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SUPPURATIVE LYMPHADENITIS FOLLOWING INTRADERMAL BCG VACCINATION OF PRE-SCHOOL CHILDREN

WHO TUBERCULOSIS RESEARCH OFFICE *

SYNOPSIS

Regional lymph-node abscesses often occur among infants and young children following BCG vaccination, and the purpose of this study was to find ways to avoid glandular complications, or at least minimize their frequency, without jeopardizing the success of vaccination.

Over 1,700 children ranging in age from 6 months to 7 years were vaccinated by one of nine different procedures obtained by various combinations of two strengths of vaccine, two depths of injection, and three volumes of vaccine, in an attempt to reproduce, experimentally, some of the kinds of variation that may occur in practical programmes. Follow-up examinations were made at 10 weeks and at one year, the local and glandular responses being observed and measured and the degree of tuberculin sensitivity assessed by an intradermal 10 TU test.

Both the dose of vaccine and the age of the child were found to have a striking effect on the frequency and severity of lymphadenitis : the larger the dose and the younger the child, the higher the frequency of enlarged or perforated axillary lymph nodes. Furthermore, there was a close association between the findings at the two follow-up periods : with only one exception, children with negligible enlargement of the nodes at the 10-week examination had negligible findings at one year, whereas all the children with enlarged and adherent nodes at 10 weeks had evidence of perforation at one year.

The size of the vaccinal lesion was also affected by vaccine dose and by age of child : the lesion was larger in the younger children and with the stronger doses. The degree of tuberculin sensitivity was affected only slightly by the variations in dose and still less by the age of the child.

The size of the wheal raised by intradermal injection of vaccine was found to vary with the age of the child and with the depth of injection as much as it varied with the volume of vaccine injected. There can be no doubt that gauging the dose by the size of the wheal, rather than by the calibrations on a non-leaking syringe, is a very inaccurate procedure. When the dose of vaccine can be accurately measured, a stronger vaccine can be given (and perhaps a stronger degree of immunity attained) without causing an intolerable frequency of suppurative lymphadenitis.

* This study was carried out in co-operation with the Danish tuberculosis mass campaign and the Central Tuberculosis Dispensary of Aarhus, Denmark.

Inger Vig-Nielsen from the Central Tuberculosis Dispensary and Minna Madsen, Julie Allfather, Lis Halkjær-Lassen, and Marit Schultz from the WHO Tuberculosis Research Office participated in the field work. The study was planned by Johannes Guld, the follow-up was supervised by Ruth Rasmussen, and Hans F. Helweg-Larsen was largely responsible for analysis of the material.

The high frequency of lymphadenitis often reported to follow intradermal BCG vaccination of young children, particularly infants, is considered a serious drawback to their inclusion in vaccination programmes. Yet the possible benefit of BCG vaccination in conferring protection against the acute, fatal forms of tuberculosis in infants and young children demands that efforts be made to find the causes of the glandular complications, or at least ways to reduce their frequency.

While there may be considerable uncertainty about where to draw the line between " normal " and abnormal local reactions at the site of intradermal injection of BCG vaccine, there can be little doubt that a high frequency of regional lymph-node abscesses constitutes a serious practical problem. The technique of injection has often been incriminated,[12,14] the quality of the skin of young children presumably making superficial intradermal injections the exception rather than the rule, with the result that the vaccine may be injected into the deeper layers of the skin, or even subcutaneously. Yet other vaccination techniques, such as scarification, multiple puncture, or even oral administration, have also often resulted in high frequencies of glandular complications.[7,8]

The purpose of the present investigation was to study the responses to intradermal BCG vaccination in infants and young children—children of pre-school age—in an attempt to identify the factor, or factors, responsible for glandular complications. The work was planned by the WHO Tuberculosis Research Office and carried out in co-operation with the Danish tuberculosis mass campaign and the Central Tuberculosis Dispensary of the city of Aarhus. It involved the vaccination of over 1,700 children with various intradermal techniques and with various doses of vaccine, and follow-up examinations at 10 weeks and one year, including observation for glandular complications and measurement of local responses and the degree of tuberculin sensitivity induced.

Material and Methods

All persons examined in the Danish mass campaign, which operated throughout the country during the years 1950-52, were given a routine test with an intradermal dose of 10 tuberculin units (TU), and those with reactions of less than 6 mm were offered BCG vaccination. For purposes of the present study, arrangements were made for all children of pre-school age covered by the mass campaign in the city of Aarhus during the 3-week period 8-29 November 1952, and who would normally have been vaccinated by the campaign teams, to be referred to a special research team for vaccination.

The study was designed to reproduce experimentally some of the variations in vaccination technique that may occur in practice in vaccination

programmes and to investigate the effect of such variations on the response to vaccination. Two strengths of vaccine, two depths of injection, and two volumes of vaccine were combined in various ways to make a total of eight different vaccination procedures. One strength of vaccine was the regular standard strength containing 0.75 mg per ml, the other was one quarter of the standard strength (0.19 mg per ml). Injection with both strengths was made either very superficially, just under the epidermis, or rather deeply into the cutaneous tissues. The volume of vaccine injected was either 0.20 ml or 0.05 ml—twice or half the usual volume of 0.10 ml. In addition, the procedure prescribed for routine use—very superficial injection of 0.10 ml of standard strength vaccine—was included as a ninth procedure against which to evaluate the effect of the various controlled deviations. The nine vaccination procedures were used in a random order, derived from a table of random numbers. All vaccinations were given in the left deltoid region.

Vaccine for the study was obtained from the Statens Seruminstitut, Copenhagen. Batch 1022, prepared on 31 October 1952, was used during the first half of the 3-week vaccination period, and batch 1024 during the second half. The quarter-strength vaccine was prepared at the institute by diluting the standard strength vaccine with an appropriate volume of the regular suspension diluent. The vaccines were kept refrigerated until use and were protected from light during use. Syringes pre-tested for leakage were used for all the injections, and the volume injected was measured by the calibrations on the barrel of the syringe. After each injection the vaccinator measured and recorded the transverse diameter of the wheal raised by the injection.

At both the 10-week and one-year follow-up examination, tuberculin tests were given by injecting intradermally on the dorsal aspect of the forearm 0.10 ml of a 10 TU dilution of tuberculin. PPD tuberculin batch RT XXII from the Statens Seruminstitut was used for the tests, the 10 TU dilutions being prepared to contain 0.00013 mg of the powdered tuberculin per 0.10 ml of dilution. The tuberculin reactions were read at four days by measuring the transverse diameter of induration in millimetres. Reactions were not interpreted as "positive" or "negative". No revaccinations were made during the entire study period.

