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ADVERSE EVENTS TEMPORALLY ASSOCIATED WITH VACCINES — 1992 REPORT

The postmarketing surveillance of medical events following the receipt of vaccines permits: (1) identification of infrequent adverse events that may be caused by vaccines, (2) estimation of rates of occurrence of more serious post-immunization events by type of vaccine, (3) monitoring of unusually high rates of adverse events, (4) raising of health care providers' awareness to the risks and/or safety measures in administering vaccines, and (5) identification of areas that require immediate epidemiologic investigation or further research.

In Canada, surveillance of adverse events temporally associated with the administration of vaccines at the federal level is the responsibility of the Bureau of Communicable Disease Epidemiology (BCDE), Laboratory Centre for Disease Control, Ottawa. The main source of information is a passive reporting network that begins with health care providers submitting relevant information concerning adverse events thought to be due to the administration of vaccines to local (municipal) health departments. They, in turn, relay this information to provincial or territorial authorities. The information, in addition to information from manufacturers and other agencies, is then forwarded to BCDE.

Vaccine distribution data are also provided to the BCDE by vaccine manufacturers on a monthly basis. The lot database consists of the number of doses of specific products by lot number and by province or territory.

Surveillance data are maintained in a computerized database that includes epidemiologic and medical data on adverse events occurring in persons vaccinated since 1 January, 1987. For events to have been included in the database, they had to have met the criteria listed in Appendix I and II. As well, events eligible for inclusion should not have been attributable to any co-existing condition. **Acceptance of an adverse event report does not imply a causal relationship between the administration of the vaccine and the medical outcome.** Reports are verified, particularly for serious events, to the extent that information is provided by the reporting source. The type of vaccine delivery system (public versus private) varies greatly among the provinces and territories and impacts on the sensitivity, specificity and timeliness of the reporting system within a province or territory.

The BCDE has published annual reports on the first five years of surveillance. This report constitutes the sixth annual national summary of adverse events temporally associated with the administration of vaccines. It presents an analysis of reports pertaining to events associated with vaccine administered between 1 January and 31 December, 1992. It also compares some of the 1992 figures with those published earlier[1,2].

For 1992, 4,279 (87%) of 4,923 reports received met the adverse event definitions and temporal eligibility criteria (as outlined in Appendix I and II). This proportion is comparable to that for 1991 (86%) and much higher than the proportion of eligible reports received in 1990 and 1989, i.e., 69% and 79%, respectively. The proportion of eligible reports has continued to increase since 1987 and most likely reflects better knowledge of the reporting criteria.

Geographic Distribution

Figures 1 and 2 show the distribution of reports by province or territory for 1990, 1991 and 1992 based on the number of adverse event reports and the reporting rates per 100,000 population, respectively (according to post-censal estimates). In 1992, approximately 62% of all reports were submitted by Alberta and British Columbia and another 17% from Quebec. The distributions differ from what one might expect on the basis of population alone and are probably due, in part, to differences in provincial and territorial reporting systems. The reporting differences are not well quantified thus making it difficult to compare data between jurisdictions.

From 1990 to 1992 there were significant increases in the number of reports received from all provinces, with the exception

Figure 1

Vaccine-associated adverse events — number of reports by province/territory, Canada, 1990–1992

