

# Acellular and Whole-Cell Pertussis Vaccines in Japan

## Report of a Visit by US Scientists

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Since the introduction of acellular pertussis vaccines in Japan late in 1981, more than 20 million doses have been administered, mostly to children 2 years of age and older. Clinical studies indicate that mild local and febrile reactions are less frequent after administration of acellular pertussis vaccines than after whole-cell vaccines. Serious adverse events with sequelae occurred in 2-year-old children at approximately the same low rate during the period 1975 through August 1981, when whole-cell vaccines were used, and during August 1981 through 1984, when acellular vaccines were used exclusively. Five household contact studies have yielded vaccine efficacy estimates ranging from 78% to 92% in children 1 year of age or older. In addition, there has been a continuing decrease in reported pertussis incidence from the epidemic peak in 1979. Additional data on the safety and efficacy of acellular pertussis vaccines administered to infants would be useful in consideration of acellular pertussis vaccine licensure in the United States.

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FROM Dec 2 to Dec 14, 1985, a group of Public Health Service (PHS) scientists representing the PHS Interagency Group to Monitor Vaccine Development, Production, and Usage traveled in Japan to obtain information about the epidemiology of pertussis and the impact and characteristics of acellular pertussis vaccines in use since late 1981.

See also p 1375.

(Through a request made by James O. Mason, MD, DrPH, Acting Assistant Secretary for Health, PHS, to the Honorable Hiroyuki Masuoka, Minister of Health, Japan, we were invited to represent PHS Interagency Group. The visit was extremely useful in providing information on the safety and efficacy of pertussis vaccines used in Japan.) Considerable effort was taken by our hosts to make available to us all pertinent data. Our questions were answered willingly and with candor. We are

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deeply indebted to our hosts for their courtesy and patience and for providing information that should prove useful in the development and introduction into the United States of improved pertussis vaccines.

This report summarizes findings and lists selected references concerning recent Japanese investigations. For additional current information on pertussis and pertussis vaccines, the reader is referred to other reviews, especially the *Proceedings* of the Third and Fourth International Pertussis Symposia, held in 1978 and 1984, respectively.<sup>1,2</sup>

### BACKGROUND

Whole-cell pertussis vaccines came into use in Japan in 1947, and their administration became mandatory as part of the Preventive Immunization Law of 1948.<sup>3,4</sup> Vaccination consisted of three doses given approximately one to two months apart beginning at approximately 3 months of age, with a booster dose approximately one year after the third dose. Most vaccinations were and still are provided free in mass immunization clinics. The reported incidence of pertussis in Japan fell rapidly after the introduction of the vaccine (Fig 1); deaths decreased correspondingly.

Concerns about reactions to smallpox vaccine prompted the Japanese government in 1970 to organize a system for receiving and reviewing claims for injuries associated with vaccinations carried out under the Preventive Immunization Law. Implementation of the compensation system subsequently served to draw increased attention to adverse events associated with pertussis vaccine, and continued use of pertussis vaccine was questioned, particularly in light of the low incidence of reported cases of pertussis in Japan between 1970 and 1975.

In a two-month period in the winter of 1974-1975, two infants died within 24 hours after receiving diphtheria and tetanus toxoids and pertussis vaccine (DTP). While these events were being investigated, recommendations were made for temporary suspension of the use of DTP. Two months later, routine use of the DTP vaccine was again recommended.<sup>5</sup> However, the recommended age at initial administration was raised from 3 months to 2 years as a precautionary measure to avoid other coincidental occurrences; also, it was believed the incidence of adverse events caused by, or temporally associated with, pertussis vaccine might be higher during infancy. In addition, it was believed that vaccinating children at 2 years of age and older would prevent transmission of disease to infants and younger children. The recommended immunization schedule was to administer three doses after the second birthday at intervals of approximately one to two months, with a fourth dose 12 to 18 months after the third dose. In situations of increased risk of disease, or in private practice settings, the vaccine could be given as early as 3 months of age.

