Clinical Reactions in Children After Rubella Vaccination

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DURING 1970, after a vaccine against rubella became commercially available, a concerted effort was made by many local health agencies to create herd immunity by organizing mass, citywide vaccination programs for children. As a result, thousands of children received the vaccine in some cities. Because of the large number of children vaccinated, serious complications from the vaccine, were they to arise, might have been expected to occur in numbers sufficiently great or in degree sufficiently impressive to come to the attention of the medical profession. Such was the case in Minneapolis, Minn., where during 2 weeks in January 1970, 50,800 children, or 80 percent of those presumed to be susceptible, were immunized, primarily by jet-gun injector. The program was open to all children in the city between 1 year old and the sixth grade age levels. Approximately 80 percent of those immunized received the HPV-77DK$_{12}$ vaccine (Phillips Roxanne Laboratories), while the other 20 percent received the HPV-77DE$_5$ vaccine (Merck Sharp & Dohme).

Beginning 3 weeks after the start of the immunization program and continuing for 2½ months, scores of cases of severe arthralgia or arthritis, with or without associated paresthesia, were reported throughout the city to local physicians. We, personally, received information on 80 cases during this period. From knowledge of the date of the immunization and the school at which the immunization had been given, it was possible to relate all 80 episodes to the HPV-77DK$_{12}$ vaccine.

The question then naturally arose whether similarly severe complications had occurred in children who had received the HPV-77DE$_5$ vaccine. To investigate this possibility, our attention was directed to a local suburb (Robbinsdale, Minn.) and to Duluth, Minn., where only the HPV-77DE$_5$ vaccine had been used.

Essentially all of the injections in both locales were given by jet-gun injector. In neither city did the local physicians receive more than a few calls regarding severe complications during the first 2½ months after the immunization programs. From a retrospective survey of these two populations, it became possible to assess the extent and frequency of the complications which followed the use of the HPV-77DE$_5$ vaccine. To the best of our knowledge, clinical rubella was not present in any of the communities during or after the vaccination programs.

Materials and Methods

We learned of the symptoms of 80 children from Minneapolis who had received the HPV-77DK$_{12}$ vaccine through an initial telephone call to one of our offices from the child's mother or the child's school nurse. These 80 cases represented only a small fraction of the cases known

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School vaccination records were made available to the authors by Dr. Arvid J. Hoaglum, Commissioner of Health, St. Louis County, Minn. Dr. D. S. Fleming, director of the Division of Disease Prevention and Control, Minnesota State Board of Health, assisted the authors in this project.

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to have been reported citywide to local physicians. The families of the 80 children were telephoned within 24 hours of the initial call to obtain more complete information. Three and one-half months after the immunization program, the mother of each child was sent a questionnaire requesting additional information. All questionnaires were immediately returned. It was not possible to conduct a statistically sound, retrospective survey of the total population of children who had received the HPV-77DK$_2$ vaccine because we could not gain access to the immunization records.

Nevertheless, retrospective, statistically sound surveys were conducted in Robbinsdale and Duluth. Approximately 9,600 children had been immunized in the Minneapolis suburb during a 2-week period in January 1970 and 14,350 children in Duluth during a 2-week period in April 1970. The surveys were begun in each locale 3½ months after the completion of the immunization programs. In Robbinsdale, all immunization records were collected by the local school district nurse from grade school immunization records (hence, no children under 5 years or more than 13 years of age were included) and, from that number, every 10th record, a total of 955, was randomly selected. In Duluth, all immunization permit slips for children from pre-kindergarten through the sixth grade level were supplied to us by the St. Louis County health officer and, from that number, every eighth slip, a total of 1,793, was selected. Every eighth slip was selected in Duluth, as opposed to every 10th in Robbinsdale, because we anticipated, incorrectly as it turned out, that parental cooperation would be less complete in Duluth.

