tective effect of exercise, as suggested by studies of mortality among longshoremen.[18] A simple explanation for these findings may well be that adaptation to reduced oxygen tension at higher altitudes is never complete, and, therefore, that exertions associated with the activities of daily living represent increased physical exercise.

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EPIDEMIC MEASLES IN A HIGHLY VACCINATED POPULATION

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Abstract During November, 1975, to May, 1976, measles occurred at a rate of 20.3 cases per 1000 in a purported immunized population, of whom historical and serologic survey revealed that 9 per cent had no history of either measles illness or vaccination and 18 per cent did not have detectable measles antibody. Antibody was detectable in 92 per cent of those vaccinated at ⩾13 months, 80 per cent at 12 months and 67 per cent of those vaccinated when less than one year old ($P<0.001$), but no significant differences existed with increasing years since vaccination ($P>0.1$). A second vaccination increased detectable antibody prevalence only in those originally vaccinated when less than nine months old (42 to 80 per cent, $P<0.02$). During a measles outbreak, more cases occurred in those receiving vaccine when less than 12 months old than in those vaccinated at ⩾12 months (37 per cent vs. 9 per cent, $P<0.001$). A second vaccination protected those originally vaccinated at <12 months (35 per cent ill without a second vaccination vs. 2 per cent with, $P<0.001$). Thus, a single measles vaccination of children <12 months old does not protect; a second vaccination will protect this group. (N Engl J Med 296:585-589, 1977)

MEASLES vaccine (live, attenuated virus) was licensed in 1963, and by early 1967, a marked decline in reported cases had occurred. In general, vaccinated youngsters remained free of measles. Scattered outbreaks continued to occur, however, and reports called attention to practices that left vaccinated children susceptible to wild virus. Age of the child at vaccination was found to be important for successful immunization,[1-3] and in 1969 the Advisory Committee on Immunization Practices advised that measles vaccine be administered only to children 12 months or older.[4]

During October-December, 1975, 33 cases of measles occurred in northeast metropolitan Detroit, an area where more than 95 per cent of children entering school in 1975 had a history of measles vaccination. Investigation revealed that many cases occurred in

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children previously vaccinated. In view of an apparently high attack rate in such cases, a historical and serologic survey was conducted in January, 1976, in five schools in the outbreak area that had not yet had cases of measles. The survey was conducted to determine if a large fraction of the children had been improperly vaccinated by today's standards or lacked serologic evidence of protection despite adequate vaccination practices. In addition, we hoped to determine the efficacy of measles booster vaccination during epidemic exposure.

After the serologic survey, an outbreak of measles occurred in the school system surveyed, but in a school not initially included. We conducted a historical survey in this school (School Y).

This report describes the results of the investigation of the initial cases, results of the historical and serologic survey, and results of the School Y investigation. On the basis of these results we recommend selective revaccination of groups likely to be susceptible.

Methods and Materials

Cases in October-December, 1975

Cases of measles are reported to the Michigan Department of Public Health, and follow-up histories are obtained on each report to confirm the diagnosis and establish an accurate vaccination history. Cases were defined as typical rash illness of four days or more in duration, with temperatures of 38.3°C or above and at least one of the triad of cough, conjunctivitis or coryza. Serologic data confirming measles (fourfold or greater increase in hemagglutination inhibitory titer or single titer >640) were available in five cases. The vaccinating physician confirmed the vaccination history in most cases.

Historical-Serologic Survey

Part of the outbreak area is served by a school system isolated from the rest of metropolitan Detroit. Most of the children's social interactions are within the geographic area served by the school system. This upper-middle-class community is remarkably homogeneous socioeconomically and has very few families of short-term residence.

Grades 1 and 4 were surveyed in five of 10 elementary schools in this school system. Of the 603 children in Grades 1 and 4, 345 (57 per cent, range of 43 to 79 per cent for individual schools) participated. Parents of each participant were asked for exact date of measles vaccination (or vaccinations), age at vaccination, vaccinating physician and history of measles diagnosed by a physician.