At the same time, a Pertussis Vaccine Study Group was formed by the Japanese Ministry of Health and Welfare (MOHW) to accelerate research and development of improved pertussis vac-

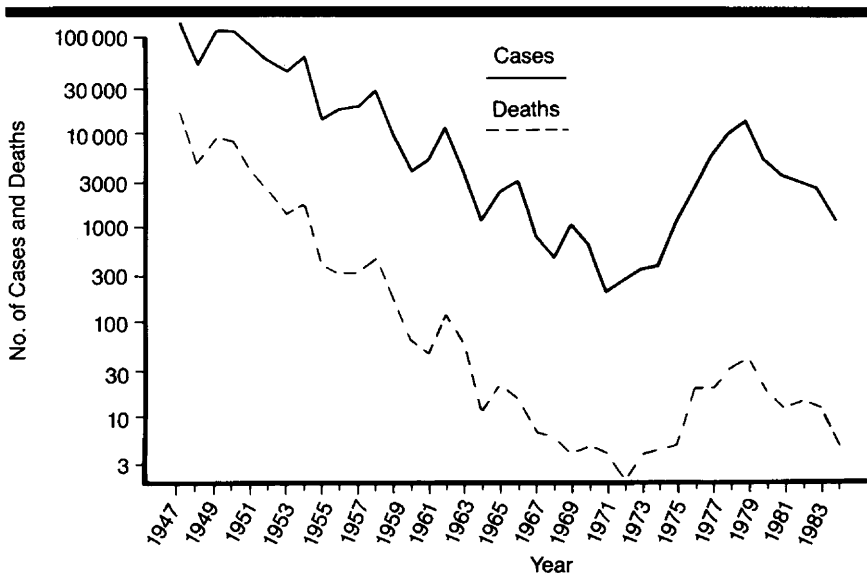


Fig 1.—Reported cases of pertussis and pertussis-related deaths in Japan, 1947 through 1984. Source: Japanese Ministry of Health and Welfare.

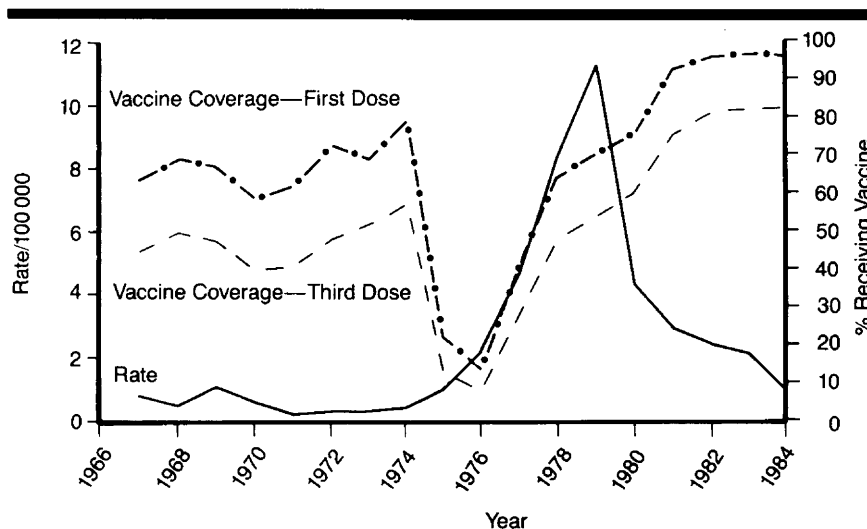


Fig 2.—Reported pertussis rate per 100 000 population and percentage of eligible children receiving pertussis vaccine in Japan, 1967 through 1984. Source: Japanese Ministry of Health and Welfare.

cines. This research culminated in initial clinical studies with acellular vaccines in 1979 and their introduction for routine use in late 1981.

Despite the recommendation for universal use of the whole-cell pertussis vaccine and the fact that vaccines were administered free in mass immunization clinics, vaccine coverage declined in the mid-1970s (Fig 2), and the number of doses of DTP distributed declined. Because of the recommendation that vaccination age be raised from 3 months to 2 years, a decline in vaccine administration was expected for a period of approximately two years. In 1977, the first year in which a cohort of eligible 2-year-olds would be expected, coverage with

the first dose of pertussis vaccine was 41.7%, rising to 64.4% in 1978. Corresponding figures for coverage with the third dose in 1977 and 1978 were 28.4% and 47.9%, respectively. Following the decline in vaccine use, there was a significant increase in the reported incidence of pertussis, reaching a peak in 1979, when 13 105 cases were reported, and 41 deaths were recorded. Vaccine acceptance gradually rose, reaching 75.5% for a first dose and 60.2% for a third dose in 1980, and increased further after introduction of acellular pertussis vaccines for mass immunization in late 1981, reaching 95.8% for a first dose and 82.3% for a third dose in 1984. Increasing vaccine acceptance was associated

with a further decline in the incidence of pertussis.