A letter explaining the study and a reply post card were then sent to the parents of each child selected for these two surveys. If a response was not received within 2 weeks of the initial mailing, a second letter and reply post card were mailed. On the card, the parent could indicate whether the child had experienced fever, skin rash, swollen glands, sore or swollen joints, sore legs, sore feet, sore arms, sore hands, soreness only at site of injection, or none of these signs or symptoms.

From the Robbinsdale survey, 949 post cards were ultimately returned; 89 of these indicated signs or symptoms other than soreness at the injection site. Six children had moved from the area and could not be located. From the Duluth survey, 1,773 post cards were returned; they indicated 119 children had experienced complications other than soreness at the injection site. Despite numerous attempts by the authors, school nurses, and district public health nurses, it was not possible to locate 20 children.

Table 1. Response to surveys of children's reactions to rubella vaccination with HPV-77DE$_5$ vaccine in Robbinsdale and Duluth, Minn.

Item	Robbinsdale	Duluth
Letters mailed	955	1,793
Post card replies	949	1,773
Percent post cards returned	*99.3*	*98.8*
Followup questionnaires mailed	89	[1] 119
Followup questionnaires completed	89	119

[1] Parents questioned over the telephone by the authors or at a home visit by the public health nurse.

A questionnaire requesting more detailed information was next mailed to each of the 89 Robbinsdale families that had indicated that their child had experienced one or more of the complications mentioned on the post card other than the single complication of soreness at the site of the injection. All of the questionnaires were immediately returned. It was necessary to call a few families and discuss the response because it appeared to us that a question had been misinterpreted or an answer was ambiguous.

Rather than mail a questionnaire to the Duluth families, it was decided to telephone each household to obtain the answers to the questions concerning complications experienced by 119 children. Accordingly, these data were collected by telephone by Deinard and Hoban. If a family did not have a telephone, a public health nurse took the questionnaire to the home to be answered. Finally, when it became evident that several children from Duluth were still having apparent discomfort which may have been related to the immunization 11 months after the immunization program, Deinard and Venters traveled to that city to examine the children.

Results

Response. The first result which we think needs to be emphasized is the highly successful surveys (table 1). These superior responses were produced by two mailings only, as described previously. The response to the followup questionnaires mailed to Robbinsdale parents who had indicated that a child had had one or more complications was also impressive in that all parents

promptly returned the forms so that a second mailing was not needed. In Duluth, most parents were telephoned and asked the questions. The public health nurses' performance in obtaining information from families without a telephone was commendable; all families were located, and the questionnaires were filled out and returned to us promptly.

HPV-77DK$_{12}$—Minneapolis. Because the data on reactions to HPV-77DK$_{12}$ in Minneapolis children were not obtained in random fashion, but instead were collected on cases brought to our attention, no statistically significant conclusions can be drawn from them. Therefore, they are not presented in detail here; they are available upon request. We were impressed by the severity of the complications and by the fact that none of the 80 children had received the HPV-77DE$_5$ vaccine. All complained of severe arthralgia or arthritis, with or without associated paresthesia. The cases were equally divided between boys and girls, with the majority occurring in children between 4 and 9 years of age.

Knees, wrists, and metacarpal joints were most often involved, frequently in combination. Discomfort was related more frequently to the tendons attached to the joints than to the joints themselves. Onset of symptoms occurred, in most cases, 30 days or more post vaccination (range of 10–70 days) and persisted, on the average, for 15 days (range of 1–56 days). More than one-quarter of the children had one or more recurrences of joint discomfort. Most children had discomfort throughout the day and night, occasionally so severe as to interfere with sleep. Administration of salicylates was generally without salutory effect.

HPV-77DE$_5$—Robbinsdale and Duluth. For the purposes of this report, the results of the two surveys, covering 2,722 children, have been combined. A summary of the results by age and sex of the children is given in table 2. There were 2,266 who had had no complications, 248 who had soreness only at the site of the injection, and 208 who had experienced one or more of the other complications listed on the reply post card.

The complications of arthralgia and arthritis, with or without associated paresthesia, were analyzed relative to day of onset following vaccination. Nine days' post vaccination was arbitrarily chosen as the low-end cutoff point because it represents the period following exposure to naturally occurring virus when viral activity is greatest with regard to antibody production and to the generation of secondary signs or symptoms such as fever, rash, lymphadenitis, and malaise.