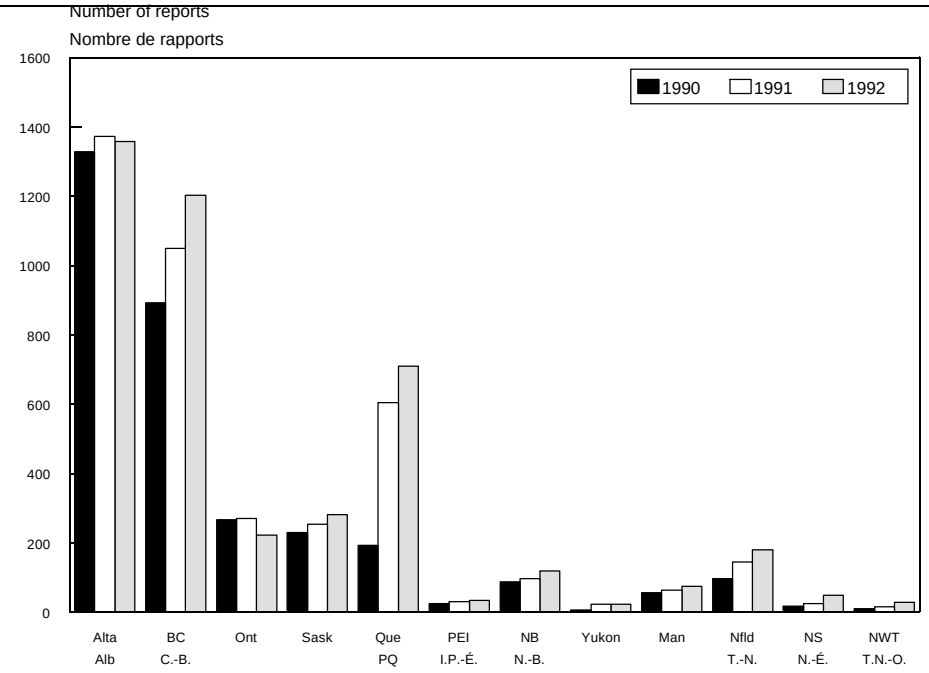
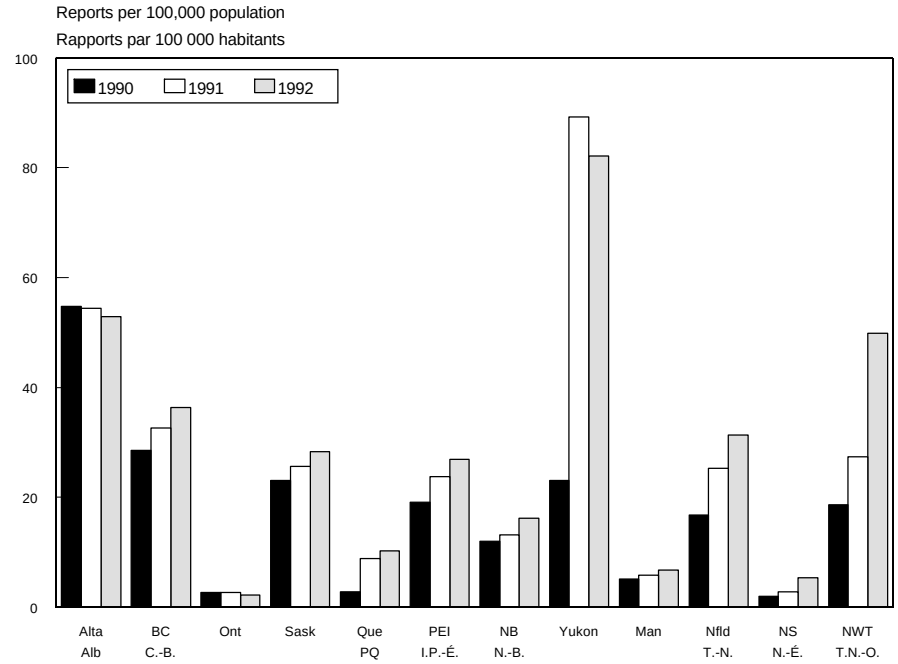


Figure 2

Vaccine-associated adverse events — reports per 100,000 population, by province/territory, Canada, 1990–1992



of Ontario. Consequently, the relative proportion of reports received from Alberta fell from 41% in 1990 to 32% in 1992.

Age and Sex Distribution

The distribution of vaccine-associated adverse event reports indicates that a large proportion of events (41%) occurred among children < 1 year of age (Table 1). Given the multiple dose scheduling of childhood immunization programs across the country, this finding is not unexpected. An additional 30% pertained to children in the 1- to 4-year age group. Overall, children < 2 years of age accounted for 60% of all reports. The median age was 1.5 years and the mean age, 6.5 years.

There were no appreciable sex differences; 2,170 (50.7%) of the reports where gender was listed involved males and 2,094 (48.9%) females.

Vaccines

Table 2 shows the various antigen combinations listed in the reports. Some reports indicated more than one vaccine for a given patient. For this reason, the number of individual reports analyzed (4,279) is less than the number of associated vaccines (7,870). Approximately 38% of the reports submitted pertained to a single vaccine while about 41% cited two vaccines and another 22% cited three. Only two reports related to four vaccines. By far, the commonest combination of vaccines administered was diphtheria and tetanus toxoids and pertussis antigen (DPT) with oral polio vaccine (OPV). Other common combinations were DPT with *Haemophilus influenzae* type b conjugate vaccine (Hib), and DPT, OPV and Hib.