The overall reported incidence of pertussis was higher in 1984 than in the early 1970s, in spite of higher reported coverage levels with vaccine. The reason for the apparently higher incidence cannot be established with certainty; however, the difference between the two time periods could be due to improved reporting of disease in the later period, or other factors. In addition, the increase may reflect the higher incidence in children less than 3 years old.

#### CURRENT ACELLULAR PERTUSSIS VACCINES: PRODUCTION, TESTING, AND IMMUNOGENICITY

Following the 1975 mandate to seek new types of pertussis vaccine, a cooperative arrangement between the Japanese National Institute of Health, manufacturers, the various committees, and the MOHW was reached, seeking to reduce all toxic activities to approximately one-tenth those of whole-cell vaccines, while maintaining potency. The first sample was obtained in 1976 and the new vaccines were introduced for mass use in 1981. There are six manufacturers of acellular pertussis vaccines in Japan.

In general, the procedures described by Sato et al<sup>6</sup> are applicable to all manufacturers, although some aspects of the manufacturing process may be unique to each. Compositional variations between products are said to depend on modifications of media or culture conditions used by some manufacturers and variations in purification steps or conditions of formaldehyde inactivation. There are two basic types of vaccine (B and T), both containing primarily lymphocytosis-promoting factor (LPF), which is inactivated, and filamentous hemagglutinin (FHA); the T type also contains significant amounts of agglutinogens. There have been no significant changes in manufacture since 1981, although minor modifications may have occurred. The MOHW considers all pertussis vaccines currently in use to be equivalent or identical since they meet all appropriate requirements for licensure and distribution.

The products are tested for potency and toxicity according to the Japanese Minimum Requirements of Biological Products. The same types of tests were used for whole-cell vaccines, but different acceptable limits apply to whole-cell and acellular products. Each manufacturer's product meets the World Health Organization requirements for potency in international units per milliliter. However, the time from vaccination to challenge and the weight of the mice used in the intracerebral mouse potency

Table 1.—Age-Specific Attack Rates and Vaccine Efficacy for Acellular Vaccines

Age, y	Kimura and Hikino <sup>5</sup>		Isomura et al <sup>12</sup> (Study 1)		Aoyama et al <sup>13</sup> (Study 1)		Isomura et al <sup>12</sup> (Study 2)		Aoyama et al <sup>13</sup> (Study 2)		Total		Age-Specific Efficacy
	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	
<1	21/25	0	0	0	31/35	0	8/9	0	...	...	60/69	0	...
1-2	16/18	0/9	9/10*	1/9	32/42	3/5	9/9	0/5	...	...	66/79	4/28	0.83 (0.57, 0.93)†
3-5	13/17	2/28	8/10*	0/3	8/18	1/21	3/5	0/19	...	...	32/50	3/71	0.93 (0.80, 0.98)
≥6	9/12	1/5	0	0	12/26	0	8/11	2/6	...	...	29/49	3/11	0.54 (0, 0.83)
<b>Total</b>	<b>59/72</b>	<b>3/42</b>	<b>17/20</b>	<b>1/12</b>	<b>83/121</b>	<b>4/26</b>	<b>28/34</b>	<b>2/30</b>	<b>14/18‡</b>	<b>1/10‡</b>	<b>201/265</b>	<b>11/120</b>	...
Efficacy§	0.91 (0.74, 0.97)†		0.90 (0.35, 0.99)		0.78 (0.44, 0.91)		0.92 (0.69, 0.98)		0.87 (0.16, 0.98)		0.88 (0.79, 0.93)		...

\*Estimated.

†Numbers in parentheses are 95% confidence intervals.

‡Totals for this study are included in totals at right (age breakdown not available during visit).

§Calculated as  $VE = (ARU - ARV) / ARU \times 100$ , where VE is vaccine efficacy; ARU, attack rate in unvaccinated group; and ARV, attack rate in vaccinated group.