Arthralgia or arthritis, beginning 9 days or later after immunization and with or without associated paresthesia, was reported as the primary complication in 26 percent (54 of 208) of the

Table 2. Complications among 2,722 Robbinsdale and Duluth, Minn., children given HPV-77DE$_5$ rubella vaccine, by age and sex

Age	No complications				Sore at injection site only				All other complications			
	Boys		Girls		Boys		Girls		Boys		Girls	
	Number	Percent [1]	Number	Percent [1]	Number	Percent [1]	Number	Percent [1]	Number	Percent [1]	Number	Percent [1]
1	18	0.7	18	0.7	2	0.1	0	.....	1	(2)	4	0.2
2	32	1.2	30	1.1	1	(2)	4	0.2	5	0.2	2	.1
3	37	1.4	42	1.5	8	.3	1	(2)	5	.2	1	(2)
4	38	1.4	25	.9	5	.2	13	.5	5	.2	7	.3
5	81	3.0	83	3.0	9	.3	12	.4	6	.2	8	.3
6	141	5.2	126	4.6	8	.3	16	.6	15	.6	18	.7
7	158	5.8	142	5.2	15	.6	9	.3	14	.5	17	.6
8	152	5.6	160	5.9	13	.5	22	.8	6	.2	10	.4
9	149	5.5	145	5.3	10	.4	11	.4	11	.4	18	.7
10	138	5.1	142	5.2	12	.4	22	.8	9	.3	16	.6
11	126	4.6	141	5.2	17	.6	14	.5	8	.3	14	.5
12	62	2.3	73	2.7	8	.3	15	.6	4	.2	3	.1
13	3	.1	2	.1	0	.....	1	(2)	1	(2)	0	.....
14	2	.1	0	.....	0	.....	0	.....	0	.....	0	.....
Total	1,137	41.8	1,129	41.5	108	4.0	140	5.1	90	3.3	118	4.3

[1] Expressed as a percentage of the 2,722 vaccinees.
[2] Less than 0.1 percent.

children with complications. This number represents a frequency of 198 cases per 10,000 children vaccinated. The age and sex composition of this group follows:

Age group	*Boys*	*Girls*
1–3 years	2	1
4–6 years	6	6
7–9 years	9	18
10–12 years	5	7

Discomfort, as with the Minneapolis children, was reported as more frequently being related to the tendons attached to the joints than to the joints themselves. Details on the joint involvement of the 54 children were as follows:

Joint involvement	*Boys*	*Girls*
Knees[1]	20	31
Ankles	4	8
Metatarsals[1]	0	4
Elbows	2	5
Wrists[1]	5	11
Metacarpals[1]	2	2
Shoulders	1	1
Cervical spine	1	0
Hips	1	2

[1] Includes symptoms of tendonitis.

Scatter diagrams of the data suggested, but did not unequivocally prove because of the small numbers involved, that girls had a later onset of symptoms than boys. However, it was not possible to establish any sort of age- or sex-dependent relationship relative to the duration of the symptoms or to their recurrences.

Data on the onset and duration of symptoms and recurrences for the 54 children follow:

Symptoms	*Boys*	*Girls*
Mean day of onset	22	26
Range of day of onset	10–56	14–60
Mean duration, days	13	14
Range of duration, days	1–60	1–120
Number of children with 1 or more recurrence	5	7

Some of these 54 children were awakened at night; some had discomfort only with activity; some had the most discomfort upon arising in the morning. In general, all 54 children experienced a salutory effect from salicylate therapy.

Although the joint discomfort usually was reported as an isolated complication, a few children had fever (either low grade or above 101° F.), rash, posterior cervical adenopathy or a sore throat, either alone or in combination, before or at the same time as the joint discomfort. One boy, whose discomfort began on the 56th day, had at least 12 recurrences. He was frequently awakened at night, particularly if he had had a day of strenuous activity. He was examined by Deinard and Venters and was found to have a left popliteal Baker's cyst. We also examined a girl whose discomfort began on the 56th day and who had several recurrences of discomfort, especially after much walking. She was found to have a significant degree of bilateral pronation of her feet.

