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BCG vaccination of children against leprosy: nine-year findings of the controlled WHO trial in Burma *

L. M. BECHELLI,[1] KYAW LWIN,[2] P. GALLEGO GARBAJOSA,[3] MG MG GYI,[4] K. UEMURA,[5] T. SUNDARESAN,[6] C. TAMONDONG,[7] M. MATEJKA,[8] H. SANSARRICQ,[9] & J. WALTER [10]

The leprosy incidence rates so far in the vaccinated and unvaccinated children aged 5–9 and 10–14 years are similar. The BCG-vaccinated children aged 0–4 years at intake had an incidence rate lower than that of children in the control group. BCG vaccination did not protect household contacts or children aged 5–14 years not exposed in the household, and did not influence the distribution of the forms of leprosy in the cases detected. The lepromin reaction in relation to the age at intake was consistently stronger in the vaccinated children than in those of the control group; the younger the age group the more pronounced was the difference, which was only slight in the age group 10–14 years at intake. If the results of the late lepromin reaction are related to the age at onset (when the children are older than at intake), the differences between the BCG and the control groups tend to decrease. It does not seem that the BCG-vaccinated children suffer from a less serious form of leprosy than the nonvaccinated children (most of them nonreactors to tuberculin).

The results of this WHO trial after 4 years and 7 years have been published before (1–3), as well as a comparison of the results with those from the Uganda and Karimui trials, and a summary of the technical outline (2).

The present report describes the latest findings after approximately 9 years of field work. Although the data provided here are provisional and minor changes may be necessary after the final analysis, it is not expected that the main conclusions will change. Some emphasis will be given to the results among children aged 0–4 years at intake, on whom BCG had conferred, up to the end of June 1971, a protection of 44% that applied only to early cases of leprosy, the great majority being tuberculoid cases.

MATERIAL AND RESULTS

At the end of March 1973, a total of 28 220 children (less than 14 years of age) had been included in the trial. By this time they had been subjected to varying periods of follow-up, with a minimum of 5 years and a maximum of 8 years, which amounted to approximately 83 283 and 82 978 person-years of observation for the BCG and control groups respectively. A total of 768 cases of leprosy developed during this period, 425 in the control group and 343 in the BCG-vaccinated children, giving incidence rates of 5.1 and 4.1, respectively, per 1 000 person-years of observation in the two groups.

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[1] Formerly Chief Medical Officer, Leprosy, WHO, Switzerland. Present address: Professor of Dermatology, Faculdade de Medicina de Ribeirão Preto, University of São Paulo, Brazil.

[2] Assistant Director of Health Services (Leprosy Control), Rangoon, Burma.

[3] Team Leader, WHO Leprosy BCG Trial, Burma.

[4] National Counterpart Team Leader, Leprosy Team, Mandalay, Burma.

[5] Chief Statistician, Health Statistical Methodology, WHO, Geneva, Switzerland.

[6] Statistician, Health Statistical Methodology, WHO, Geneva, Switzerland.

[7] Statistician, WHO Leprosy BCG Trial, Burma.

[8] Former Scientist, WHO Leprosy BCG Trial, Burma.

[9] Chief Medical Officer, Leprosy, WHO, Geneva, Switzerland.

[10] Medical Officer, Leprosy, WHO, Geneva, Switzerland.

Table 1. Number of cases and protection in each follow-up

Follow-up No.	No. of cases		Protection (%)
	BCG group	control group	
1	82	71	-15
2	70	89	21
3	61	80	24
4	55	68	19
5	31	53	42
6	26	25	-4
7	11	24	54
8	7	15	53

The protective effect of BCG vaccination is calculated to be about 20% (with the 95% confidence interval ranging from 7% to 31%). Analysis by follow-ups is shown in Table 1. Valid comparisons can be made only on the results of the first 5 follow-ups, since only a part of the study population had been subjected to more than 5 follow-up examinations. In the first follow-up, fewer cases were detected in the control group than in the BCG group, but the difference was not statistically significant. Thus, the higher figure in the BCG group may be a chance occurrence or may reflect some boosting effect of the vaccine. A consistent protection of the order of 20% was seen during the second, third, and fourth follow-ups. It is difficult to state at this stage whether the 42% protection seen during the fifth follow-up will be maintained during subsequent follow-ups.