Table 2.—Claims Paid by Vaccine Compensation System Japan, 1970 Through 1984\*

Reactions	1970–January 1975		February 1975–August 1981		September 1981–1984	
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths
<b>With sequelae</b>						
Encephalopathy	29	21	2	1	0	0
Encephalitis	2	1	0	0	2	0
Acute infectious hemiplegia	2	0	1	0	1	0
Convulsions	8	1	3	1	1	1
Infantile spasm	2	0	0	0	0	0
Sudden death	11	11	0	0	0	0
Other	3	3	2	1	1	1
<b>Total</b>	<b>57</b>	<b>37</b>	<b>8</b>	<b>3</b>	<b>5</b>	<b>2</b>
<b>Without sequelae</b>						
Mild encephalopathy	14	...	1	...	0	...
Acute cerebellar ataxia	0	...	1	...	1	...
Convulsions	4	...	0	...	0	...
Febrile seizure	27	...	12	...	1	...
Mild shock	8	...	3	...	1	...
Exanthem	7	...	3	...	0	...
Abscess	5	...	3	...	0	...
Local reactions	8	...	7	...	11	...
Others	9	...	4	...	0	...
<b>Total</b>	<b>82</b>	<b>...</b>	<b>34</b>	<b>...</b>	<b>14</b>	<b>...</b>

\*Source: Mikio Kimura, MD, written communication, December 1985.

assay are different from those used in the United States and in the assay described in the World Health Organization requirements for whole-cell vaccines. In addition, the strain of mouse used for the assay of potency may critically affect the results and hence the unitage assigned to the product.<sup>7,8</sup>

The products appear to be stable when stored at the recommended temperature of 4°C, but there is evidence that storing vaccine at higher temperatures may result in a lack of stability. A variety of experimental procedures are being used in different laboratories for the evaluation of toxicity and stability, including the tests defined in the minimum requirements as well as tests for permeability factors in rabbit skin and swelling of mouse foot pads.<sup>9</sup>

In general, the mean anti-LPF and anti-FHA titers, as measured by enzyme-linked immunosorbent assay, are

reportedly greater after administration of type B vaccine than after vaccination with type T or whole-cell vaccines. In contrast, mean titers of antibody to agglutinin are reportedly higher with whole-cell vaccine and type T vaccine than with type B vaccine. Additional antibody data can be found in the review by Kimura and Hikino.<sup>5</sup> Data presented for whole-cell vaccines and for acellular vaccines suggest that comparable antibody titers to various *Bordetella pertussis* antigens are achieved regardless of age at vaccination.

Mean antibody titers elicited by acellular pertussis vaccines were reportedly equal to or greater than the mean anti-LPF and anti-FHA antibody titers in convalescent sera.<sup>10</sup> However, the level of antibody to LPF, FHA, or agglutinogens that correlates with prevention of disease has not yet been

established with certainty for any pertussis vaccines.<sup>11</sup>

### CLINICAL EFFICACY STUDIES

Overall efficacy of acellular pertussis vaccines in Japan may be inferred from the continuing downward trend in pertussis incidence since these vaccines were introduced. Specific clinical efficacy studies include three published family-contact studies by Kimura and Hikino,<sup>5</sup> Isomura et al,<sup>12</sup> and Aoyama et al<sup>13</sup> carried out in the period from 1978 to 1983. They differ in certain methodologic aspects, such as the definition of coprimary and secondary cases, laboratory confirmation, and the age distribution of vaccinated and unvaccinated groups. The results of these three studies are summarized in Table 1 (first three columns). Some of these data have previously been summarized by Sato et al.<sup>6</sup> In Isomura and colleagues' study, a control (unvaccinated) family was selected by matching the control index patient to an index patient in a vaccinated family by age and place of residence. The vaccine used in this study was from a single manufacturer (Takeda, lot T7). When these three studies are combined, the clinical efficacy of acellular vaccine in preventing pertussis is 87%.