Thirteen percent of the 208 children (15 boys, 12 girls) had some degree of isolated joint discomfort, with or without associated paresthesia, commencing within the first 8 days following the immunization. This number represents a frequency of 99 cases per 10,000 children vaccinated. The average time of onset was 1.7 days (range 0.5–4.0) for boys and 2.3 days (range 0.5–7.0) for girls, while for boys the average duration of symptoms was 2.8 days (range 1–14) and for girls, 3.7 days (range 1–21).

Nonspecific minor symptoms were reported for the remaining 61 percent (127 of 208) of the children. They consisted of fever (both low grade and above 101° F.), rash, malaise, posterior cervical adenopathy, or sore throat occurring in all possible combinations within 9 days of the immunization but persisting for only 1 or 2 days.

Discussion

Before the licensing of rubella vaccine for commercial distribution and its subsequent widespread use during 1970 in community immunization programs, extensive field trials of two derivatives of the HPV-77 strain (attenuated by propagation in either dog kidney or duck embryo cell culture lines) were conducted. The published data indicate that the complications of arthralgia, arthritis, or paresthesia, which were noted to occur in the vaccinees, were mild and transient and affected only a small percentage of the immunized children, regardless of the strain of vaccine used (*1–5*). These investigators reported that seronegative persons were more often affected than were seropositive ones and that children were less often affected than were adults. That such complications did arise is not unexpected, however, in view of earlier observations on the occurrence of such symptoms following natural infection with rubella virus (*6, 7*).

Our studies were prompted by reports of serious arthralgic and arthritic complications after the use of the HPV-77DK$_{12}$ vaccine. Two large-scale surveys of children who received the HPV-77DE$_5$ vaccine were then undertaken because we wished

to know whether that vaccine had generated comparable complications. Our data indicate, for the HPV-77DE$_5$ vaccine, that the time of onset, duration, and frequency of joint involvement differ from comparable data reported from the field trial studies (*1–5*). In addition, our observations suggest that recurrences were perhaps more common for those who received the HPV-77DK$_{12}$ vaccine. We acknowledge, however, that our observations may be biased because these cases were voluntarily brought to our attention because of their severity. Hence, because they were severe, recurrences may have been more likely to occur.

One apparent shortcoming of the field trial studies is the length of time, 2 to 4 weeks, following the immunization, during which the vaccinees were observed. With regard to those children who received the HPV-77DK$_{12}$ vaccine, the mean day of onset (30 days or more) of arthralgia or arthritis, with or without associated paresthesia, exceeded the period of observation of earlier investigators (*1–3, 5*). In addition to the longer interval between immunization and the onset of symptoms, our observations on those who had received the HPV-77DK$_{12}$ vaccine also differ from earlier studies in that the mean duration of symptoms was 15 days rather than less than 1 week.

That these observations have no statistical significance is freely admitted, since this portion of our survey was not conducted on a random sample of those vaccinated with the HPV-77DK$_{12}$ vaccine. Admittedly, had we been able to conduct a proper survey, the mean values would have been diluted by less serious cases which we know occurred throughout the city but were never brought specifically to our attention. However, even though our mean values are artificially high, the upper levels of the range for the time of onset and duration of arthralgia or arthritis are not.

Our observations also reveal that children's knees were much more frequently involved following immunization with the HPV-77DK$_{12}$ vaccine than has been described (*4*). This observation, again, may be related to the fact that our observations were made of the more severe cases that were voluntarily reported to us. Unfortunately, because of the nonrandom nature of the sample of Minneapolis children, we are unable to make definitive statements about the frequency with which complications occurred in children vaccinated with the HPV-77DK$_{12}$ vaccine. In addition, we have no information as to whether the most serious complications arose in seronegative or seropositive children. Our only contention relative to the HPV-77DK$_{12}$ vaccine is that the symptoms of arthralgia and arthritis which did occur were less transient and more severe than the field trial reports led us to believe would occur (*1–5*). In this regard, recent reports have shown agreement with our observations (*8–12*).