An attempt has been made to analyse whether covariables such as the tuberculin reaction at intake and the sex and age at intake could have a bearing on the differential incidence in the two groups (Table 2).

Tuberculin reaction at intake

It is well known that the proportion of reactors to the tuberculin test increases with age. An attempt has been made to compare the incidence in different tuberculin reaction groups within each age group. Unfortunately, when such a detailed breakdown is attempted, the number of cases in each of the subcategories becomes rather small and does not permit valid conclusions. Further, the analysis is only by tuberculin reaction at intake. Many of the children in the control group who were nonreactors at intake may have become reactors subsequently. Nevertheless, it is believed that if natural infection (indicated by tuberculin reactions of 10 mm or more) by the tubercle bacilli causes substantial protection against leprosy, this would appear from the data. The observations do not seem to support this hypothesis. The children with intermediate-sized reactions to the tuberculin test (reactions of 5–9 mm), who may be presumed to have been infected by nonpathogenic mycobacteria, behave more or less in the same way. In conclusion, the status of the tuberculin reaction at intake does not appear to have had much influence on the subsequent development of leprosy, either in the control or in the BCG groups.

Sex distribution

In the BCG group, leprosy has so far been detected in 171 males and 172 females. The corresponding numbers in the control group are 220 and 205. A further analysis of the sex differences in the incidence by age groups did not reveal any consistent pattern and it may be concluded that from the data so far available there is no evidence that BCG vaccination has a different protective effect on the two sexes.

Age at intake

The highest protection (38%) was observed in the children aged 0–4 years at intake and is statistically significant. The observed protection in the other age groups was much lower and not statistically significant (Table 2).

Classification of new cases in relation to tuberculin reaction at intake [a]

In the control group, the distribution of the forms of leprosy was similar in children with tuberculin reactions of 0–9 mm and 10 mm (Table 3). In children with tuberculin reactions of 0–9 mm, whether they were vaccinated or not, the distribution of the forms of leprosy was similar. With regard to the 2 tuberculin-reactive subgroups (56 of 343 cases arising in the vaccinated children, and 66 of 425 cases arising among unvaccinated children), a statistically significant difference is observed in the frequency of T and I forms, which suggests that BCG vaccination after a natural infection apparently stimulated the

[a] The following designations are used throughout this report: B, borderline; I, indeterminate; I→T?, indeterminate with a possible trend towards tuberculoid; L, lepromatous; T, tuberculoid; Tr, tuberculoid in reaction.

Table 2. Provisional estimates of leprosy incidence and 95% confidence limits for the percentage decrease in the vaccinated group

At intake		Control group			Vaccinated group			Decrease	95% conf. limits	
age group (years)	Mantoux reaction (mm)	person-years	incidence	rate (%)	person-years	incidence	rate (%)	(%)	lower	upper
0–4	0–4	27 174	70	2.58	27 300	48	1.76	31.7	1.6	53.9
	5–9	2 583	18	6.97	2 550	6	2.35	66.2	24.6	92.0
	0–9	29 757	88	2.96	29 850	54	1.81	38.8	14.5	57.5
	10 +	855	1	1.17	882	2	2.27	...	...	...
	all	32 725	89	2.72	33 201	56	1.69	38.0	13.6	56.7
5–9	0–4	18 347	110	6.00	18 256	96	5.26	12.3	−15.9	34.0
	5–9	8 089	56	6.92	8 138	41	5.04	27.2	− 9.0	52.7
	0–9	26 436	166	6.28	26 394	137	5.19	17.3	− 4.0	34.6
	10 +	3 437	26	7.57	3 494	26	7.44	1.6	−73.9	44.4
	all	29 873	192	6.43	29 902	163	5.45	15.2	− 4.8	31.6
10–14	0–4	8 022	57	7.11	7 591	57	7.51	−5.7	−54.4	27.7
	5–9	6 621	48	7.25	6 842	39	5.70	21.4	−20.7	49.8
	0–9	14 643	105	7.17	14 433	96	6.65	7.2	−23.0	30.3
	10 +	5 729	39	6.81	5 748	28	4.87	28.4	−16.3	57.8
	all	20 381	144	7.07	20 181	124	6.14	13.0	−11.0	32.2
all	0–4	53 543	237	4.43	53 146	201	3.78	14.6	− 3.4	29.6
	5–9	17 293	122	7.06	17 827	86	4.82	31.6	9.8	48.9
	0–9	70 836	359	5.07	70 973	287	4.04	20.2	6.6	32.0
	10 +	10 019	66	6.59	10 124	56	5.53	16.0	−20.6	42.2
	all	82 978	425	5.12	83 283	343	4.12	19.6	7.1	30.6