Preliminary data from further studies carried out in the period from 1983 through 1985 by Isomura's and Aoyama's groups are also shown in Table 1 (fourth and fifth columns). Isomura's second study identified 80 index patients with 30 vaccinated contacts and 34 unvaccinated contacts. The attack rate was 7% (2/30) for the vaccinated group and 82% (28/34) for the unvaccinated group, indicating vaccine efficacy of 92%. Aoyama's second study identified 48 culture-positive index patients and studied their family contacts. Of 18 unvaccinated children aged 0 to 6 years, 14 (78%) became ill; one of ten vaccinated children became ill (vaccine efficacy, 87%). All secondary cases were

Table 3.—Adverse Reactions After Pertussis Immunization, Based on Claims Paid by Compensation System\*

	1970-1974†	1975-1980†	1981-1984†
Vaccine type	Whole-cell	Whole-cell	New DTP‡
Age at initiation, mo	3-5	3-5	24
Doses of vaccine, millions	25.1	19.8	20.4
Severe reactions with sequelae (deaths)	57 (37)	8 (3)	5 (2)
Incidence/million doses (deaths)	2.27 (1.47)	0.40 (0.15)	0.25 (0.10)
Mild reactions without sequelae	82	34	14
Incidence/million doses (mild reactions)	3.27	1.72	0.69

\*Source: Mikio Kimura, MD, written communication, December 1985.

†Whole-cell vaccines were routinely administered to infants at 3 months of age until February 1975, when the recommended age was raised to 2 years. Use of whole-cell vaccines in this group continued until September 1981, when acellular vaccines were introduced for routine use in 2-year-old children. In this table, vaccine distribution is based on calendar year but adverse reaction data correspond to the vaccine type and strategy used.

‡DTP indicates diphtheria and tetanus toxoids and pertussis vaccine.

confirmed by culture.

If all of the studies are combined, the attack rate for the unvaccinated group is 76% (201/265) and for the vaccinated group 9% (11/120), for an estimated vaccine efficacy of 88% (95% confidence intervals, 79% to 93%).

As Table 1 indicates, there were no vaccinated children less than 1 year old, yet children in this age category constitute 26% (69/265) of the patients with pertussis in the unvaccinated group. Restricting calculation of vaccine efficacy to children 1 year old or older indicates a similar vaccine efficacy estimate of 87%.

Age-specific attack rates from the family contact studies and from national surveillance data show that young children (<3 years old) are at increased risk for clinical pertussis. Table 1 shows that children 1 to 5 years of age are protected by the acellular vaccine. For children 6 years of age or older, the point estimate of efficacy is relatively low, although the confidence interval is very wide.

Efficacy for infants has not been evaluated. Private physicians as well as health departments in some areas are administering vaccine to children younger than 2 years of age. The practice of vaccinating infants ( $\leq 1$  year of age) is consistent with the Preventive Immunization Law, which provides for immunization at ages 3 to 48 months.

#### ADVERSE EVENTS ASSOCIATED WITH ACELLULAR VACCINES

The safety of Japanese acellular pertussis vaccines has been evaluated for relatively common local and systemic reactions in several small- and large-scale clinical studies and by using a special surveillance system in the Sendai area. To evaluate the occurrence of rare events that cannot practically be assessed in clinical follow-up studies, Japanese investigators have compiled data from claims submitted to the MOHW requesting compensation for injuries alleged to have resulted from

receipt of pertussis vaccine. Overall, the experience of Japanese clinicians has been that local and febrile reactions are less frequent with component vaccines than with whole-cell vaccines.

#### Clinical Studies

The occurrence of local reactions (including erythema, swelling, and induration) and systemic reactions (including fever) has been evaluated in most clinical studies of safety in Japan. For each of these reactions, the characteristics examined have most often included the rate of occurrence, time of appearance, severity, and dose effects. In a few studies, the vaccines from different manufacturers have been studied separately. In most studies, the vaccine recipients have been children 2 years of age and older, but in at least one study, infants also have been observed for reactions. In addition, the rate of occurrence of reactions using different routes of administration has been examined.<sup>14</sup>

#### Fever

The reported frequency of low-grade fever (temperature, 37.5°C to 37.9°C, usually taken as an axillary temperature), has ranged from 0.1% to 12.0% in the different studies reviewed, but generally has not exceeded 2% to 3%. For more clinically significant fever (temperature, 38.0°C to 38.9°C), the frequency has been lower, ranging from less than 1% to 6.3%. The frequency of high fevers (temperature,  $\geq 39.0^\circ\text{C}$ ) has not been measured separately in most clinical studies, but is reported to be low.