Examinations was also made, at both follow-up periods, of the vaccination site, and the widest transverse diameter of the lesion (or scar) was measured and recorded. Notation was made of abscesses at 10 weeks and of discolouration, induration, or retraction of the scar at one year.

Both the left and right axillary and clavicular regions were carefully palpated, palpable nodes being classified according to size in five categories. Any other abnormality, such as perforation, was described and a brief history of its development given.

On each follow-up examination, the same operation was performed by

the same person. All observations were dictated to a clerk who recorded them on the individual record card made out for each child. As a further precaution against bias, a new set of record cards that gave no information on the vaccination procedure employed was used for the follow-up examinations.

A total of 1,719 children under 7 years of age, not previously vaccinated and considered tuberculin negative by the mass campaign team, were vaccinated by the research team. These children constitute the study group. As shown in appendix table 1, the children were rather evenly distributed throughout the years of birth 1945-51, with a relatively small number born in 1952. The youngest child in the study population was 6 months old at the time of vaccination. The table also shows the number of children examined at each follow-up period for tuberculin sensitivity, vaccinal lesions, and lymph-node enlargements.

The children who did not appear for follow-up examination were compared with those who did appear, but no clear differences were found between the two groups : children not examined were about evenly distributed with regard to vaccination procedure (as may be seen from appendix table 1) and had about the same age distribution as the total study population. Children examined at one period only did not differ in their response to vaccination from those examined at both periods. At one year, home visits were paid to children who did not come in for examination after three invitations, and the children who were hardest to reach did not show any higher frequency of complications. Thus, the children examined seem representative of the entire study population.

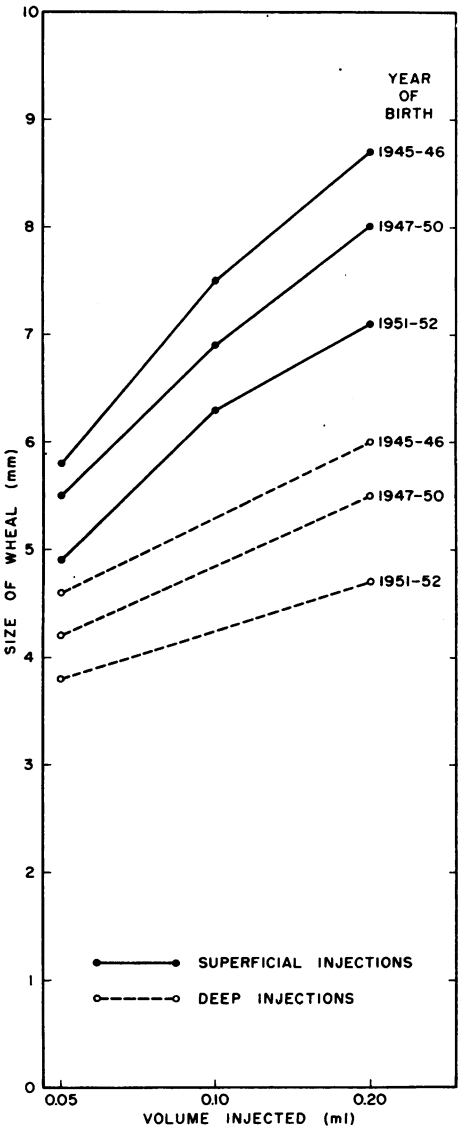
Results

Size of wheal after intradermal injection

Often, in routine work, the volume of fluid injected into the skin must be gauged by the size of the wheal raised in the skin : the calibration on the barrel of the syringe cannot be used when fluid leaks out between the piston and barrel or around the needle attachment. A wheal of about 8 mm is usually taken to correspond to a volume of 0.10 ml. In the present study, all the syringes were pre-tested for leakage, and only those meeting a fixed standard [6] were used. The volume of vaccine injected was measured, as accurately as possible, by the calibration on the syringe and, immediately after the injection, the diameter of the resulting wheal was measured in millimetres.

How the wheal size varies with the volume injected, depth of injection, and age of the child, is shown in fig. 1 and appendix table 2. The horizontal axis of fig. 1 gives the measured volumes injected—0.05, 0.10 and 0.20 ml—

FIG. 1. MEAN SIZE OF WHEAL ACCORDING TO VOLUME OF VACCINE, FOR TWO DEPTHS OF INTRADERMAL INJECTION IN CHILDREN OF THREE AGE-GROUPS



the vertical axis gives the mean diameter of the resulting wheals. The six curves show the results for injections made superficially or deeply, for children in three age-groups. Superficial injection, as shown by the three upper curves, clearly gives larger wheals and a greater increase in size with increasing volume than deep intradermal injection. And younger children consistently have smaller wheals than the older ones when given the same volume in the same depth.

Thus 0.20 ml injected deeply into the skin results in the same average wheal size as 0.05 ml injected superficially; and, as an illustration of the age effect, 0.20 ml injected deeply in a one-year-old child produced wheals about the same size as 0.05 ml injected deeply in a 6-year-old child.

It is not permissible to extrapolate the lowest curve of fig. 1 and not possible to predict the volume that must be injected " strictly intradermally ", if a little deeply, in a one-year-old child to obtain an 8 mm wheal. But it must be a large volume, and it seems fortunate that most vaccination syringes hold no more than one millilitre.

Tuberculin sensitivity

Distributions by diameter of induration of the 10 TU tuberculin reactions at the 10-week and one-year examinations are given in fig. 2 for the group of children vaccinated by superficial injection of 0.10 ml of standard strength vaccine. The results for this group represent the results obtained with the technique ordinarily recommended and with the dose of vaccine ordinarily used for routine vaccination work in Denmark. As shown in the figure, the tuberculin reactions at both post-vaccination periods are distributed fairly symmetrically around a central value. A strong degree of tuberculin sensitivity was produced—the reactions averaged 13.9 mm in diameter 10 weeks after vaccination and ranged in size from 9 mm to 21 mm. None of the children failed to develop a demonstrable degree of post-vaccination allergy. The reactions at one year show the same unimodal pattern as at 10 weeks. The apparent increase in mean size of reactions may reflect a real

FIG. 2. DISTRIBUTIONS BY SIZE OF TUBERCULIN REACTIONS TO INTRADERMAL 10 TU TEST 10 WEEKS AND ONE YEAR AFTER VACCINATION FOR CHILDREN GIVEN 0.10 ml OF STANDARD STRENGTH BCG VACCINE INJECTED SUPERFICIALLY