Table 3. Classification of new cases in the vaccinated and control groups in relation to the tuberculin status at intake. Data up to the end of March 1973 [a]

Group	Tuberculin reaction (mm)	Forms of leprosy					Total
		T	Tr	I	I → T?	B	
BCG	0–9	176 (61.3)	4 (1.4)	76 (26.5)	31 (10.8)	0	287 (100.0)
	⩾ 10	50 (89.3)	1 (1.8)	3 (5.3)	1 (1.8)	1 (1.8)	56 (100.0)
	total	226 (65.9)	5 (1.5)	79 (23.0)	32 (9.3)	1 (0.3)	343 (100.0)
Control	0–9	228 (63.5)	11 (3.1)	91 (25.3)	29 (8.1)	0	359 (100.0)
	⩾ 10	40 (60.6)	1 (1.5)	21 (31.8)	4 (6.1)	0	66 (100.0)
	total	268 (63.1)	12 (2.8)	112 (26.3)	33 (7.8)	0	425 (100.0)

[a] Percentages are given in parentheses.

Table 4. Late lepromin (Mitsuda) reaction in new cases in the vaccinated and control groups in relation to the tuberculin reaction at intake. Data up to the end of March 1973

Lepromin reaction	Tuberculin reaction 0–9 mm				Tuberculin reaction ⩾ 10 mm			
	BCG		control		BCG		control	
	No.	percentage of total	No.	percentage of total	No.	percentage of total	No.	percentage of total
– or +	6	2.1	14	4.0	1	1.8	3	4.7
+	54	19.0	110	31.7	8	14.5	13	20.3
++	50	17.6	63	18.2	3	5.5	8	12.5
+++	174	61.3	160	46.1	43	78.2	40	62.5
total	284	100.0	347	100.0	55	100.0	64	100.0
not read[a]	3		12		1		2	

[a] Seventeen cases (14 in the control group and 3 in the BCG group) were discovered in March 1973 for which the late lepromin (Mitsuda) reactions were not yet read. One case (an I→T? discovered in October 1966) died in 1966 before the late lepromin reading could be made.

evolution of I forms towards T leprosy. Up to the end of June 1973, no L cases appeared in either the vaccinated or unvaccinated children.

At registration, there was 1 B case in the BCG group; during the follow-ups, 1 case evolved to B in the BCG group and also 1 in the control group.

Incidence and forms of leprosy in children with tuberculin reactions of 5–9 mm

A possible sensitization by acid-fast nonpathogenic organisms did not appear to influence the rates and the forms of leprosy in children whether they were vaccinated or not.

Late lepromin reaction

A higher proportion of stronger lepromin reactions (3+) was found among BCG-vaccinated children and among those with tuberculin reactions of >10 mm (Table 4). These results and other factors suggest that BCG and a natural infection had some influence on the Mitsuda reaction. In the control group, children with tuberculin reactions of 0–9 mm and $\geqslant 10$ mm had 4–5% of negative or doubtful lepromin reactions; among BCG-vaccinated children, the proportions were around 2%.

In relation to the forms of leprosy. 6% of I cases in the control group and 5% of the BCG group had a negative or doubtful Mitsuda reaction (Table 5).

New cases according to household status

The incidence among household contacts is about 3.2 times that among others, irrespective of BCG vaccination (Table 6). The observed protection among BCG-vaccinated children is of the order of 20% whether these children are household contacts or not.

Cases positive for mycobacteria

Of the 343 cases detected in the BCG group up to the end of March 1973, 5 (1.5%) were positive at registration or in the annual follow-up examination; for the control group the figure was 13 (3.1%) of 425 cases. The difference is not significant. The difference would be smaller if only negative, doubtful, or 1+ lepromin reactions were considered: bacterial positivity in 5 and 8 cases, respectively, in the BCG and control groups. In fact, in the control group the lepromin reaction was 2+ in two patients and 3+ in 3; a favourable prognosis could be expected in these patients. Very often the bacterial positivity was observed only in one annual examination.