Serum specimens were obtained by venipuncture, and serologic analyses were performed by the Bureau of Laboratories, Center for Disease Control, Atlanta, Georgia, a measles hemagglutination inhibitory method described by Rosen, with minor modifications,[5] being used. Initially, all serums were tested starting at a 1:10 dilution. Serums with measles hemagglutination inhibitory titers <1:10 were retested at a 1:5 dilution. Only three of 65 samples were positive at 1:5 and not at 1:10; all these samples were from children with a single vaccination at ⩾12 months of age.

School Y Survey

School Y, a sixth elementary school in the same system, is not different from the other survey schools. School Y had an enrollment of 446, of whom 400 (90 per cent) participated. Participants were asked for the exact date of measels vaccinations, age at vaccinations and history of measles illness diagnosed by a physician.

Statistical Analyses

Categorical data were analyzed by chi-square or Fisher's exact test. We performed tests for correlation with time from vaccination by Spearman's rank-correlation test.

Results

Cases in October-December, 1975

A total of 33 cases occurred in October-December, 1975, involving seven elementary schools — five from the subsequently surveyed system. Although cases continued to occur through May, 1976, the characteristics of the first 33 are presented since they prompted the subsequent studies. Sizable outbreaks occurred in two schools. In one of them, seven of the nine children had previously been vaccinated; in the other, all 18 cases of measles were in vaccinated children. The rest of the cases tended to occur sporadically, with little transmission within the schools, where measles vaccination levels in children recently entering school were 97 to 100 per cent as reported in surveys to the Michigan Department of Health.

Detailed histories demonstrated that although 29 of the 33 patients had previously been vaccinated, only 13 had been adequately vaccinated (vaccinated at one year or more of age and without gamma globulin with vaccine).

Excluding two teen-age and two preschool sibs, 23 of the remaining 29 cases were in children in the fourth to sixth grades. Analysis of the vaccination histories in the 29 cases suggested that inadequate vaccination or waning protection might be more frequent in the fourth to sixth grades (15 of 23 vs. two of six in the first to third grades).

Historical-Serologic Survey

Serum samples were available from 343 of the 345 participants, and analyses were confined to these 343. Two hundred and fifty-seven (75 per cent) of the participants had had a single vaccination, 42 (12 per cent) had received a second vaccination, 13 (4 per cent) had had measles diagnosed by a physician, and only 31 (9 per cent) had no definite history of vaccination or measles illness.

Of the 257 children who had received a single vaccination, 19 had been vaccinated at less than nine months of age and 54 at nine to 11 months of age; thus, 28 per cent had been vaccinated at <12 months. There was no difference between the first and fourth grades in the proportion vaccinated (88 vs. 85 per cent respectively) or age at vaccination ($P>0.05$). Likewise, there was no difference between the first and fourth grades in the prevalence of no detectable antibody (17 vs. 22 per cent respectively, $P>0.5$).

The geometric mean titer in children with a single vaccination was 15.6±2.27 (S.D.) — similar to that in children with a second vaccination, 15.6±2.28. Children with a history of measles illness had a titer of 58.1±2.73.

Table 1 shows the frequency of detectable titers in

Table 1. Detectable Measles Hemagglutination Inhibitory Titers According to Age at Vaccination* and Interval since Vaccination.†

Data on Vaccination	No. with Titer <5	No. with Titer ≥5
Age (mo):		
<9	11 (58)‡	8
9–11	13 (24)	41
12	13 (20)	53
≥13	9 (8)	107
Unknown	1	1
Totals	47	210§
Interval since vaccination (yr):		
≤4	1 (4)	24
5	1 (3)	38
6	5 (11)	42
7–8	7 (21)	27
9	3 (9)	31
Totals	17	162¶

*For children with a single vaccination.

†For children with a single vaccination at ≥12 mo.

‡Figures in parentheses represent % of children in each time category.

§Chi-square = 23, P<0.001.