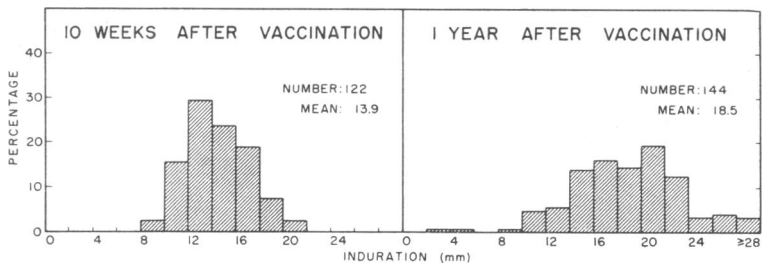


TABLE I. MEAN SIZE OF INDURATION (mm) OF REACTIONS TO INTRADERMAL 10 TU TEST AT 10 WEEKS AND AT ONE YEAR AFTER VACCINATION, ACCORDING TO VACCINATION PROCEDURE

Strength of vaccine in fractions of standard	Depth of intradermal injection	10 weeks after vaccination			1 year after vaccination		
		volume of vaccine injected (ml)		dose of BCG (mg)	volume of vaccine injected (ml)		dose of BCG (mg)
		0.05	0.20		0.05	0.20	
1/1 (0.75 mg/ml)	Superficial	13.5	13.8		18.3	19.0	
	Deep	13.3	14.5		18.8	19.8	
				0.150			0.150
1/4 (0.19 mg/ml)	Superficial	12.5	13.0		15.6	18.0	
	Deep	12.0	13.3		16.3	17.6	
				0.037			0.037
				0.009			0.009

increase in allergy but, more probably, a systematic difference in tuberculin-testing technique, particularly as the work at the two follow-up periods was not done by the same person.

The tuberculin reactions of the groups vaccinated by the various other procedures were distributed in the same characteristic unimodal form. The results are summarized in table I, which gives the mean reaction size for each of the eight groups according to strength of vaccine, depth of injection, and volume of vaccine injected. (Complete distributions for each vaccination group are given in appendix table 3.) The horizontal rows in table I show the mean size of tuberculin reactions at 10 weeks and at one year for the groups given different volumes (0.05 ml or 0.20 ml) of the same strength of vaccine. Corresponding data for groups injected with different strengths but the same volume of vaccine are read vertically. The diagonal rows give the results when different volumes and strengths of vaccine are combined to make the same total dose (in milligrams) of BCG organisms.

The dose of vaccine influenced the degree of post-vaccination allergy at 10 weeks as well as at one year. Whereas the strongest dose (0.150 mg) produced reactions of nearly the same average size as those resulting from the standard dose (0.075 mg), shown in fig. 2, the 0.009 mg dose produced reactions averaging 2-3 mm less.

The depth of injection of vaccine apparently had no effect on the resulting tuberculin allergy, as may be seen by comparing results for groups given the same strength or the same volume of vaccine by superficial and by deep injection.

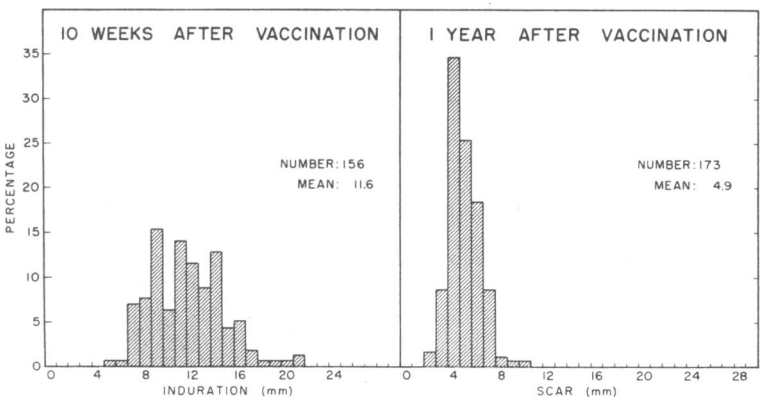
The volume of diluent, in which a constant dose of 0.037 mg was suspended, as seen from the diagonal rows in the table, was apparently unimportant for the resulting tuberculin sensitivity. However, the 0.05 ml volume tended to give a slightly stronger allergic response than the 0.20 ml volume. Possibly this tendency may only reflect small systematic errors in measuring the prescribed volumes.

The age of the child seemed to have a negligible influence on the allergic response to vaccination, and the results will not be shown here. It might be mentioned, however, that for the small number of children under one year of age the tuberculin reactions at 10 weeks averaged several millimetres less than for the older groups, whereas at one year the mean reaction size tended to decrease with increasing age.

Vaccinal lesions

Local reactions at the site of vaccination, hereinafter called vaccinal lesions, are expressed in terms of the transverse diameter of induration at the 10-week examination and the transverse diameter of the scar at one year.

FIG. 3. DISTRIBUTIONS BY SIZE OF VACCINAL LESIONS AT 10 WEEKS AND ONE YEAR FOR CHILDREN VACCINATED WITH 0.10 ml OF STANDARD STRENGTH BCG VACCINE INJECTED SUPERFICIALLY



Results are given in fig. 3 for the group vaccinated according to the routine procedure—0.10 ml of standard strength vaccine (0.75 mg/ml) injected as superficially as possible—by showing the distributions by size of vaccinal lesions at 10 weeks and of scars at one year.

The distribution of vaccinal lesions is moderately skewed to the right—a finding characteristic for all nine vaccination groups (appendix table 4) and consistent with results reported from previous studies.[3,10] However, the mean of the distribution gives a fair expression of the size of the lesions. As shown in the figure, with standard strength vaccine injected superficially, the vaccinal lesions averaged 11.6 mm in diameter at 10 weeks and the scars averaged 4.9 mm at one year.

Deviations from the routine technique for intradermal vaccination caused appreciable differences in the local response, as summarized in table II, which gives the mean size of vaccinal lesions at 10 weeks (left) and of scars at one year (right) for the eight other groups.

The dose of vaccine clearly affected the size of the vaccinal lesions : the 0.150 mg dose produced lesions averaging 2 mm larger than the standard 0.075 mg dose, and about 5 mm larger than the 0.009 mg dose. The scars at one year showed a corresponding decrease in size with decrease in dose.

The depth of injection influenced the vaccinal lesions in two ways : the mean size of the indurated lesions at 10 weeks was significantly larger after deep than after superficial injections; and the scars sometimes showed qualitative differences described as irregularities in shape, retraction, induration, and the like. As shown in appendix table 4, the scars were also more varied in size after deep than after superficial injection of vaccine.

The volume of diluent in which a constant dose of 0.037 mg of BCG was suspended had no systematic effect on the size of either the vaccinal lesion or the resulting scar.

The age of the child as a factor possibly affecting the mean size of the vaccinal lesions was studied by computing the average change in the size of the lesion per year of age by analysis of regression. Slopes of the lesion size, by age, are given in table III according to dose of vaccine and depth of injection.