Table 1
Distribution of adverse event reports by age group, Canada, 1992

Age (months)	Frequency	Percent
< 2	14	0.3
2 - 3	488	11.4
4 - 5	565	13.2
6 - 11	688	16.1
12 - 23	793	18.5
Total (< 2 years)		59.5
Age (Years)		
2 - 4	503	11.8
5 - 9	539	12.7
10 - 19	242	5.7
20 - 29	101	2.4
30 - 39	93	2.2
40 - 49	94	2.2
50 - 59	68	1.6
60+	68	1.5
Unknown	28	0.7
Total (All ages)	4,279	**100.0**

The distribution of adverse event reports by type of vaccine is presented in Table 3. The types of vaccines most frequently reported in association with adverse events has remained fairly constant over the last 6 years of surveillance with DPT still having the highest frequency of associated events. Of 2,057 reports involving OPV, only nine pertained to the sole administration of OPV. In addition, there was one report of paralysis in an adult contact of an OPV-immunized child[3]. In all other cases OPV was given at the same time as another vaccine (usually DPT) and any adverse event was more likely attributable to the other vaccine.

Table 4 compares the distribution of adverse event reports by selected vaccines for 1990, 1991 and 1992. Increased reporting of events associated with the meningococcal vaccine occurred following a mass immunization campaign initiated in 1991 in Quebec. However, as seen in Table 3, the adverse event rate for the vaccine is still within the lower range of adverse event rates for all vaccines.

For almost all vaccines, reporting rates for 1992 are higher when compared with the two preceding years. The interval between the calendar year of analysis and the actual time of analysis has been greater for 1992 than for preceding years. This observation gives rise to two possible explanations for the higher rates observed in 1992. First, the longer interval almost certainly resulted in more reports being received at BCDE in 1992. The majority of adverse event reports are received at BCDE more than 2 months after they are first submitted at the local level; in 1992, only 20% of reports were received within a 2-month lag period while the lagtime exceeded 6 months for 53% of reports.

Secondly, we expect that the information on number of vaccine doses returned to manufacturers would be more complete given the delay before analysis thereby allowing a more accurate and possibly a lower proxy estimate of the number of doses administered and, in turn, a higher rate. It is possible that the rates obtained are, therefore, a much more accurate estimate of the true rates of adverse events.

Table 2
Distribution of adverse event reports by vaccine combination patterns, Canada, 1992

One product given	Frequency
Diphtheria, Pertussis, Tetanus (DPT)	486
Meningococcal Vaccine (MENING)	195
Diphtheria, Pertussis, Tetanus, Polio (DPTP)	164
Measles, Mumps, Rubella (MMR)	164
Hepatitis B (HB)	144
Tetanus, Diphtheria (Td)	113
Influenza (FLU)	93
Haemophilus influenzae type b (Hib)	75
Typhoid (TYPH)	33
Tetanus, Diphtheria, Poliovirus (TdP)	23
Diphtheria, Tetanus (DT)	21
Rabies (RAB)	20
Bacille Calmette-Guérin (BCG)	12
Rubella (R)	12
Tetanus (T)	12
Oral Poliovirus Vaccine (OPV)	9
Pertussis (P)	6
Yellow Fever (YF)	5
Diphtheria (D)	4
Pneumococcal Vaccine (PNEUMO)	3
Measles (M)	2
Inactivated Poliovirus (IPV)	1
Others	6
Total	1,603
Two products given	
DPT OPV	1,056
DPT Hib	338
Td OPV	25
DT OPV	31
DPT MMR	7
DPTP Hib	124
DPT IPV	5
Other combinations	162
Total	1,748
Three products given	
DPT OPV Hib	664
DPT OPV MMR	11
DT OPV Hib	4
Other combinations	247
Total	926
Four products given	
DPT Hib MMR OPV	1
BCG DPT Hib OPV	1
Total	2

In contrast to data obtained for 1991, a much higher rate of reports was observed for DPTP (250.1 per 100,000 doses) compared to DPT (136.2 per 100,000 doses). This artefactual increase in relative rates is most likely due to a change in product from DPTP to DPT in Ontario. The extremely low reporting pattern from Ontario has long been recognized, thus, such a