¶r_s (Spearman's rho) = 0.6, P>0.10.

children administered a single vaccination according to age at vaccination. In keeping with previous reports,[3,6] a large fraction of children vaccinated at an early age had no detectable antibody, especially those vaccinated at less than nine months. There was a significant difference in the prevalence of detectable antibody in those vaccinated at <12 months, and those vaccinated at ≥12 months (chi-square = 14.6, P< 0.001). There was also a difference between those vaccinated at 12 months and ≥13 months (chi-square = 5.83, P<0.025).

In contrast to the importance of age at vaccination, Table 1 shows no significant differences in the frequency of titers <5 with increasing time from vaccination. Although there appeared to be a trend to a higher fraction with nondetectable titers at increasing years from vaccination this difference was not significant by Spearman's rank-correlation test (P>0.1, 1 tailed).

Differences in the frequency of detectable titers were also noted among vaccinating physicians. Table 2 demonstrates the differences among the six physicians most frequently named and all others combined. Although some of the differences could be attributed to age at vaccination (44 per cent of Doctor No. 3's patients and 50 per cent of Doctor No. 1's patients were vaccinated at <12 months vs. 24 per cent for all others), age did not account for all the differences. Whereas Doctor No. 25 had vaccinated 30 per cent of his patients at <12 months, only 15 per cent had no detectable antibody. Further investigation revealed at least one physician, whose patients had a high rate of no detectable antibody, had given gamma globulin with further attenuated vaccine as late as 1971.

Table 2. Detectable Measles Hemagglutination Inhibitory Titers According to Vaccinating Physician.*

Physician No.	Children with Titer <5†	Children with Titer ≥5
3	7 (39)	11
1	7 (25)	21
All others	20 (19)	86
4	5 (19)	21
25	3 (15)	17
2	5 (11)	39
14	0 (0)	15‡

*Children with single vaccination only. †Figures in parentheses represent %.

‡Chi-square (differences among physicians in frequency of detectable antibody as determined by conventional R × C chi-square) = 15, P<0.02.

Forty-two of the participants had been vaccinated more than once. However, the frequency of detectable titers was increased only in children originally vaccinated at less than nine months (Table 3). As noted above, the geometric mean titer of those given a second vaccination was not different from that in those given only one.

School Y Survey

The School Y vaccination profile was almost identical to that of the other schools. Seventy-one per cent of the 400 participants had had a single vaccination, and of these, 25 per cent had been vaccinated at <12 months. Three per cent had a history of previous measles, and only 4 per cent had not had either measles illness or vaccination for measles. Twenty per cent of School Y participants had been vaccinated more than once. In 1.7 per cent the vaccination history could not be adequately evaluated.

Table 3. Detectable Hemagglutination Inhibitory Titers in Children Given One or More than One Vaccination According to Age at Initial Vaccination.

Age at Initial Vaccination (Mo)	Children with Titer ≥5 Total	
	1 vaccination	>1 vaccination
<9*	8/19 (42)†	16/20 (80)
9–11	41/54 (76)	13/17 (76)
≥12	160/182 (88)	4/5 (80)

*Chi-square (difference in frequency of detectable titers in children originally vaccinated at <9 mo of age) = 5.94, P<0.02.

†Figures in parentheses represent %.

Of the 400 participants, 51 had measles during the spring of 1976; 45 of 365 previously vaccinated (attack rate of 12.3 per cent), and six of 17 unvaccinated children (attack rate of 35.3 per cent). The attack rates were highly dependent upon the age at vaccination, however (Table 4). Regarding those vaccinated at <12 months as susceptible decreases the attack rate in vaccinated children to 8.4 per cent.

