEPATITIS B		*H INFLUENZAE* TYPE B		MEASLES, MUMPS, AND RUBELLA		TYPHOID		TETANUS-DIPHTHERIA (ADULT)	
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
Adenopathy	16	0.9	11	0.4	1	1.2	0	0.0	1	0.0	1	0.3	3	0.6	13	1.9	1	1.4	4	0.4
Allergic reaction	72	4.1	64	2.3	10	11.7	2	1.8	15	0.5	7	2.0	20	6.4	20	2.9	5	6.8	19	2.0
Anesthesia or paresthesia	2	0.1	1	0.0	0	0.0	0	0.0	0	0.0	4	1.2	1	0.3	0	0.0	0	0.0	4	0.4
Anaphylaxis	2	0.1	1	0.0	0	0.0	0	0.0	4	0.1	2	0.6	0	0.0	1	0.1	1	1.4	3	0.3
Arthralgia or arthritis	12	0.7	13	0.5	3	3.5	2	1.8	4	0.1	10	2.9	2	0.6	10	1.4	2	2.7	3	0.3
Convulsion or seizure	93	5.3	53	1.9	6	7.0	0	0.0	0	0.0	0	0.0	22	7.1	27	3.9	1	1.4	1	0.1
Encephalopathy	2	0.1	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0	0	0.0
Fever																				
• 39.0°C-40.4°C	669	37.8	403	14.2	60	70.1	12	11.0	4	0.1	0	0.0	69	22.1	74	10.6	1	1.4	2	0.2
• ≥40.5°C	279	15.7	180	6.3	12	14.0	5	4.6	3	0.1	0	0.0	40	12.8	31	4.5	0	0.0	0	0.0
• Unrecorded	314	17.7	211	7.4	21	24.5	5	4.6	12	0.4	2	0.6	34	10.9	30	4.3	7	9.6	9	1.0
Guillain-Barré syndrome	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypotonic or hyporesponsive episode	197	11.1	131	4.6	15	17.5	3	2.8	6	0.2	1	0.3	19	6.1	9	1.3	1	1.4	3	0.3
Infective abscess	12	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0	1	0.1
Meningitis or encephalitis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Orchitis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other severe or unusual event	123	6.9	88	3.1	4	4.7	4	3.7	48	1.7	34	9.9	17	5.5	30	4.3	5	6.8	27	2.9
Paralysis	1	0.1	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Parotitis	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	13	1.9	0	0.0	0	0.0
Rash	37	2.1	27	1.0	2	2.3	2	1.8	5	0.2	2	0.6	5	1.6	60	8.6	2	2.7	5	0.5
Screaming episode or persistent crying	706	39.8	451	15.8	88	102.9	5	4.6	0	0.0	0	0.0	17	5.5	10	1.4	0	0.0	0	0.0
Severe pain or severe swelling	390	22.0	N/A	N/A	14	16.4	16	14.7	9	0.3	4	1.2	43	13.8	9	1.3	11	15.1	47	5.0
Severe vomiting or diarrhea	197	11.1	143	5.0	11	12.9	1	0.9	12	0.4	3	0.9	25	8.0	24	3.5	3	4.1	3	0.3
Sterile abscess, nodule, or necrosis	68	3.8	N/A	N/A	2	2.3	1	0.9	0	0.0	0	0.0	3	1.0	1	0.1	2	2.7	2	0.2
Thrombo-cytopenia	1	0.1	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
TOTAL	3194	180.3	1780	62.5	249	291.0	58	53.3	125	4.4	70	20.4	322	103.2	363	52.1	42	57.5	133	14.2

N/A = *not available.*

provinces, the vaccine delivery system (public health versus private) affects reporting. In addition, reporting practices can also vary considerably from one health unit to another within a province. The more active reporting system in Alberta could explain the high rate of reporting in that province. Nevertheless, it is important to point out that Alberta, which accounted for 56% of all reports analyzed for the year 1987,[3] accounted for only 44% of those analyzed in 1990. This indicates a trend toward a better representation of other provinces and territories in the database. However, these differences still emphasize the need to improve the sensitivity and timeliness of the reporting system.

Given that childhood immunization programs across the country emphasize early immunization,[4] it is unsurprising that most adverse event reports were for children younger than 1 year.

The differences in results from 1987 through 1990 should be interpreted with caution because the surveillance system was started in 1988 with retrospective classification of 1987 data; the number of doses distributed is a proxy denominator; and adjustments were made in reporting. However, the decrease in the rate of adverse reactions reported after using the MMR vaccine between 1987 and 1988 was accentuated between 1988 and 1989 and appears to have stabilized between 1989 and 1990, while the number of parotitis reports has declined from 271 in 1987 to 68 in 1988 and 15 in 1990.[1-3]

The number of adverse events reported for passive immunizing agents probably underestimates the true number because these agents are administered mainly by private physicians and clinics, whose reporting rates are lower than the public health system.

In 1990 there was a shift from using inactivated polio (Salk) (IPV) to OPV because of a shortage of IPV. This change resulted in an apparent sudden rise in the rate of adverse events to the DPTP vaccine, as the provinces switching to OPV were among those with the lowest reporting rates of adverse events. The large decrease in the number of doses distributed was not offset by a correspondingly large drop in the number of adverse event reports for the vaccine, and thus the rate of reactions seemed to increase.

In addition to this reporting system, other tools or sources of information are used to complete the postmarketing surveillance of adverse vaccine reactions.

Monitoring adverse events

The Statistics Canada mortality database and the hospital discharge databases are reviewed both to monitor vaccine-associated adverse reactions and to assess the background rates of conditions that could be interpreted as vaccine-associated adverse events, such as Guillain-Barré syndrome.

The Laboratory Centre for Disease Control is also funding a test surveillance system to monitor the incidence of severe adverse events after childhood immunizations and to measure the background rates of neurologic, infectious, and other diseases that might be mistaken for vaccine reactions or are being considered for future vaccine development. Other projects are developing reliable methods for active postmarketing surveillance, able to capture timely information about common adverse events associated with newly released vaccines. A proactive and global approach to surveillance of adverse vaccine reactions has been outlined in the proceedings of a workshop on postmarketing surveillance of adverse vaccine reactions.[5]

Finally, although this report focuses on vaccine-associated adverse events, it is important to view these events in their proper context. More than 12 million doses of vaccine were distributed in 1990. Even if some of the doses were never administered and some severe events were not recognized or reported, the rate of occurrence of such events appears to be very low. The morbidity and mortality prevented by vaccination far outweighs this very low risk of severe adverse events.

The Laboratory Centre for Disease Control continues to improve the Vaccine Associated Adverse Events surveillance system. With its impending move to a more powerful computer and better integration of its components, the goal will be to provide even more timely

feedback to provincial and territorial Ministries of Health and to respond quickly to special requests from health care providers. Canada's reporting rate of adverse events is among the best in the world (which does not imply our vaccines are of poorer quality but rather is a credit to health care providers), and we urge all physicians and nurses who administer vaccines to continue to participate actively in the timely reporting of any adverse events temporally associated with vaccine administration. Ultimately, the public and the health care system will benefit from all our efforts. ■

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