All the slopes are negative for vaccinal lesions at 10 weeks: the older the child at the time of vaccination, the smaller the size of the vaccinal lesion. This age effect is highly significant for the children vaccinated by superficial injection, and the effect seems to be independent of the dose of vaccine injected.

One year after vaccination the older children had larger scars, particularly after deep injection and after the stronger doses of vaccine. As shown in the lower section of the table, the slopes (with one exception) are significantly positive.

The reason for the discrepancy between the findings at 10 weeks and one year might be that the vaccinal lesion develops more rapidly in older than in younger children so that at 10 weeks the lesion in older children is healing while it is still flourishing in the younger ones.

TABLE II. MEAN SIZE OF INDURATION (mm) OF VACCINAL LESIONS AT 10 WEEKS AND OF SCAR (mm) AT ONE YEAR AFTER VACCINATION, ACCORDING TO VACCINATION PROCEDURE

Strength of vaccine in fractions of standard	Depth of intradermal injection	10 weeks after vaccination			1 year after vaccination		
		volume of vaccine injected (ml)		dose of BCG (mg)	volume of vaccine injected (ml)		dose of BCG (mg)
		0.05	0.20		0.05	0.20	
1/1 (0.75 mg/ml)	Superficial	11.1	13.5		4.4	5.5	
	Deep	13.0	15.1	0.150	4.1	5.2	0.150
1/4 (0.19 mg/ml)	Superficial	7.9	11.0		2.8	3.7	
	Deep	11.2	13.9	0.037	3.3	4.3	0.037
				0.009			0.009

TABLE III. REGRESSION ANALYSIS OF MEAN SIZE OF VACCINAL LESION ACCORDING TO AGE OF CHILD AT TIME OF VACCINATION

Time after vaccination	Dose of vaccine (mg)	Superficial injection		Deep injection	
		slope of size of lesion by age (mm/year)	standard error of slope	slope of size of lesion by age (mm/year)	standard error of slope
10 weeks (induration)	0.150	— 0.53	0.18	— 0.24	0.13
	0.075	— 0.44	0.12		
	0.037 *	— 0.50	0.09	— 0.08	0.09
	0.009	— 0.57	0.11	— 0.31	0.16
1 year (scar)	0.150	0.24	0.07	0.45	0.09
	0.075	0.15	0.05		
	0.037 *	0.12	0.03	0.37	0.04
	0.009	— 0.04	0.04	0.17	0.06

*** The results are pooled by dose in spite of heterogeneity of variance of the groups receiving different volume of diluent.**

Regional lymphadenitis

Regional lymph-nodes found to be enlarged at either the 10-week or the one-year post-vaccination examination were classified according to size into one of five broad categories. Very small, barely palpable nodes were described simply as micro-adenitis. Larger nodes were judged, very roughly, as corresponding in size to a pea, bean, hazel-nut, or plum. While such a classification is obviously not precise, it serves the purpose of providing an estimate of the degree of enlargement. The findings have, for simplicity, been grouped for summary presentation as either " negligible", which includes no palpable nodes, micro-adenitis, and pea-sized nodes (up to 10-15 mm), or " enlarged ", which includes nodes the size of a bean, hazel-nut, or plum. Enlarged nodes are subdivided according to the presence or absence of adherence to the overlying skin; and perforated nodes, or evidence of past perforation, are listed separately irrespective of size.

Detailed findings are given in appendix table 5 as complete distributions by size-categories of lymph-node findings in both the left and right axilla, according to each vaccination procedure. No clavicular glandular enlargements were detected. The very low frequency of palpable nodes in the right axilla (vaccination was given on the left side) showed no correlation with any of the variable factors under study. As regards the findings in the left axilla, the depth of injection and volume of diluent had no demonstrable effect, but the dose of vaccine was a relevant factor. Thus, findings will be presented only for left axillary lymph-nodes, with all children grouped according to dose of vaccine given.

The dose of vaccine had a pronounced effect on the frequency and severity of enlarged left axillary lymph-nodes, as shown in table IV. At 10 weeks after vaccination, children vaccinated with 0.150 mg of BCG vaccine had a significantly higher frequency of enlarged nodes than those vaccinated with a dose of 0.037 mg—about 21% compared with 11%—and the group vaccinated with 0.009 mg had a frequency of only 6%. The findings at one year corresponded to those at 10 weeks, although the frequency of enlarged nodes was consistently much lower. Perforated nodes, or evidence of perforation before the one-year examination, were almost twice as frequent in children given a dose of 0.150 mg as in those vaccinated with half that dose; there were no perforated nodes in the group vaccinated with the weakest (0.009 mg) dose of BCG.

Table V shows the relation between the 10-week and one-year findings for the entire study population irrespective of dose of vaccine. There is an unmistakable association between the findings at the two examination periods: with one exception, children with negligible enlargement of the nodes at the 10-week examination had negligible findings at one year. On the other hand, all the children with adherent nodes at 10 weeks had perforated nodes at one year.

TABLE IV. PERCENTAGE OF ENLARGED OR PERFORATED LEFT AXILLARY LYMPH-NODES AT 10 WEEKS AND AT ONE YEAR AFTER VACCINATION, ACCORDING TO DOSE OF BCG INJECTED

Lymph-node findings	10 weeks after vaccination				1 year after vaccination			
	dose of BCG injected (mg)							
	0.150	0.075	0.037	0.009	0.150	0.075	0.037	0.009
Negligible	79.1	82.7	88.5	94.1	96.5	97.1	99.5	100.0
Enlarged, not adherent to skin	20.2	16.7	11.3	5.9	—	1.2	0.1	—
Enlarged, adherent to skin	0.7	0.6	0.2	—	1.2	0.5	—	—
Perforated	—	—	—	—	2.3	1.2	0.4	—
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Number examined	292	156	644	322	341	174	748	382

TABLE V. CORRELATION BETWEEN RESULTS OF LEFT AXILLARY LYMPH-NODE FINDINGS AT 10 WEEKS AND AT ONE YEAR AFTER VACCINATION, FOR ALL VACCINATION PROCEDURES

Lymph-node findings at 10 weeks after vaccination	Lymph-node findings at 1 year					
	negligible	enlarged	perforated	number examined	number not examined	total
Negligible	1,201	—	1	1,202	31	1,233
Enlarged, not adherent to skin	160	8	6	174	3	177
Enlarged, adherent to skin	—	—	4	4	—	4
Number examined	1,361	8	11	1,380	34	1,414
Number not examined	263	—	2	265	40	305
Total	1,624	8	13	1,645	74	1,719

The age of the child in relation to the percentage of enlarged or perforated left axillary lymph-nodes is shown in table VI for all children vaccinated with the two strongest doses of vaccine (0.150 mg or 0.075 mg). At the one-year examination the occurrence of perforated glands clearly depends on the age of the child at vaccination: the younger the child, the higher the frequency of lymphadenitis. The trend is less obvious at the 10-week follow-up, although at this examination too the youngest age-group tended to present a higher incidence of enlarged lymph-nodes than the remaining age-groups.