In contrast to the age at vaccination, the years since vaccination did not make a significant difference in the attack rates (Table 4), in agreement with the serologic data. To avoid the possible effects of boosters and killed-virus vaccines, this analysis was restricted

Table 4. Measles Illness in School Y According to Age at Vaccination* and Interval since Vaccination.†

Data on Vaccination	No. Ill	No. not Ill
Age (mo):		
<9	6(38)‡	10
9–11	20(36)	35
12	8(13)	53
≥13	10(7)	142
Totals	44(15)	240§
Interval since vaccination (yr):		
≤4	3 (9)¶	29
5–6	6 (10)¶	54
7–8	1 (2)	40
≤9	8 (15)	44
Totals	18	167‖

*For children with a single vaccination.

†For children with a single vaccination at ≥12 mo.

‡Figures in parentheses represent % of children in each time category.

§Chi-square (differences among attack rates for children vaccinated at different ages) = 32, P<0.001.

¶Includes 1 vaccinated child in whom measles occurred before 1975-76.

‖Chi-square (differences in attack rates for different years since vaccination) = 4.3, P>0.1; r_s (Spearman's rho) = 0.4, P>0.1.

to children with a single vaccination after 1965 and before 1976.

Analyzing the attack rates in children with a second vaccination also confirmed the serologic data (Table 5). A booster significantly lowered the attack rate for those originally vaccinated at <12 months.

Discussion

In the community described in this report, there were 121 cases of measles among an estimated 3600 children between November, 1975, and May, 1976, an attack rate of 33.6 per 1000. Similarly, epidemic measles occurred in St. Louis in 1971, where up to 50 per cent of the cases were in vaccinated children, and the attack rate was 17 per 1000.[2] The present cases were also similar to those described by Schaffner et al.[8] in that they tended to be sporadic, with few large outbreaks.

Unlike many viral infections, such as poliomyelitis, in which a large fraction of cases are subclinical, almost all cases of measles are apparent. In addition, because measles is highly contagious, infection might be expected to occur in virtually all exposed persons who lack immunity. Therefore, if the presence of specific antibody indicates immunity, observations of clinical measles should closely match serologic determinations.

Table 5. Measles Illness in School Y Children with and without a Second Vaccination According to Age at Initial Vaccination.

Age at Initial Vaccination (Mo)	No. Ill/Total	
	1 vaccination	>1 vaccination
<9	6/18 (33)*	1/6 (17)
9–11	20/55 (36)	0/49 (0)
≥12†	18/195 (9)	0/22 (0)

*Figures in parentheses represent %.

†Chi-square = 19.9, P<0.001 for 1 vaccination vs >1 vaccination in children vaccinated at <12 mo; P>0.14 by Fisher's exact test for 1 vaccination vs >1 vaccination in children vaccinated at ≥12 mo.

Previous reports of antibody prevalence among vaccinated children have suggested that age at vaccination is an important determinant of the frequency of detectable antibody. Wilkins[9] and Linnemann[10] and their colleagues reported that 46 and 45 per cent, respectively, of children vaccinated before 11 months had no detectable antibody. These figures are similar to our 33 per cent without detectable antibody among children vaccinated at <12 months and 58 per cent among children vaccinated at <9 months. Likewise the finding of Cherry et al.[2] that 10 per cent of a group of 246 children vaccinated at 12 months had no antibody is comparable to our figure of 12 per cent for the same age group.

The occurrence of epidemic measles at School Y confirms the importance of age at vaccination suggested by the serologic data. At School Y, children vaccinated once at <12 months had an attack rate of 36 per cent, whereas in the serologic survey, children vaccinated at <12 months had a nondetectable-antibody rate of 33 per cent. For those vaccinated at ≥12 months, the School Y attack rate was 8.5 per cent — very close to the 12 per cent frequency of nondetectable antibody in the similar group in the serologic survey. Thus, it appears that a significant portion of children vaccinated too early fail to become immunized, and that at some time after 12 months, durable immunity is achieved in most children. Although the prevalence of detectable antibody in children vaccinated at ≥13 months was greater than that in those vaccinated at 12 months (P<0.05), the difference was not quite significant in the attack rates between these groups in School Y (chi-square = 2.46, 0.1<P<0.2).