The onset of fever after vaccination has been measured at different times after vaccination on the first day and up to a maximum of two days after vaccination. There are no striking differences in the frequency of fever when measured at these times, although some studies suggest that low-grade fever may be most frequent at approximately 24 hours after vaccination.

For low-grade fever, some studies

have noted a slight increase in frequency with successive doses, particularly after the booster dose, but this pattern has not been observed in all studies.

Information on the occurrence of fever after administration of acellular vaccines produced by different manufacturers or after the use of different lots from the same manufacturer has been collected in some of the studies reviewed. Impressions gained from discussions with various investigators are that there are no striking or obvious differences between products.

There are few data on the occurrence of fever after vaccination of infants. In one study in which this information was available, there was no apparent difference in the occurrence of low-grade fever between infants less than 1 year old and older children.

#### Local Reactions

The frequency of redness and induration measured in centimeters at the site of inoculation, in all of the clinical studies have been reviewed. The frequency of mild local reactions has ranged widely, from 0% to 68% for 1 cm or more to less than 1% to 23.5% for 5 cm or more. The frequency of redness and swelling of more than 10 cm after the booster dose is approximately 4% in one report, and reports of children with swelling of the arm down to the elbow or wrist have been received. Most of the clinicians interviewed considered these extreme reactions rare and relatively benign since they appeared to resolve spontaneously over a period of a few days, but they are an obvious source of concern for the parents of these vaccinees.

The time of appearance of the local reactions after vaccination has been measured starting at one day and extending up to one month, most frequently at one to three days and seven days. The time of appearance of local reactions is related to the dose of vaccine administered. After the first dose, local reactions are observed more frequently at seven days than immediately after vaccination. After subsequent doses, the time of appearance is more rapid. Thus, the average number of days from inoculation to appearance of redness in one study dropped from 7.9 days after dose 1 to 2.6, 2.2, and 1.9 days after the second, third, and booster doses, respectively. Late reactions were not more severe than early reactions. The reason for the later appearance of local reactions after the first dose has not yet been elucidated.

Convincing evidence exists from these clinical studies to suggest that the frequency of local reactions increases

with increasing dose in the four-dose series, particularly after the fourth (booster) dose. In one study combining vaccines from several different manufacturers, the frequency of redness and induration one day after vaccination rose from 6% after dose 1 to 25%, 30%, and 41% after each succeeding dose. Other studies that have not shown increases in frequency between doses 2 and 3 have shown higher rates after the booster.

The degree of redness or severity of the local reactions also appears to be dose related, although differences are slight. Mean size of redness increased from 3.3 cm after the first dose in one study to 4.2, 4.7, and 4.9 cm after each subsequent dose. Redness greater than 10 cm in this study most frequently followed the booster dose.

One study observed local reactions in infants compared with children over one year of age. Redness and induration were measured at 24 hours and at seven days. Although differences were slight, there was a consistently higher frequency of redness and induration in infants after the first and second doses. It is not possible to conclude at present whether age is related to the frequency of subsequent reactions.

### Surveillance System

A special surveillance system for vaccine reactions was established in the Sendai area in July 1977 by the Miyagi Prefecture Association of Pediatrics (Tsunoda). Monthly reports are received from 59 reporting units representing approximately 60% of the potential reporting units in the area, and these reporters administer approximately 30% of the vaccine administered in the Sendai area. Physicians provide monthly totals of vaccine administered by dose in the series DTP. For adverse events defined only as "more severe than usual" by the reporting physicians, the age of the child, the dose received, symptoms, manufacturer, lot number, the time of appearance of the reaction, and prognosis are noted on a postcard. More than 100 000 vaccinations with acellular pertussis vaccine have been monitored in this manner since October 1981 in the Sendai area. A total of seven unusually high temperatures have been reported, for a rate of 6.9 per 100 000 doses. The rate was 9.5 per 100 000 doses for the period July 1977 to September 1981, when whole-cell vaccine was being used in this area. Differences in the reported incidence of local reactions "more severe than usual" have been more marked. Physicians have reported 159 such reactions for a rate of 1.6 per 1000 doses administered. The comparable rate with whole-cell vaccine was