TABLE VI. FREQUENCY OF ENLARGED AND PERFORATED LEFT AXILLARY LYMPH-NODES AT 10 WEEKS AND AT ONE YEAR AFTER VACCINATION ACCORDING TO YEAR OF BIRTH *

Year of birth	10 weeks after vaccination			1 year after vaccination		
	number examined	enlarged nodes		number examined	perforated nodes	
		number	%		number	%
1945-46	107	19	17.8	125	1	0.8
1947-48	140	24	17.1	159	2	1.3
1949-50	125	25	20.0	143	2	1.4
1951-52	76	20	26.3	88	5	5.7

* Including only children given the two strongest doses of vaccine (0.150 mg and 0.075 mg)

Discussion

The results of the present study among children of pre-school age bring out the major importance of two factors, dose of vaccine and age of the child, for the frequency and severity of lymphadenitis following intradermal BCG vaccination : in general, the stronger the dose and the younger the child, the more frequent and severe the regional lymph-node enlargements. The size of the local vaccinal lesion at 10 weeks was also affected by the dose of vaccine and age of the child, whereas the degree of tuberculin sensitivity induced by vaccination was only slightly affected. These findings are in agreement with previous studies [3] on schoolchildren aged 7-14 years, although the trends with age were less pronounced in the school-age groups than in children under 7 years of age.

Similar observations on post-vaccination lymphadenitis have been reported by other workers. In a follow-up study of children vaccinated in the Danish tuberculosis mass campaign, Møller & Løvgreen [9] found a higher frequency of glandular abcesses in the age-group 1-3 years than in children aged 4-6 years, and no abscesses at all in children over 14 years of age. (Children 7-13 years old were not included in the mass campaign.)

In Taipei, Taiwan, a high frequency (23%) of enlarged axillary lymph-nodes has been reported [13] following intradermal BCG vaccination of infants below one month of age, in contrast with a much lower frequency (about 3%) in children 3-6 years of age. As the technique of injection apparently could not be held accountable, the Taipei workers concluded that the dose (in milligrams) of BCG vaccine should probably be adjusted to correspond to the child's body-weight. Investigations along this line are now under way in Taipei (J. C. Tao—personal communication).

Gaisford & Griffiths [4] have recently reported from England that a reduction of the dose of Danish BCG vaccine (0.75 mg/ml) from 0.2 ml to 0.05 ml in the newborn lowered the incidence of axillary glandular abscesses from 11.7% to 0.3%. Similarly, de Bruijne et al.,[1] working with

the newborn in Holland, found 13% with suppurative lymph-nodes when 0.1 ml (0.033 mg) of BCG was given in each arm, whereas the percentage was reduced to less than 1 by lowering the dose to 0.05 ml in each arm.

Results from the BCG Pilot Station in Paris show the same striking effect of dose of vaccine on the frequency of lymphadenitis in children under 6 years of age. The studies have included vaccines prepared in different production centres, including the Institut Pasteur in Paris and in Tunis, the Sahlgrenska Institutet in Göteborg, Sweden, and the Statens Seruminstitut in Copenhagen, and various techniques of administering the vaccine, including intradermal, scarification, and multiple puncture. From their extensive work, the French investigators [8] have concluded that " . . . la fréquence des adénites est directement proportionnelle à la quantité de B.C.G. qui a pénétré dans l'organisme ; les adénites sont d'autant plus fréquentes que l'on utilise une émulsion vaccinale de concentration plus élevée, et ceci quelle que soit la voie d'introduction du vaccin. ... La fréquence des adénites suppurées est inversement proportionnelle à l'âge des sujets vaccinés " (pp. 123-124).

In a previous study in 1949-50 [2] by the Tuberculosis Research Office among schoolchildren 7-14 years of age, both four times the standard strength Danish BCG and standard strength (0.75 mg/ml) were given to groups of more than 1,000 children. The frequency of enlarged, suppurative axillary lymph-nodes was 2.1% with the fourfold strength but only 0.2% with the standard strength 10 weeks after vaccination ; the results at one year (not published) showed the same trend. Many thousands of school-children have been vaccinated by TRO since 1950 with the Danish standard strength vaccine and the frequency of lymph-node enlargements has remained negligible. A slight decrease in frequency of enlarged nodes with age from 7 to 14 years was found by further analysis of the material reported by Edwards & Gelting.[2] However, the decrease is less pronounced than the one found in the present study among pre-school children. Thus, there is a continuous and diminishing decrease in the frequency of enlarged lymph-nodes with increasing age up to 14 years.

The general agreement in findings among the various studies referred to would seem to leave little doubt that the frequency and severity of lymphadenitis following BCG vaccination depends largely on the age of the child and the dose of the vaccine—and apparently the results are the same, in principle, whether the studies were carried out with vaccine prepared in Tunis, Paris, or Copenhagen. With each vaccine, the frequencies of lymph-node abscesses were reduced markedly by reducing the dose to about one quarter.

With the frequency of complications so closely dependent on dose of vaccine, the accuracy with which the prescribed volume of vaccine is injected must be important. The present study, as well as previous studies, [5, 11] indicates clearly that the size of the wheal raised in the skin may be a very

inaccurate measure of the volume of vaccine injected : the volume may vary far beyond the range deliberately given in the present study, even when the wheal is of a prescribed size, such as 8 mm. In practice it has, without doubt, been very common to gauge the volume by the size of the wheal particularly in the younger children : the skin of young children offers much more resistance to intradermal injection than that of older children. Leakage from the syringe will therefore frequently occur in vaccinating young children and make it necessary to gauge the volume by the wheal size. Furthermore, when a single wheal size is used as the criterion for a specified volume, irrespective of age, younger children will be given a much larger volume than the older ones because the wheals are smaller in young children when the same volume is injected. Thus it may be considered that when, in BCG programmes, a high frequency of enlarged nodes occurs in small children, this may be the result of an unlucky combination of frequent and excessive over-dosage and of the greater tendency towards enlargement of the lymph-nodes in early childhood.

It would be simple enough, when high frequencies of lymphadenitis are encountered in practice, to reduce the strength of the vaccine enough so that no complications would occur even with severe over-dosage. But in any discussion of dosage the possible relation between dose of BCG and acquired resistance to tuberculous disease must not be overlooked. While we have little information on the relation between dose of BCG and acquired resistance in human beings, animal experiments now in progress (see page 13) would seem to indicate that the degree of acquired resistance in large groups of vaccinated animals is related to the dose of living BCG given by intradermal injection.