Table 3
Distribution of adverse event reports by immunizing agents, Canada, 1992

Vaccine	Frequency	(hospitalized)	Rate per 100,000 doses distributed
DPT	2,795	(135)	136.2
OPV/Sabin	2,057	(94)	83.7
Hib	1,520	(100)	90.8
DPTP	288	(17)	250.1
MMR/ROR	286	(46)	53.7
MENING	202	(4)	17.0
Td (adults)	171	(2)	13.7
FLU	154	(10)	3.9
HB	99	(9)	14.0
DT (children)	70	(2)	78.0
TYPH	53	(5)	54.0
TdP	27	(1)	44.0
IPV/Salk	26	(0)	13.4
P/C	25	(0)	236.3
RAB	21	(1)	73.2
YF	17	(1)	28.0
BCG	13	(2)	19.5
D	13	(0)	82.6
T	13	(0)	5.6
R	12	(0)	40.8
PNEUMO	3	(1)	12.2
JE	2	(1)	22.4
M/R	2	(0)	67.8
CHOL	1	(0)	2.7
MUMPS	0	(0)	0.0
Total	7,870	**(431)**	

Table 4
Distribution of adverse event reports by selected vaccines, Canada, 1990-1992

Vaccine	Frequency (Rate per 100,000 doses distributed)					
	1990		1991		1992	
DPT	2,137	(120.6)	2,506	(113.9)	2,795	(136.2)
Hib	220	(70.5)	325	(69.6)	1,520	(90.8)
DPTP	162	(189.3)	256	(221.6)	288	(250.1)
MMR	196	(28.1)	275	(31.3)	286	(53.7)
MENING	2	(2.8)	4	(5.3)	202	(17.0)
Td (adults)	91	(9.7)	160	(12.7)	171	(13.7)
FLU	75	(2.6)	110	(3.0)	154	(3.9)
HB	53	(15.5)	78	(21.7)	99	(14.0)
DT (children)	38	(34.9)	64	(63.7)	70	(78.0)
TYPH	30	(41.1)	48	(48.7)	53	(54.0)

product switch would introduce an underreporting bias and, consequently, a dilution effect in the estimation of DPT rates while, conversely, the DPTP rates would recover from previous biases.

Adverse events

The number of adverse events reported in each adverse event category is presented in Table 5 (see Appendix I for a detailed description of the categories). As with the vaccines, most reports indicate more than one adverse event, thus, the number of adverse events reported (6,908) is more than the number of individual reports analyzed (4,279). The most commonly reported adverse event was fever (all fever categories combined), which was cited in 2,095 reports (30%). Of these, 428 (20%) indicated a temperature $\geq 40.5^{o}$ C.

The non-specific category of "other severe or unusual events" was applicable to 652 (9.4%) reports. The majority of these events are not considered severe or life-threatening but are unusual because they do not fit the more common specific categories. Approximately 14% of these reports cite respiratory disorders, including apnea or dyspnea, and abnormal breath sounds such as wheezing or stridor. Other common groups are myalgias and malaise (8.0%); rashes and other skin disorders (7.4%); cardiovascular events, including both hypertensive and

Table 5
Distribution of adverse event reports by nature of event, Canada, 1990-1992

Adverse Events	Frequency	Percent	Rate per 100,000 doses distributed
Fever	2,095	30.3	14.1
Severe pain and/or swelling	1,290	18.7	9.4
Screaming episodes	877	12.7	5.9
Other events	652	9.4	4.4
Severe vomiting and/or diarrhea	431	6.2	2.9
Allergic reaction	366	5.3	2.5
Hypotonic-hyporesponsive episode	355	5.1	2.4
Rashes	234	3.4	1.6
Convulsion/Seizures	217	3.1	1.5
Sterile abscess/	113	1.6	0.8
Arthralgia/Arthritis	93	1.3	0.6
Adenopathy	59	0.9	0.4
Anaesthesia/Paresthesia	24	0.3	0.2
Infective abscess	24	0.3	0.2
Anaphylaxis	23	0.3	0.2
Parotitis	13	0.2	0.1
Paralysis	12	0.2	0.1
Encephalopathy	8	0.1	0.1
Guillain-Barré Syndrome	7	0.1	0.0
Thrombocytopenia	7	0.1	0.0
Meningitis/Encephalitis	4	0.1	0.0
Orchitis	4	0.1	0.0
Total	4,279		

hypotensive episodes, cyanosis, and rarely myocardial infarctions (6.3%); central nervous system disorders, including infantile spasms, neuropathies, and ataxia (6.0%); and behavioural disorders, including hallucinations, confusion, and amnesia (6.0%).

Table 6 compares the frequencies and reporting rates of the 10 most frequently reported adverse events for 1990, 1991 and 1992. In general, the 1991 and 1992 rates are quite comparable.