A negative or doubtful lepromin reaction was seen in 7 cases from the BCG group and in 17 from the control group, 3 and 4 of these, respectively, being bacterially positive. Of 62 cases in the BCG group and 123 in the control group showing 1+ reactions, 2 and 4, respectively, had positive smears.

Table 5. Late lepromin (Mitsuda) reaction in new cases in the vaccinated and control groups in relation to the forms of leprosy. Data up to the end of March 1973[a]

Group	Forms of leprosy	Lepromin reaction					Not read[b]
		− or ±	+	++	+++	total	
BCG	T	2 (0.9)	38 (17.0)	33 (14.8)	150 (67.3)	223 (100.0)	3
	Tr	0	0	2	3	5	0
	I	4 (5.1)	21 (26.6)	11 (13.9)	43 (54.4)	79 (100.0)	0
	I→T?	0 (0)	3 (9.7)	7 (22.6)	21 (67.7)	31 (100.0)	1
	B	1	0	0	0	1	0
	total	7 (2.1)	62 (18.3)	53 (15.6)	217 (64.0)	339 (100.0)	4
control	T	7 (2.8)	68 (26.8)	42 (16.5)	137 (53.9)	254 (100.0)	14
	Tr	3	4	2	3	12	0
	I	7 (6.2)	41 (36.6)	17 (15.2)	47 (42.0)	112 (100.0)	0
	I→T?	0 (0)	10 (30.3)	10 (30.3)	13 (39.4)	33 (100.0)	0
	total	17 (4.1)	123 (29.9)	71 (17.3)	200 (48.7)	411 (100.0)	14

[a] Percentages are given in parentheses.
[b] See footnote in Table 4.

In addition, of the 13 cases with bacterial positivity in the control group, 3 were T, 9 Tr, and 1 I→T?.

The epidemiological significance of the bacterial findings seems to be rather limited.

Leprosy cases in the trial groups among children 0–4 years at intake by age at onset

Up to the end of March 1973, it appeared that the number of leprosy cases in children of the control group was higher than in the BCG-vaccinated children only when they were 3 or 4 years old at intake; below 3 years, the figures were similar in both groups (Table 7). On the whole, 38% protection was found in these children aged 0–4 years at intake and this limited protection became manifest when these children were over 5 years of age.

When these findings were related to the forms of leprosy (Table 8), the proportion of T cases (about 70%) and other forms of leprosy was similar in both groups. It also appeared that the greater number

Table 6. Number of leprosy cases and rates per 1000 person-years in the vaccinated and control groups among household contacts and other children up to the end of March 1973[a]

Group	Household contacts			Other children		
	No. of person-years of observation	No. of leprosy cases	rate/1000	No. of person-years of observation	No. of leprosy cases	rate/1000
BCG	8 911	96	10.8	74 372	247	3.3
control	8 713	114	13.1	74 265	311	4.2

[a] Person-years of observation used as denominators for calculating the rates are person-years of observation until June 1971 only.

Table 7. Leprosy cases in trial groups 0–4 years old at intake up to the end of March 1973 by age at onset

Age at intake (years)	Age at onset (years)	No. of cases	
		BCG group	control group
0–1	1–	0	0
	2–	0	0
	3–	2	0
	4–	1	3
	5–	1	3
	6–	0	1
	7–	0	0
	8–	1	0
	total	5	7
1–2	2–	0	0
	3–	0	0
	4–	1	1
	5–	2	2
	6–	0	1
	7–	2	1
	8–	2	1
	total	7	6
2–3	3–	1	0
	4–	1	2
	5–	2	2
	6–	3	3
	7–	2	2
	8–	1	2
	9–	0	1
	10–	1	1
	total	11	13
3–4	4–	1	3
	5–	1	5
	6–	0	3
	7–	3	4
	8–	3	6
	9–	3	1
	10–	0	1
	11–	1	1
	total	12	24
4	5–	6	4
	6–	5	9
	7–	4	7
	8–	2	8
	9–	3	3
	10–	0	5
	11–	1	2
	12–	0	1
	total	21	39

Table 8. Leprosy cases in trial groups 0–4 years old at intake up to the end of March 1973 by the form of leprosy

Age at intake (years)	Trial group	Form of leprosy				Total
		T	I	I → T?	Tr	
0–1	BCG	4	1	0	0	5
	control	7	0	0	0	7
1–2	BCG	6	0	0	1	7
	control	5	1	0	0	6
2–3	BCG	7	4	0	0	11
	control	8	4	1	0	13
3–4	BCG	8	2	2	0	12
	control	18	4	2	0	24
4	BCG	14	5	2	0	21
	control	25	9	5	0	39
0–4	BCG	39	12	4	1	56
	control	63	18	8	0	89

of patients in the control group consisted mainly of T cases.