Despite the possible pitfalls in reasoning by analogy from animals to man, it would seem reasonable at present to keep the dose of BCG vaccine as strong as possible. Constant potency of vaccine from batch to batch, vaccinators well trained in giving superficial intradermal injections, and, at least as important, tight-fitting syringes, the calibrations of which can be used to measure the dose, should make it possible to keep the dose of vaccine constant and controlled—just below the dose that produces an intolerable frequency of lymphadenitis.

RÉSUMÉ

La fréquence élevée des abcès des ganglions lymphatiques régionaux, observée chez les nourrissons et les jeunes enfants après vaccination par le BCG, a parfois fait exclure ces deux catégories de sujets des campagnes de vaccination de masse. Or, comme le BCG peut conférer aux jeunes enfants une protection contre les formes aiguës et mortelles de la tuberculose, il importe de rechercher les moyens permettant d'éviter les complications ganglionnaires, ou du moins de réduire leur fréquence, sans compromettre l'efficacité de la vaccination.

Un peu plus de 1.700 enfants âgés de 6 mois à 7 ans ont été vaccinés par voie intradermique, suivant neuf modalités différentes, afin de pouvoir se rendre compte de l'influence des techniques sur les réactions post-vaccinales. Les variantes ont comporté deux concentrations différentes de vaccin, deux degrés de profondeur pour l'injection et trois volumes gradués de vaccin ; on a combiné ces variantes de diverses manières afin d'essayer de reproduire expérimentalement la diversité des conditions qui peuvent intervenir dans les campagnes de vaccination effectives. Dix semaines puis une année plus tard, on a observé et mesuré les réactions locales et ganglionnaires et l'on a évalué, au moyen d'une épreuve intradermique à 10 UT, le degré de sensibilité à la tuberculine que présentaient les sujets.

On a pu constater ainsi que — conformément d'ailleurs à des observations antérieures — la dose de vaccin administrée et l'âge de l'enfant influent tous deux notablement sur la fréquence des adénites : plus la dose est forte et plus l'enfant est jeune, plus est élevée la fréquence des ganglions lymphatiques axillaires hypertrophiés ou fistulisés. De plus, les résultats observés respectivement lors des deux examens de contrôle concordaient étroitement : à une exception près, les enfants dont les ganglions lymphatiques étaient pratiquement normaux lors du premier examen, effectué dix semaines après la vaccination, se présentaient dans les mêmes conditions un an plus tard ; d'autre part, tous les enfants qui avaient des ganglions lymphatiques hypertrophiés et adhérents dix semaines après la vaccination accusaient une fistulisation lors de l'examen pratiqué une année plus tard.

La dimension de la lésion vaccinale dépendait aussi de la dose de vaccin administrée et de l'âge de l'enfant : elle était d'autant plus grande que l'enfant était plus jeune et que la dose administrée avait été plus forte. Le degré de sensibilité à la tuberculine n'était en revanche influencé que dans une faible mesure par l'importance de la dose injectée, et dans une mesure plus faible encore par l'âge de l'enfant.

On a observé que la dimension de la papule produite par l'injection intradermique du vaccin variait avec l'âge du sujet et avec la profondeur de l'injection tout autant qu'en fonction du volume de vaccin injecté. Il ne fait aucun doute qu'en évaluant la quantité de vaccin administrée d'après la dimension de la papule, plutôt que d'après la graduation d'une seringue parfaitement étanche, on pèche contre la précision et l'on risque de tomber dans l'erreur. Lorsqu'il est possible de mesurer exactement la dose administrée, on peut inoculer un vaccin plus concentré (et éventuellement conférer ainsi une plus forte immunité) sans qu'il en résulte une fréquence inadmissible d'adénites suppurées.

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APPENDIX TABLE I. STUDY POPULATION BY VACCINATION PROCEDURE AND YEAR OF BIRTH *

Year of birth	Superficial injection					Deep injection				Total
	1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)		
	0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	
1945	11	17	17	16	19	14	13	18	17	142
1946	29	35	21	32	31	22	20	35	30	255
1947	32	29	24	34	31	37	34	40	27	288
1948	20	23	39	15	30	24	29	29	27	236
1949	34	24	22	29	38	23	45	31	28	274
1950	21	17	30	26	31	34	31	30	25	245
1951	22	29	31	25	32	37	29	29	31	265
1952	1	1	—	4	2	3	—	1	2	14
Total vaccinated	170	175	184	181	214	194	201	213	187	1,719
10 TU tuberculin tests given and read at:										
10 weeks	110	122	117	112	130	116	120	139	106	1,072
1 year	120	144	136	124	156	141	142	155	138	1,256
Vaccinal lesions examined at:										
10 weeks	136	156	154	151	175	156	159	180	149	1,416
1 year	158	173	181	170	208	184	196	203	174	1,647
Lymph-node examinations at:										
10 weeks	136	156	153	151	173	156	159	181	149	1,414
1 year	158	174	181	170	208	183	195	202	174	1,645

*** The vaccinations were carried out between 8 and 29 November 1952.**

APPENDIX TABLE II. DISTRIBUTIONS BY SIZE OF WHEALS ACCORDING TO VOLUME AND DEPTH OF INJECTION OF VACCINE AND YEAR OF BIRTH OF CHILD *

Size of wheal (mm)	0.20 ml injected								0.10 ml injected				0.05 ml injected							
	superficial injection				deep injection				superficial injection				superficial injection				deep injection			
	year of birth				year of birth				year of birth				year of birth				year of birth			
	1952-51	1950-49	1948-47	1946-45	1952-51	1950-49	1948-47	1946-45	1952-51	1950-49	1948-47	1946-45	1952-51	1950-49	1948-47	1946-45	1952-51	1950-49	1948-47	1946-45
0	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	1	1	3	2
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3	2	1	—
3	—	—	—	—	5	2	2	1	—	—	—	—	—	—	—	—	12	18	11	8
4	—	—	—	—	23	18	9	4	—	—	1	—	16	4	2	1	36	80	47	21
5	1	1	—	1	27	50	45	20	1	—	—	—	39	67	48	23	8	23	42	35
6	12	10	4	1	12	31	41	31	16	16	4	—	8	46	64	55	2	3	11	9
7	16	30	11	2	—	8	27	20	8	20	36	31	—	3	8	8	—	—	—	2
8	15	46	46	27	—	2	2	9	—	4	11	17	—	—	—	—	—	—	—	—
9	1	17	36	45	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—	—
10	—	2	3	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	45	106	100	86	67	111	126	86	25	40	52	51	63	120	122	87	62	127	115	77
Mean size	7.1	7.7	8.2	8.7	4.7	5.3	5.7	6.0	6.3	6.7	7.1	7.5	4.9	5.4	5.6	5.8	3.8	4.0	4.3	4.6
Standard deviation	0.9	0.9	0.8	0.8	0.9	0.9	1.0	1.3	0.5	0.6	0.7	0.6	0.6	0.6	0.6	0.6	0.9	0.8	1.1	1.2