Table 6
Distribution of adverse event reports by ten most frequently occurring events, Canada, 1990-1992

Adverse event	Frequency (Rate per 100,000 doses distributed)					
	1990		1991		1992	
Fever	1,556	(12.9)	1,796	(14.1)	2,095	(14.1)
Severe pain and/or swelling	506	(4.2)	1,054	(8.3)	1,290	(8.7)
Screaming episodes	809	(6.7)	830	(6.5)	877	(5.9)
Other events	296	(2.5)	722	(5.7)	652	(4.4)
Severe vomiting and/or diarrhea	257	(2.1)	350	(2.7)	431	(2.9)
Allergic reaction	156	(1.3)	247	(1.9)	366	(2.5)
Hypotonic-hyporesponsive episode	231	(1.9)	343	(2.7)	355	(2.4)
Rashes	118	(1.0)	199	(1.6)	234	(1.6)
Convulsion/Seizures/	129	(1.1)	181	(1.4)	217	(1.5)
Sterile abscess	85	(0.7)	126	(1.0)	113	(0.8)

Table 7 presents the distribution of adverse events for a selected group of vaccines. It is emphasized that in most cases it is difficult to attribute a particular event to a specific vaccine because, in the majority of reports, more than one vaccine was cited in association with the adverse event(s). Adverse events were tabulated for each vaccine as long as it was among those administered to the patient. This does not imply a causal relationship with that vaccine but only that it was identified as one of a combination of associated vaccines.

The delay between administration of a vaccine and onset of the initial adverse event ranged from 1 minute to 60 days. Because these estimates are often based on a subjective recollection of events following immunization, they have a high potential to be imprecise, therefore, careful interpretation of the information is advised. Two hundred and thirty-one reports (5.4%) indicated events starting < 1 hour after vaccine administration, 2,880 (67.3%) with events occurring within 1 day, and 3,769 (88.1%) within 1 week (Table 8). Overall, 91.8% of reports indicated onset within 1 month while only 0.2% occurred after 1 month. Information was missing on 343 reports (8.0%). The median delay from vaccine administration to onset of symptoms was 5 hours.

Outcome

Of the reports with information on outcome, 3,928 (91.8%) indicated full recovery at the time of initial reporting while 27 (0.6%) indicated recovery with residual effects. Outcome information was unavailable for 324 patients (7.6%).

Special effort is made to follow up patients with residual effects approximately 1 year after the initial report is received. Among the 27 patients originally reported as having residual effects, 18 (67%) had fully recovered while there was no information available for the rest.

Among 234 patients hospitalized, the duration of hospitalization was known for 154 and ranged from 1 to 23 days. The mean duration was 3.3 days and the median was 2 days. The events most frequently associated with hospitalization were fever and convulsions. These were by no means exclusive of each other, or of other adverse event categories because hospitalized vaccinees often had experienced more than one event or illness.

Dose Number in Series for DPT and DPTP Combined

The National Advisory Committee on Immunization recommends, in the *Canadian Immunization Guide*[4], that children be immunized with DPT or DPTP at 2, 4, 6 and 18 months and be given a booster dose between the ages of 4 to 6 years.

An analysis of DPT- and DPTP-associated adverse event reports by the dose number in the series indicates that the frequency of reported adverse events, when all events are combined, appeared to fluctuate randomly with each subsequent dose (Table 9). However, a separate analysis of severe local reactions shows a general increase in the number of adverse events with increasing dose number. Assuming that almost all children receive all four doses of the primary series of DPT or DPTP and the booster dose, and assuming similar birth cohorts, the frequency of administration of these vaccines should be similar in any given year. Given such a stable denominator, the observed increase in the number of local reactions reported suggests an actual increase in occurrence of adverse events to successive doses of the DPT and DPTP vaccines.

Discussion

The major shortcomings of the vaccine-associated adverse event reporting system include the following: (1) a temporal reporting bias, (2) underreporting, (3) lack of baseline rates of certain conditions in the populations, (4) lack of accurate denominator data, and (5) attribution difficulty when multiple antigens or vaccines are given simultaneously. All of these factors can artificially increase or decrease the rate of adverse reactions and make it difficult to obtain a true estimate. The frequent use of multiple antigens makes it difficult to evaluate the causality of a relationship between a specific vaccine or vaccine component and a specific medical outcome. Many are not caused by any component but are temporal coincidences. The prolonged lagtime between initial reporting and reporting to BCDE has already been mentioned. This makes it difficult to take corrective action in a timely manner or to obtain additional information when required.