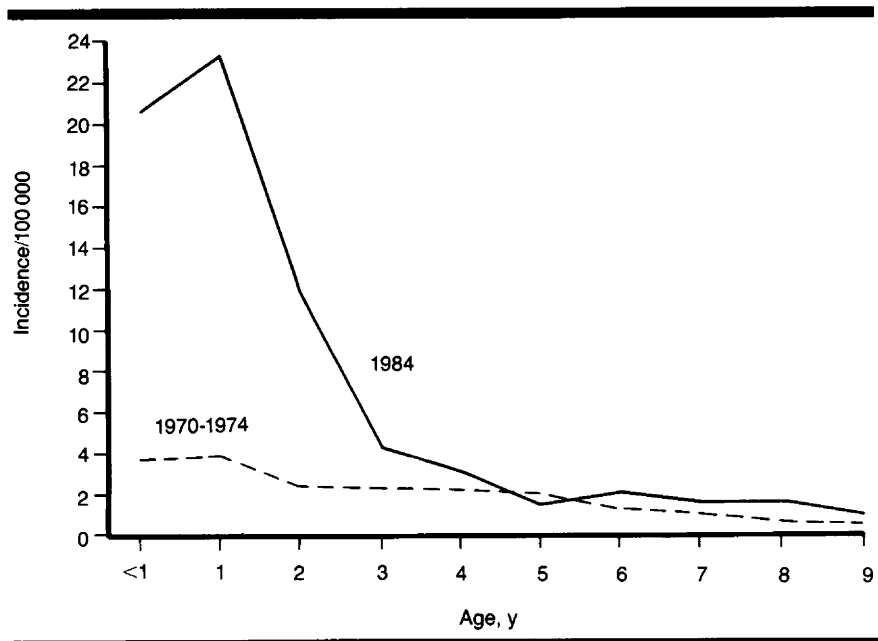


Fig 3.—Incidence of pertussis by year of age, 0 to 9 years, in Japan, 1970 through 1974 average and 1984. Source: Japanese Ministry of Health and Welfare.

lower (0.06 per 1000 doses). Rates of reactions following acellular vaccine have been approximately twofold to fourfold higher after the third and fourth doses than after the first and second doses. No permanent sequelae are known to have resulted from these "more severe" local and febrile reactions. The formation of vesicles on the skin at the site of inoculation in association with the more pronounced local reactions has also been reported, but there are no separate estimates of the frequency of these reactions. The etiology of these vesicular reactions has not been established.

### Vaccine Compensation System

Information about rare reactions possibly associated with acellular pertussis vaccines is based on review of claims submitted for compensation for injuries occurring after receipt of pertussis vaccine. Table 2 summarizes the number and types of injuries for which compensation was made in three time periods.

In the period 1970 through 1974, when whole-cell pertussis vaccine was administered beginning in infancy, a total of 57 severe reactions with 37 deaths were accepted for compensation because the injuries or deaths were possibly caused by pertussis vaccine. This yields an estimated incidence of 2.27 serious reactions and 1.47 deaths per million doses of vaccine administered (Table 3). During the same period, an approximately equal incidence of serious but milder reactions without permanent sequelae was noted (3.27 per million doses). Dur-

ing the period 1975 through August 1981, when whole-cell vaccine was given to older children ( $\geq 2$  years old), the rate of reported serious reactions decreased significantly, from 2.27 to 0.4 per million doses of vaccine administered, and deaths decreased from 1.47 to 0.15 per million doses (two deaths). In contrast, less serious reactions decreased less, from 3.27 to 1.72 per million doses. During the period 1982 through 1984, when acellular pertussis vaccines were in use (primarily in 2-year-old children), the rate of serious reactions was 0.25 per million doses, similar to the period 1975 through July 1981, and also with two deaths. Milder reactions showed a greater decrease than serious reactions in the most recent period.

The degree of underreporting of serious adverse events possibly associated with pertussis vaccine is unknown. Since persons thought to have been injured by vaccine are eligible for greater benefits than are provided through the routine medical care system, it seems likely that underreporting is minimal. Approximately two thirds of the claims submitted are accepted.

The degree of overreporting is also unknown. Compensation is commonly awarded for sequelae considered possibly caused by pertussis vaccine unless proved otherwise. It is difficult to exclude pertussis vaccine as a causal factor even when other etiologies are suspected, particularly when the adverse events occur in close temporal association with vaccination.

