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Revaccination with BCG: its effects on skin tests in Kuwaiti senior school children

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Revaccination with BCG: its effects on skin tests in Kuwaiti senior school children. M.A. Shaaban, M. Abdul Ati, G.M. Bahr, J.L. Stanford, D.N.J. Lockwood, I.C. McManus.

ABSTRACT: Following a policy of BCG vaccination adopted in Kuwait more than 20 yrs ago, children receive their first vaccination just before starting school. Those who have a response of less than 10 mm induration to 2 tu of RT23 PPD, when they are 13 yrs old, are revaccinated. The effects of this revaccination on skin test positivity in a group of 18 yr old senior school children have been investigated. In a random study group 23% were found to have received BCG a second time. Revaccination resulted in a significant increase in positivity to tuberculin, and to the other 6 reagents tested, that was much more than would have been expected due to the passage of time alone in low responders. Scars of the second BCG vaccination were larger than those after the first vaccination, and showed a sex difference, with scars being significantly larger in boys than in girls. Boys also tended to show the largest responses to skin tests, with the notable exception of tuberculin to which girls showed the largest response. In most cases responses to skin tests were larger after revaccination than after a single vaccination. Based on this study, it is impossible to be sure that revaccination improved protective immunity, but the increase in tuberculin responsiveness, and recognition of environmental mycobacterial species may be indirect evidence supporting this conclusion.

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Very little is known of the long-term effects of revaccination with BCG. It is often advocated without there being any evidence that it is beneficial. There appears to be a greater chance of developing adverse local side-effects [1] after revaccination then there is after primary vaccination, and in theory repeated vaccination could be deleterious to immunity in some situations [2, 3]. If revaccination materially improved protection from mycobacterial infection in the majority, the possible disadvantages would be out-weighed.

For more than 20 yrs a BCG policy has been in force in Kuwait in which children receive their first vaccination at the age of 4 yrs just before starting school if they produce less than 10 mm induration to a skin test with 2 tu of RT23 PPD. At the age of 13 yrs they are tuberculin tested again and those producing less than 10 mm of induration are given a second vaccination.

The present study, using a battery of 7 new tuberculins, was carried out to determine the effects of the policy on children 5 yrs after some of them had been revaccinated. An earlier study [4] has shown a remarkably high level of sensitization by environmental mycobacteria in Kuwait, although the niche that they occupy in an environment apparently so hostile has not yet been identified. Since BCG vaccination enhances the immunological capacity to recognize casually met mycobacteria, skin test reagents prepared from environmental species have been included.

Materials and methods

Skin test reagents

These were new tuberculins [5], and 4 tests were carried out by intradermal injection of 0.1 ml, 2 on each forearm of each child. All children were tested with tuberculin, about half of the senior school children were tested with Leprosin A, Chitin (*M. chitae*), and Flavescin (*M. flavescens*), and the remainder were tested with Gilvin (*M. gilvum*), Gordonin (*M. gordonae*) and Xenopin (*M. xenopi*). With the exception of Leprosin A used at a concentration of 10 $\mu g \cdot ml^{-1}$, all reagents were used at 2 $\mu g \cdot ml^{-1}$. Reactions were measured in mm 72 h after

injection and a positive response was taken as 2 mm or more of induration.

Children studied

These were 795 senior school children aged 18 yrs. Every child was examined for BCG scars. When only 1 scar was present its diameter in mm was measured, and when 2 scars were present, the lower one (known to be the site of revaccination) was measured. As well as looking for scars, documentary evidence was checked in each childs vaccination record.

Data available from studies already published [4, 6] on elementary school children with a mean age of 9.2 yrs, and intermediate school children with a mean age of 13.1 yrs, were analysed in comparison. These studies and the present one were carried out concurrently, using the same batches of skin test reagents.