The results presented should be interpreted with the following caveats: (1) the number of vaccine doses distributed is a proxy for denominator data, and (2) reporting practices differ among the various jurisdictions. Provincial and territorial differences with respect to rates of reported adverse events emphasize the need to improve the sensitivity and timeliness of this reporting system.

As with all previous reports on vaccine-associated adverse events, it is important to view the occurrence of such events in their proper context. Over 14 million doses of vaccine were distributed in 1992. Even assuming a high margin of error for the number of vaccine doses administered and the number of events reported, it appears that the rate of occurrence of adverse events is very low. Given the nature of the reporting system there is reason

Table 7
Distribution of adverse event reports by events and selected vaccines, Canada, 1992

	Frequency (Reports/100,000 doses distributed)																
	DPT Total	DPT alone	DPT OPV	DPT other	DPTP	DT	FLU	HB	Hib	IPV Salk	MENING	MMR	R	RAB	TYPH	Td	YF
Total number of reports Nombre total de rapports	**2,795 (136.2)**	**486**	**1,954**	**355**	**288 (250.1)**	**70 (78.0)**	**99 (2.5)**	**154 (21.8)**	**1,520 (90.8)**	**26 (13.4)**	**202 (17.0)**	**286 (53.7)**	**12 (40.8)**	**21 (73.2)**	**53 (54.0)**	**171 (13.7)**	**17 (28.0)**
Individual adverse events Effets secondaires individuels																	
Adenopathy	13 (0.6)	2	10	1	2 (1.7)	0 (0.0)	1 (0.0)	7 (1.0)	9 (0.5)	0 (0.0)	4 (0.3)	12 (2.3)	3 (10.2)	3 (10.5)	4 (4.1)	7 (0.6)	0 (0.0)
Allergic reaction	151 (7.4)	13	128	10	12 (10.4)	9 (10.0)	18 (0.5)	26 (3.7)	106 (6.3)	4 (2.1)	66 (5.6)	36 (6.8)	0 (0.0)	2 (7.0)	8 (8.1)	22 (1.8)	5 (8.2)
Anaesthesia/Paresthesia	2 (0.1)	1	1	0	0 (0.0)	0 (0.0)	4 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	8 (0.7)	1 (0.2)	0 (0.0)	4 (13.9)	2 (2.0)	2 (0.2)	0 (0.0)
Anaphylaxis	5 (0.2)	1	4	0	1 (0.9)	1 (1.1)	3 (0.1)	5 (0.7)	4 (0.2)	0 (0.0)	3 (0.3)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (1.6)
Arthralgia/Arthritis	21 (1.0)	1	19	1	1 (0.9)	1 (1.1)	10 (0.3)	24 (3.4)	4 (0.2)	0 (0.0)	3 (0.3)	8 (1.5)	6 (20.4)	5 (17.4)	1 (1.0)	8 (0.6)	2 (3.3)
Convulsion/Seizures	135 (6.6)	23	88	24	13 (11.3)	7 (7.8)	0 (0.0)	4 (0.6)	105 (6.3)	0 (0.0)	1 (0.1)	48 (9.0)	0 (0.0)	0 (0.0)	2 (2.0)	4 (0.3)	0 (0.0)
Encephalopathy	7 (0.3)	2	4	1	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever: ≥ 40.5°C	336 (16.4)	53	222	61	31 (26.9)	5 (5.6)	0 (0.0)	2 (0.3)	204 (12.2)	1 (0.5)	4 (0.3)	44 (8.3)	0 (0.0)	0 (0.0)	2 (2.0)	2 (0.2)	0 (0.0)
Fever: 39.0°C – 40.4°C	793 (38.6)	147	521	125	96 (83.4)	11 (12.3)	7 (0.2)	12 (1.7)	467 (27.9)	2 (1.0)	31 (2.6)	93 (17.5)	0 (0.0)	3 (10.5)	4 (4.1)	10 (0.8)	0 (0.0)
Fever: Not recorded	367 (17.9)	47	275	45	46 (39.9)	9 (10.0)	20 (0.5)	14 (2.0)	209 (12.5)	4 (2.1)	9 (0.8)	38 (7.1)	1 (3.4)	6 (21.0)	19 (19.3)	39 (3.1)	4 (6.6)
Guillain-Barré Syndrome	0 (0.0)	0	0	0	0 (0.0)	0 (0.0)	6 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hypotonic-hyporesponsive episode	249 (12.1)	39	172	38	36 (31.3)	4 (4.5)	1 (0.0)	5 (0.7)	156 (9.3)	2 (1.0)	27 (2.3)	16 (3.0)	0 (0.0)	1 (3.5)	3 (3.1)	11 (0.9)	0 (0.0)
Infective abscess	19 (0.9)	4	15	0	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis/Encephalitis	2 (0.1)	0	2	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orchitis	1 (0.0)	0	1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other events	296 (14.4)	52	217	27	24 (20.8)	10 (11.1)	39 (1.0)	68 (9.6)	142 (8.5)	2 (1.0)	62 (5.2)	60 (11.3)	1 (3.4)	10 (34.8)	18 (18.3)	42 (3.4)	8 (13.2)
Paralysis	1 (0.0)	1	0	0	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parotitis	1 (0.0)	0	1	0	1 (0.9)	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	10 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Rashes	90 (4.4)	8	66	16	6 (5.2)	2 (2.2)	8 (0.2)	21 (3.0)	87 (5.2)	1 (0.5)	9 (0.8)	72 (13.5)	3 (10.2)	2 (7.0)	2 (2.0)	9 (0.7)	1 (1.6)
Screaming episodes	730 (35.6)	128	491	111	117 (101.6)	7 (7.8)	0 (0.0)	0 (0.0)	464 (27.7)	1 (0.5)	1 (0.1)	13 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe pain and/or severe swelling	944 (46.0)	170	702	72	42 (36.5)	36 (40.1)	26 (0.7)	31 (4.4)	315 (18.8)	13 (6.7)	9 (0.8)	21 (3.9)	2 (6.8)	5 (17.4)	28 (28.5)	98 (7.8)	2 (3.3)
Severe vomiting and/or diarrhea)	293 (14.3)	37	219	37	25 (21.7)	2 (2.2)	10 (0.3)	9 (1.3)	160 (9.6)	2 (1.0)	23 (1.9)	37 (6.9)	0 (0.0)	2 (7.0)	6 (6.1)	12 (1.0)	0 (0.0)
Sterile abscess	83 (4.0)	37	34	12	7 (6.1)	2 (2.2)	0 (0.0)	0 (0.0)	35 (2.1)	1 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	6 (0.5)	3 (4.9)
Thrombocytopenia	1 (0.0)	0	1	0	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 8
Distribution of adverse event reports by time to onset of symptoms, Canada, 1992