The number of serious adverse events reported in Japan has been low since 1975, when the recommended age for administration of vaccine was raised from 3 to 24 months. It is not clear whether this decrease is related to a true difference in the risk of severe adverse events in older children compared with infants or merely to the reduction in coincidental occurrence of adverse conditions that are more frequent in infancy. If acellular vaccines have produced a reduction in the occurrence of serious reactions with sequelae in children over 2 years of age, the decrease is slight. There has been a decrease of approximately 50% in reactions without sequelae associated with the use of acellular vaccine. The decline in less serious reactions is a result of the almost complete absence of claims resulting from febrile seizures and mild shock. In contrast, there has been an increase in claims for injury attributable to more severe local reactions. This increase is consistent with findings of the passive surveillance system in the Sendai area. The rate of local reactions "more severe than usual" was higher between July 1972 and September 1981, when whole-cell vaccine was in use, than after September 1981, when acellular vaccines were used exclusively. The experience in the Sendai area is different from the general impression of Japanese clinicians, who believe there are fewer local reactions with acellular vaccines than with whole-cell vaccines.

There are no reports of the occurrence of serious reactions after vaccination with acellular pertussis vaccines in children under 2 years of age. However, there has been only limited use of the vaccine in this age group.

### IMPACT OF VACCINATION AT 2 YEARS OF AGE ON THE EPIDEMIOLOGY OF PERTUSSIS

Figure 3 shows the average annual age-specific incidence rates for children 0 to 9 years of age during the period 1970 through 1974 and the rates in 1984. The

1984 incidence rates for children less than 3 years of age are substantially higher than those seen in the early 1970s, presumably reflecting the impact of the change in age at administration of vaccine on the epidemiology of pertussis. By contrast, for all other ages, the incidence rates are comparable in the two periods. This suggests that the practice of immunizing children at 2 years of age does not protect infants indirectly to the same degree that direct immunization of infants would.

### SUMMARY AND CONCLUSIONS

More than 20 million doses of acellular pertussis vaccines have been administered in Japan since their introduction late in 1981. Several manufacturers are distributing vaccines that meet the Japanese minimum requirements. Vaccination rates are higher than they were in the mid-1970s, when public concern over reactions to whole-cell vaccines led to lower utilization rates. There has been a continuing decrease in the overall incidence of pertussis since the epidemic peak in 1979, although the reported incidence in 1984 for children under 3 years of age was above the levels of the early 1970s. The incidence of mild local and febrile reactions is lower with acellular vaccines than with whole-cell vaccines previously used in Japan. Although relatively infrequent, more severe local reactions and high temperatures (both without sequelae) may be more common after vaccination with acellular vaccines. Rare serious adverse events with sequelae have been reported with approximately the same low frequency after vaccination with either acellular or whole-cell vaccines in 2-year-old children.

Three published studies have indicated efficacy of acellular vaccines in preventing illness in household contacts of patients with pertussis. Preliminary results from two further studies support this conclusion. In addition, serologic studies have indicated that vaccinees develop antibodies that are

thought by some investigators to be protective.

The raising of the recommended age for starting vaccination may have lessened the rate of real as well as coincidental adverse events; however, the rate of disease in children less than 3 years of age is now higher than before 1975, whereas children 3 years of age and older have disease rates comparable with the rates reported from 1970 through 1974. Since the primary evaluation and use of acellular vaccines have occurred in children 2 years of age and older, only limited data have been collected on the safety and efficacy of acellular vaccines in infants. In addition, data are limited on the efficacy of vaccines produced by individual manufacturers.

These issues are key in the consideration of licensure of acellular vaccines in the United States. Some questions regarding product-specific and age-specific efficacy may be answered by the ongoing field trials begun in Sweden early in 1986 of Japanese acellular pertussis vaccines, and further valuable information may be extracted from the extensive experience gained through 1985 with these vaccines in Japan or from future studies there or elsewhere. In addition, trials are under way in the United States to determine the immunogenicity and safety of Japanese acellular pertussis vaccines combined with United States-produced diphtheria and tetanus toxoids. Based on the overall positive experiences through 1985 in Japan and on other supporting clinical and laboratory evidence, the expectation is that acellular pertussis vaccines similar or related to those used in Japan will replace whole-cell pertussis vaccines in the United States within the next several years.

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