With regard to the HPV-77DE$_5$ vaccine, our data indicate that 7.6 percent of the children experienced one or more complications. Two percent of those surveyed had specific complications of arthralgia or arthritis occurring 9 days or more post vaccination. This figure is not unlike data published previously for this vaccine. But, because the surveys in Robbinsdale and Duluth were begun 3½ months after the completion of the immunization programs, the mean time of onset of these complications is greater and the upper level of the range is farther removed from the day of immunization than comparable data reported previously from the field trial studies (*1–5*). In addition, the duration of discomfort was longer than previously described.

We recognize that there may have been errors in recalling and reporting the time of onset, extent of symptoms, and other facts because of the retrospective nature of the survey and the long interval between immunization and the start of the survey. Some mild reactions may have been totally forgotten while some unrelated symptoms may have been retrospectively reported. In all likelihood, however, those errors occurred in both directions. Hence, our data should be accepted as they stand, and it should then be recognized not only that even the HPV-77DE$_5$ vaccine may generate arthralgia or arthritis after a longer post vaccination interval, but that these complications may last longer than other published reports have indicated.

This lapse of time is an important point. Often the symptoms reported to us began so long after the vaccination that the parents had completely forgotten about the vaccination and so failed to mention to their physician that their child had been immunized at school. As a consequence, many children were unnecessarily evaluated for other diseases which are known to have an arthritic component; however, we have no notion whether those children who had the most trouble were seropositive or seronegative.

The other complications which were observed following immunization with HPV-77DE$_5$ vaccine were minor and did not differ, with respect to the

time of onset, duration, or extent, from comparable symptoms reported by others to follow rubella vaccination. Fever usually occurred within 1 or 2 days of the vaccination and more likely represented a response to a pyrogenic substance in the vaccine than to the attenuated virus. Transient malaise and rash also occurred within 1 or 2 days of the immunization; the etiology of each is obscure but neither was serious.

Although severity of arthralgia or arthritis has been difficult to assess, the severity was impressive in that salicylates were more effective in controlling those symptoms in children who received the HPV-77DE$_5$ vaccine. For those exposed to the HPV-77DK$_{12}$ vaccine, salicylates, in doses that would have been appropriate for the outpatient control of persons suffering from juvenile rheumatoid arthritis, were often not effective in controlling symptoms.

That the parental response to the two retrospective surveys of random samples was excellent must also be emphasized. No reward was offered for returning the reply post card. Parental motivation alone was responsible for the highly successful surveys. This motivation may have been created, in part at least, by the newspaper coverage of early reports of serious complications which occurred in Minneapolis following use of the HPV-77DK$_{12}$ vaccine. Although the families in Robbinsdale and Duluth did not know which vaccine their children had received, they were aware that there had been problems in Minneapolis and hence may have been encouraged to participate. Finally, despite the problems that occurred in Minneapolis, immunization of children against rubella has continued to be readily accepted by the public.

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Following reports of serious complications of arthralgia and arthritis in Minneapolis, Minn., children who had received the HPV-77DK$_{12}$ rubella vaccine, surveys were conducted of two random populations of children in Robbinsdale and Duluth, Minn., who had received the HPV-77DE$_5$ vaccine. Of 2,722 vaccinees surveyed, 208 experienced one or more complications.

Responses from parents indicated that for the HPV-77DE$_5$ vaccine, time of onset, duration of symptoms, and frequency of joint involvement differed from data on field trials of the vaccine that have been previously published. Knee joints, specifically, were observed to be more frequently involved than the previous data indicated should have occurred. Salicylates more readily controlled the joint involvement in those who had received the HPV-77DE$_5$ vaccine than those vaccinated with HPV-77DK$_{12}$.

Followup questionnaires evoked responses from 100 percent of 208 families.