DISCUSSION AND CONCLUSIONS

After 9 years of field study and 8 annual follow-up examinations, BCG vaccination has conferred relatively low protection (38% reduction in the incidence) only to children 0–4 years at intake and this applied only to early cases, the great majority tuberculoid; 2 years ago, the protection to the same group of children was 44%. The rates are only slightly higher in unvaccinated children $\geqslant$5 years old at intake.

When other factors are considered—forms of leprosy, bacterial status, lepromin reactivity, evolution of cases, and level of endemicity—it seems that the importance of the findings on incidence is greatly reduced. Up to now, not a single L case has appeared among children in either group, probably because all detected cases received treatment (often carried out irregularly by the patients).

The protective effect of BCG has to be substantial to warrant its large-scale use for immunization against leprosy. From the results so far, including previous findings (3), it seems unlikely that BCG could affect substantially the pattern or trend of the disease in the trial area or in other areas with similar characteristics. It would therefore be premature to recommend nationwide BCG vaccination of children 0–4 years old with the aim of preventing leprosy or of affecting its trend.

RÉSUMÉ

VACCINATION D'ENFANTS PAR LE BCG CONTRE LA LÈPRE: RÉSULTATS APRÈS 9 ANS DE L'ESSAI CONTRÔLÉ DE L'OMS EN BIRMANIE

Les auteurs rapportent les observations faites au cours des 9 premières années de l'essai OMS de prévention de la lèpre par le BCG organisé en Birmanie en 1964.

A la fin de mars 1973, l'essai avait porté sur un total de 28 220 enfants âgés de moins de 14 ans. Durant cette période, on a enregistré 768 cas de lèpre: 343 chez les enfants vaccinés et 425 chez les enfants témoins, soit respectivement une incidence de 4,1 et de 5,1 pour 1 000 sujet-années d'observation. L'effet protecteur de la vaccination a atteint environ 20% (avec des intervalles de confiance 95% variant de 7% à 31%).

Chez les témoins comme chez les vaccinés, la réactivité à la tuberculine au moment de la prise en charge n'a guère eu d'influence sur l'apparition ultérieure de la lèpre. Le taux de protection le plus élevé (38%), statistiquement significatif, s'est manifesté chez les enfants âgé de 0 à 4 ans au début de l'essai. Dans les autres groupes d'âge, le degré de protection a été beaucoup plus faible et sans signification statistique. Jusqu'à présent, aucun fait ne plaide en faveur d'une influence du sexe sur l'effet protecteur du BCG.

En ce qui concerne la classification des nouveaux cas, on a noté dans le groupe témoin une répartition similaire des formes de lèpre chez les enfants présentant une réaction tuberculinique de 0-9 mm ou >10 mm. La répartition était aussi semblable chez les enfants, vaccinés ou non, dont la réaction était de 0-9 mm. Aucun cas de lèpre lépromateuse n'a été constaté, jusqu'en juin 1973, parmi les enfants, vaccinés ou non. D'après les observations faites, il semble que le BCG ou une infection tuberculeuse naturelle influencent dans une certaine mesure les résultats de la réaction de Mitsuda. L'incidence de la lèpre a été environ 3,2 fois plus élevée parmi les contacts familiaux que parmi les autres enfants, indépendamment de la vaccination par le BCG. Le taux de protection chez les enfants vaccinés a été de l'ordre de 20%, qu'ils aient été exposés ou non à la contagion familiale. Quelques cas de lèpre, dans le groupe BCG et dans le groupe témoin, étaient bactériologiquement positifs, leur nombre ne différant pas de manière statistiquement significative.

A la lumière des résultats obtenus jusqu'à présent, il semble improbable que la vaccination par le BCG puisse modifier les aspects actuels ou futurs de la lèpre dans la région de l'essai ou dans des régions à caractéristiques semblables. Il semble prématuré de conseiller la vaccination au BCG des enfants de 0 à 4 ans à l'échelle nationale en vue de prévenir la lèpre ou d'agir sur les tendances de la maladie.

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