Time to onset	Frequency	Percent
0 - <1 h	231	5.4
1 - 8 h	2,183	51.0
9 - 16 h	340	7.9
17 - 23 h	126	2.9
Total (<1 day)	2,880	**67.3**
1 - 7 days	889	20.8
8 - 14 days	112	2.6
15 - 21 days	26	0.6
22 - 30 days	22	0.5
Total (<1 month)	3,929	**91.8**
≥ 1 month	7	0.2
Unknown	343	8.0
Total	4,279	**100.0**

Table 9
Distribution of adverse event reports temporally associated with DPT/DPTP vaccine, by dose number, Canada, 1992

Dose number	Frequency (Percent)					
	All reactions		Fever		Severe local reactions	
1	557	(18.1)	200	(12.0)	58	(5.9)
2	682	(22.1)	403	(24.1)	99	(10.0)
3	532	(17.3)	366	(21.9)	93	(9.4)
4	586	(19.0)	356	(21.3)	277	(28.1)
5	657	(21.3)	311	(18.6)	431	(43.7)
6	2	(0.1)	2	(0.1)	0	(0.0)
Unknown	67	(2.2)	31	(1.9)	28	(2.8)
Total	3,083	**(100.1)**	1,669	**(100.0)**	986	**(100.0)**

to believe that the more severe events do get reported. Thus, any underestimate of adverse event rates would be more likely to affect the commoner, milder and often self-limited events. Vaccination continues to be one of the most cost-effective preventive measures against communicable diseases and the morbidity and mortality prevented by vaccination far outweigh the very low risk of severe adverse events.

Acetaminophen prophylaxis at the time of inoculation is highly recommended to reduce the incidence and severity of fever and irritability, the commonest adverse events associated with childhood immunizations. This is particularly important in children with a personal or family history of convulsions because a reduction in fever may also minimize the risk of febrile convulsions.