Since vaccine-induced antibody levels decrease with time from vaccination just as disease-induced antibody levels do,[6] and since vaccine-induced antibody levels are lower than those after natural infection, we asked if the occurrence of measles in vaccinated children might be due to loss of protection as well as failure of the initial immune response. Bass et al.[7] noted increasing rates of undetectable antibody with increasing time from vaccination. Although we observed decreases in geometric mean titer with increasing years from vaccination, we did not observe a significant increase in the frequency of nondetectable antibody. Likewise, the insignificant increases in the fraction of children with no detectable antibody were not paralleled by consistent increases in rates of illness in School Y with longer time since vaccination.

Since the initial vaccination failed in a large number of children, is there value in revaccination? Serologic responses to revaccination were demonstrable only among children vaccinated before nine months. However, observations of illness in School Y showed that those originally vaccinated before 12 months and then revaccinated were better protected than those vaccinated before 12 months but not revaccinated.

In addition to age at initial vaccination, physician handling and administration of vaccine should be scrutinized. In particular, we found the use of gamma globulin with further attenuated vaccine to be associated with a high rate of unsuccessful vaccination. Since the children were vaccinated as long as 10 years before the study, evaluation of variations in individual physicians' handling and administration of vaccine was not possible.

The serologic data suggest that about 18 per cent of the once vaccinated population is at risk for measles — very close to the 16 per cent attack rate in School Y. Appropriate vaccination practices should halve this figure.

On the basis of these findings we recommend that physicians carefully review their vaccination records, with careful attention to age at vaccination, use of gamma globulin with vaccine and handling of vaccines. For children vaccinated before 12 months, or with further attenuated vaccine strains and gamma globulin at any age, revaccination should increase protection from measles. Health personnel conducting future vaccination efforts should pay close attention to age at vaccination, avoid the use of gamma globulin and stress appropriate handling of vaccines.

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GALACTORRHEA: A STUDY OF 235 CASES, INCLUDING 48 WITH PITUITARY TUMORS

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Abstract An analysis of 235 patients with galactorrhea (5.5 per cent males) showed that 20 per cent of all patients, and 34 per cent of women with associated amenorrhea, had radiologically evident pituitary tumors; these patients had the highest serum prolactin concentrations. The largest single group (32 per cent) consisted of women with idiopathic galactorrhea without amenorrhea; prolactin was normal in 86 per cent of these cases. Five patients had the empty-sella syndrome. Prolactin response was tested in selected patients by thyrotropin-releasing hormone, chlorpromazine, L-dopa, 24-hour sampling and other means. Tests with thyrotropin-releasing hormone were most useful in identifying patients with pituitary tumors. Surgery and radiotherapy lowered prolactin to a similar degree in patients with tumor, but galactorrhea and amenorrhea often persisted after treatment. The ergot derivatives, bromergocryptine and lergotrile mesylate, lowered prolactin in all 18 patients with idiopathic hyperprolactinemia or pituitary tumor, stopped galactorrhea in over 50 per cent, restored menses in over 70 per cent, and allowed pregnancy in three. (N Engl J Med 296:589-600, 1977)

SINCE the report by Chiari over a century ago[1] galactorrhea has been noted to occur with a wide variety of endocrine and nonendocrine disorders. With the exception of the study by Tolis et al.[2] previous reports have dealt with a limited number of cases. The development of a sensitive bioassay for prolactin in human blood[3,4] and subsequently of radioimmunoassays[5,6] led us to study patients with galactorrhea. The size of our series, now numbering 235 patients, has enabled us to delineate different forms of the disease and to estimate their relative frequency.

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Physiology of Lactation

Before pregnancy, initial development and differentiation of the breast take place under the influence of estrogens, progesterone and prolactin, with other hormones probably having a permissive action. The dominant role of prolactin was emphasized by Lyons, Li and Johnson,[7] who showed that in hypophysectomized, gonadectomized, adrenalectomized rats, estrogens, progesterone and other steroids were ineffective in the absence of prolactin in inducing any breast development. When prolactin was added, full growth and differentiation were obtained, up to and includ-