*** Results for 51 children are not included because the vaccinator noted a deviation from the prescribed volume.**

APPENDIX

DISTRIBUTIONS BY SIZE OF REACTIONS TO INTRADERMAL 10 TU TUBERCULIN TEST 10

Size of induration (mm)	10 weeks								
	superficial injection					deep injection			
	1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)	
	0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml
0	—	—	—	—	—	—	—	—	1
1	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—
3	—	—	—	—	1	—	—	—	1
4	—	—	—	—	—	—	—	—	—
5	—	—	—	—	1	—	—	—	1
6	—	—	1	—	—	—	2	1	—
7	—	—	—	1	1	—	—	1	4
8	—	—	—	—	2	1	2	—	5
9	4	3	5	4	11	3	4	5	7
10	12	11	12	10	22	6	11	17	13
11	10	8	8	23	11	6	13	14	12
12	13	15	22	15	14	12	25	17	13
13	17	21	21	21	26	19	13	28	22
14	7	21	8	9	12	11	8	13	7
15	9	8	9	6	7	13	9	9	4
16	18	13	11	13	10	13	15	10	5
17	10	10	11	3	7	17	8	12	7
18	3	5	3	5	2	5	5	8	2
19	5	4	2	1	2	6	2	2	1
20	2	2	3	—	—	3	—	1	—
21	—	1	—	1	1	—	3	—	1
22	—	—	1	—	—	1	—	1	—
23	—	—	—	—	—	—	—	—	—
24	—	—	—	—	—	—	—	—	—
25	—	—	—	—	—	—	—	—	—
26	—	—	—	—	—	—	—	—	—
27	—	—	—	—	—	—	—	—	—
28	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—
30	—	—	—	—	—	—	—	—	—
31	—	—	—	—	—	—	—	—	—
32	—	—	—	—	—	—	—	—	—
33	—	—	—	—	—	—	—	—	—
34	—	—	—	—	—	—	—	—	—
35	—	—	—	—	—	—	—	—	—
> 35	—	—	—	—	—	—	—	—	—
Number tested	110	122	117	112	130	116	120	139	106
Number not tested	60	53	67	69	84	78	81	74	81
Total vaccinated	170	175	184	181	214	194	201	213	187
Mean size	13.8	13.9	13.5	13.0	12.5	14.5	13.3	13.3	12.0
Standard deviation	2.8	2.7	2.9	2.5	2.9	2.8	3.0	2.8	3.3

TABLE III.
WEEKS AND ONE YEAR AFTER VACCINATION, ACCORDING TO VACCINATION PROCEDURE

1 year									Size of induration (mm)
superficial injection					deep injection				
1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)		
0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	
—	—	—	—	3	—	—	—	1	0
—	—	—	—	—	—	—	—	—	1
—	1	—	1	—	—	1	1	—	2
1	—	—	—	1	—	—	—	—	3
—	—	—	—	3	—	—	—	1	4
1	1	—	—	—	—	—	—	—	5
—	—	2	1	1	1	—	—	—	6
1	—	2	1	2	—	—	1	2	7
—	—	1	1	5	1	—	—	4	8
—	1	2	1	4	1	2	2	5	9
2	2	2	2	8	3	4	3	10	10
2	5	1	2	5	3	3	7	8	11
2	6	2	3	15	1	4	5	3	12
3	2	5	8	6	—	6	7	5	13
6	9	12	6	14	10	14	14	5	14
5	11	8	11	6	5	6	17	7	15
12	13	16	11	11	8	4	14	17	16
10	10	8	13	13	14	9	8	11	17
14	11	11	10	14	14	11	17	10	18
8	10	13	7	6	9	15	10	13	19
5	7	3	7	7	10	10	14	5	20
6	21	8	9	9	17	16	5	13	21
9	11	14	10	7	6	7	7	7	22
8	7	5	3	3	4	8	6	4	23
10	3	8	5	6	6	3	4	—	24
7	2	4	3	2	10	5	1	3	25
5	2	1	2	3	9	5	3	2	26
1	4	3	3	—	2	2	3	1	27
2	2	4	3	1	1	3	3	—	28
—	1	—	—	—	3	1	1	1	29
—	—	—	—	—	—	2	—	—	30
—	1	1	1	—	—	—	—	—	31
—	1	—	—	—	1	1	—	—	32
—	—	—	—	—	—	—	—	—	33
—	—	—	—	—	—	—	2	—	34
—	—	—	—	—	1	—	—	—	35
—	—	—	—	1 *	1 **	—	—	—	> 35
120	144	136	124	156	141	142	155	138	Number tested
50	31	48	57	58	53	59	58	49	Number not tested
170	175	184	181	214	194	201	213	187	Total vaccinated
19.0	18.5	18.3	18.0	15.6	19.8	18.8	17.6	16.3	Mean size
4.8	4.8	4.9	4.9	5.6	5.2	5.0	5.0	5.0	Standard deviation

* 36 mm ** 40 mm

APPENDIX
DISTRIBUTIONS BY SIZE OF VACCINAL LESIONS 10 WEEKS AND ONE

Size (mm)	10 weeks (induration)								
	superficial injection					deep injection			
	1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)	
	0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml
0	—	—	—	—	1	—	—	—	—
1	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—
3	—	—	—	—	3	—	—	—	1
4	—	—	1	—	15	—	—	—	—
5	—	1	5	4	17	—	1	1	4
6	1	1	3	4	19	—	—	—	5
7	2	11	7	12	30	—	2	2	12
8	5	12	12	15	28	—	3	4	17
9	16	24	20	26	20	8	16	11	20
10	7	10	16	20	12	4	12	8	14
11	10	22	22	7	11	10	14	18	13
12	11	18	16	10	5	12	11	17	12
13	18	14	25	20	6	17	34	27	13
14	17	20	9	7	4	20	24	19	12
15	15	7	4	10	1	12	14	10	4
16	10	8	7	6	1	21	11	24	8
17	8	3	3	4	2	15	5	17	4
18	4	1	1	3	—	11	5	10	4
19	4	1	3	1	—	13	5	3	2
20	3	1	—	1	—	8	1	6	1
21	2	2	—	—	—	1	1	2	2
22	1	—	—	1	—	2	—	—	—
23	—	—	—	—	—	2	—	—	—
24	—	—	—	—	—	—	—	1	—
25	—	—	—	—	—	—	—	—	1
> 25	2*	—	—	—	—	—	—	—	—
Number tested	136	156	154	151	175	156	159	180	149
Number not tested	34	19	30	30	39	38	42	33	38
Total vaccinated	170	175	184	181	214	194	201	213	187
Mean size	13.5	11.6	11.1	11.0	7.9	15.1	13.0	13.9	11.2
Standard deviation	3.8	3.1	3.0	3.4	2.9	3.2	2.9	3.2	3.8