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Appendix I
Codes and Definitions Used for Reportable Adverse Events

(01) *Fever - Temperature ≥ 40.5° C.*

(02-03) *Fever - Temperature ≥ 39.0° C and ≤ 40.4° C.*

(04) *Fever - Temperature not recorded but believed to be very high and presence of other systemic symptoms.*

(05) *Infective abscess at the site of immunization*
- One with a positive Gram stain or culture.

(06) *Sterile abscess at the site of immunization*
- One in which there was no evidence of acute microbiologic infection.

Nodule at the site of immunization
- One which persists for > 1 month and is > 2.5 cm (1 inch) in diameter and/or one in which drainage is evident.

Necrosis at the site of immunization
- Presence of morphologic changes indicative of cell death and caused by the progressive degradation of enzymes is evident.

(07) *Severe local pain at the site of immunization*
- Pain which lasts for at least 4 days or requires hospitalization.

Severe swelling at the site of immunization
- Swelling which extends past the nearest joint (as in arm past elbow).

(08) *Adenopathy - Severe (or unusual) enlargement or drainage of lymphatic nodes.*

(09) *Allergic Reaction - One in which there is evidence of hives, wheezing, puffiness or generalized edema.*

(10) *Rashes - Those that are severe (i.e., lasting at least 4 days or require hospitalization).*

(11) *Anaphylaxis - An event characterized by swelling of mouth or throat, difficulty breathing, shock, cardiovascular or respiratory collapse.*

(12) *Hypotonic-hyporesponsive episode - One in which there is evidence of decrease or loss of muscle tone, pallor or cyanosis, decreased level or loss of consciousness, or cardiovascular or respiratory arrest.*

(12) *Excessive somnolence - An event characterized by prolonged sleeping with difficulty arousing.*

(13) *Arthralgia/Arthritis - Joint pain which lasts at least 24 hours.*

(14) *Severe vomiting and/or diarrhea - This event must interfere with the patient's daily routine.*

(15) *Screaming episode - One in which the child is inconsolable and lasts at least 3 hours or in which the quality of cry is definitely abnormal for the child and not previously heard by the parents.*

(16) *Convulsion/Seizure - One that involves muscle contractions and decreased level of consciousness (may or may not be associated with fever).*

(17) *Encephalopathy - Diagnosis must be made by a physician.*

(18) *Meningitis and/or Encephalitis - Diagnosis must be made by a physician.*

(19) *Anaesthesia/Paresthesia - Lasts over 24 hours.*

(20) *Paralysis - Diagnosis must be made by a physician.*

(21) *Guillain-Barré Syndrome - Diagnosis must be made by a physician.*

(22) *Subacute Sclerosing Panencephalitis - Diagnosis must be made by a physician.*

(23) *Parotitis - Swelling and/or tenderness of parotid gland(s).*

(24) *Orchitis - Swelling with pain and/or tenderness of testicle(s).*

(25) *Thrombocytopenia - Diagnosis must be made by a physician.*

(26) *Other severe or unusual events - Those that do not fit into any of the categories listed above but were of medical or epidemiologic interest and required medical intervention.*

Appendix II
Temporal criteria for inclusion of adverse events

The interval from vaccine administration to the onset of symptoms must be within the same time frame listed in the following table according to vaccine and type of adverse event.

	Adverse Event Codes (see Appendix I)									
Immunizing Agent	1-4	5-6	7	8	9	10	11	12	13	14
MMR	5-30d	n/a	< 48h	5-30d	< 72h	5-30d	< 24h	< 72h	5-30d	5-30d
DPT/DPTP	< 72h	n/a	< 48h	< 7d	< 72h	< 7d	< 24h	< 72h	–	< 72h
Other*	< 72h	n/a	< 48h	–	< 72h	< 7d	< 24h	< 72h	–	< 7d
Immunizing Agent	15	16	17	18-19	20	21	22	23-24	25	26
MMR	72h	5-30d	5-30d	5-30d	5-30d	< 31d	n/a	5-30d	< 31d	–
DPT	72h	< 72h	< 7dj	< 15d	< 15d	< 31d	n/a	n/a	< 31d	–
Other*	72h	< 15d	< 15d	< 15d	< 15d	< 31d	n/a	n/a	< 31d	–

Legend:

d days
h hours
n/a not applicable
– undefined
* For OPV-related events, the time interval is 4-60 days. For influenza vaccine-related events, there is no time restriction.

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