* 26 mm and 30 mm

TABLE IV.
YEAR AFTER VACCINATION, ACCORDING TO VACCINATION PROCEDURE

1 year (scar)									Size (mm)
superficial injection					deep injection				
1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)		
0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	
—	—	—	—	—	—	1	—	3	0
—	—	1	1	12	—	1	1	5	1
4	3	8	23	74	5	19	18	39	2
7	15	34	48	85	27	55	42	64	3
31	60	63	63	28	43	57	72	38	4
37	44	43	31	9	45	39	35	13	5
42	32	23	2	—	27	10	17	8	6
27	15	6	2	—	17	5	6	3	7
6	2	2	—	—	12	4	8	—	8
3	1	1	—	—	4	2	—	—	9
—	1	—	—	—	1	3	1	1	10
—	—	—	—	—	1	—	2	—	11
—	—	—	—	—	—	—	1	—	12
1	—	—	—	—	1	—	—	—	13
—	—	—	—	—	—	—	—	—	14
—	—	—	—	—	—	—	—	—	15
—	—	—	—	—	—	—	—	—	16
—	—	—	—	—	—	—	—	—	17
—	—	—	—	—	—	—	—	—	18
—	—	—	—	—	—	—	—	—	19
—	—	—	—	—	—	—	—	—	20
—	—	—	—	—	1	—	—	—	21
—	—	—	—	—	—	—	—	—	22
—	—	—	—	—	—	—	—	—	23
—	—	—	—	—	—	—	—	—	24
—	—	—	—	—	—	—	—	—	25
—	—	—	—	—	—	—	—	—	> 25
158	173	181	170	208	184	196	203	174	Number tested
12	2	3	11	6	10	5	10	13	Number not tested
170	175	184	181	214	194	201	213	187	Total vaccinated
5.5	4.9	4.4	3.7	2.8	5.2	4.1	4.3	3.3	Mean size
1.5	1.3	1.3	1.1	0.9	2.1	1.6	1.7	1.4	Standard deviation

APPENDIX

LYMPH-NODE FINDINGS IN LEFT AND RIGHT AXILLA AT 10 WEEKS AND AT

Lymph-node findings		Left axilla								
		superficial injection					deep injection			
		1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)	
		0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml
		10 weeks after vaccination								
Negligible	no palpable nodes	62	78	78	85	98	78	96	100	100
	micro-adenitis	17	21	15	27	38	19	23	34	26
	pea	32	30	34	24	27	23	24	30	14
Enlarged, not adherent to skin	bean	19	21	23	15	9	28	16	15	9
	hazel-nut	5	4	2	—	1	6	—	2	—
	plum	—	1	—	—	—	1	—	—	—
Enlarged and adherent to skin	bean	—	—	—	—	—	—	—	—	—
	hazel-nut	1	—	—	—	—	1	—	—	—
	plum	—	1	1	—	—	—	—	—	—
Number examined		136	156	153	151	173	156	159	181	149
Number not examined		34	19	31	30	41	38	42	32	38
Total vaccinated		170	175	184	181	214	194	201	213	187
		1 year after vaccination								
Negligible	no palpable nodes	144	154	171	156	188	164	184	187	162
	micro-adenitis	9	10	6	10	18	9	8	10	11
	pea	2	5	2	4	2	1	3	3	1
Enlarged, not adherent to skin	bean	—	1	1	—	—	—	—	—	—
	hazel-nut	—	1	—	—	—	—	—	—	—
	plum	—	—	—	—	—	—	—	—	—
Enlarged and adherent to skin	bean	—	—	—	—	—	3	—	—	—
	hazel-nut	—	1	—	—	—	—	—	—	—
	plum	—	—	—	—	—	1	—	—	—
Perforated		3	2	1	—	—	5	—	2	—
Number examined		158	174	181	170	208	183	195	202	174
Number not examined		12	1	3	11	6	11	6	11	13
Total vaccinated		170	175	184	181	214	194	201	213	187

*** One child in this group was examined at 10 weeks in the left axilla only.**

TABLE V.
ONE YEAR AFTER VACCINATION, ACCORDING TO VACCINATION PROCEDURE

Right axilla									Lymph-node findings	
superficial injection					deep injection					
1/1 standard strength vaccine (0.75 mg/ml)			1/4 standard strength vaccine (0.19 mg/ml)		1/1 standard strength vaccine (0.75 mg/ml)		1/4 standard strength vaccine (0.19 mg/ml)			
0.20 ml	0.10 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml	0.20 ml	0.05 ml		
10 weeks after vaccination										
110	120	128	125	140	125	130	146	121	no palpable nodes	Negligible
23	29	18	21	27	24	24	25	20	micro-adenitis	
3	7	5	5	6	5	5	10	7	pea	
—	—	1	—	—	2	—	—	1	bean	Enlarged, not adherent to skin
—	—	—	—	—	—	—	—	—	hazel-nut	
—	—	—	—	—	—	—	—	—	plum	
—	—	—	—	—	—	—	—	—	bean	Enlarged and adherent to skin
—	—	—	—	—	—	—	—	—	hazel-nut	
—	—	—	—	—	—	—	—	—	plum	
136	156	152*	151	173	156	159	181	149	Number examined	
34	19	32	30	41	38	42	32	38	Number not examined	
170	175	184	181	214	194	201	213	187	Total vaccinated	
1 year after vaccination										
155	168	177	161	197	177	191	198	170	no palpable nodes	Negligible
3	4	4	8	10	6	4	3	4	micro-adenitis	
—	2	—	1	1	—	—	1	—	pea	
—	—	—	—	—	—	—	—	—	bean	Enlarged, not adherent to skin
—	—	—	—	—	—	—	—	—	hazel-nut	
—	—	—	—	—	—	—	—	—	plum	
—	—	—	—	—	—	—	—	—	bean	Enlarged and adherent to skin
—	—	—	—	—	—	—	—	—	hazel-nut	
—	—	—	—	—	—	—	—	—	plum	
—	—	—	—	—	—	—	—	—	Perforated	
158	174	181	170	208	183	195	202	174	Number examined	
12	1	3	11	6	11	6	11	13	Number not examined	
170	175	184	181	214	194	201	213	187	Total vaccinated	