Handling of results

To estimate the likely skin test status of the revaccinated senior school children prior to their revaccination, the results for intermediate school children were analysed according to whether their responses to tuberculin were less than 10 mm, or 10 mm and above. Since the tuberculin we used differed from PPD, we also studied the results for the 25% of intermediate school children with the smallest tuberculin reactions, in comparison with the remainder. This was based on the assumption that the proportion of them to be revaccinated would be the same as amongst the senior school children studied (23%). Statistical analyses were by Fisher's exact test and Student's t-test.

Table 1. – The percentages of reactions of 2 mm or more in diameter divided according to age, and number of BCG scars

School	Elementary	Intermediate	Senior	
Ages	9.2±0.9 yrs	13.1±1.1 yrs	18.0±1.0 yrs	
BCG	1 scar %	1 scar %	1 scar* %	2 scars* %
Tuberculin	86.8	89.6	98.7	98.9
Gilvin	14.6	37.3	64.1	62.0
Gordonin	42.8	55.8	86.8	93.0
Xenopin	39.8	43.5	81.8	91.5
Flavescin	23.1	26.0	66.5	70.9
Chitin	54.1	71.3	95.2	95.4
Leprosin A	82.8	76.3	93.4	95.4

*: Note that there are no significant differences between these groups. The 2 left hand columns are of data already published [4, 6].

Results

None of the elementary or intermediate school children had more than 1 BCG scar [4, 6]. In the present study 614 of the senior school children had only been vaccinated once, and 181 (23%) had received BCG twice.

The results of the skin tests are shown in table 1 for the 3 age groups. It can be seen immediately that the senior school children were the most reactive to all of the skin test reagents. Table 2 shows the sizes of BCG scars in the different age groups and according to sex. There was an increase in scar sizes between children at the elementary, intermediate, and senior schools, and amongst the senior school children scars of revaccination are significantly larger ($p<0.0001$, for the total group and for boys alone) than are those after only 1 vaccination. There were no sex differences in scar sizes in the younger children, but amongst the senior school children the scars after 1 or 2 vaccinations were significantly larger ($p<0.0001$) in boys than in girls. The differences in skin test results between the sexes are shown in table 3. There were no differences in percentage positives between the sexes, but it is interesting to note that, with the exception of responses to tuberculin, in almost every case responses are larger amongst the boys. There is also a tendency for responses to be larger after revaccination.

Table 2. – The sizes of BCG scars in relation to age and sex

	First BCG scar		Second BCG scar
Published data [4, 6]			
Boys 9–10 yrs	5.4±1.5 mm		-
		NS	
Girls 9–10 yrs	5.3±1.5 mm		-
Boys 13–14 yrs	6.3±1.9 mm		-
		NS	
Girls 13–14 yrs	6.4±1.8 mm		-
Present study			
Boys 18 yrs	7.7±2.1 mm	p<0.0001	9.0±2.3 mm
	p<0.0001		p<0.0001
Girls 18 yrs	6.8±2.1 mm	NS	7.2±2.0 mm

Table 3. – Skin test results (rate of positivity and induration in mm) obtained in senior school boys and girls, some of whom had been revaccinated with BCG some 5 yrs earlier

	BCG once			BCG twice		
	Boys		Girls	Boys		Girls
Tuberculin	461/467 (99%)		142/145 (98%)	140/142 (99%)		38/39 (97%)
	11.2±2.5*[1]	p<0.02	11.8±3.1*[2]	12.5±2.7*[1]	NS	13.6±3.5*[2]
Gilvin	166/245 (68%)		51/95 (54%)	28/40 (70%)		16/31 (52%)
	5.3±2.4	p<0.03	4.6±2.1	5.1±2.1	NS	4.4±1.6
Gordonin	210/245 (86%)		84/95 (88%)	36/40 (90%)		30/31 (97%)
	6.4±2.1*[3]	NS	6.2±2.3	7.3±2.1*[3]	NS	6.6±2.3
Xenopin	202/245 (83%)		76/95 (79%)	34/40 (85%)		31/31 (100%)
	6.1±2.2	NS	5.6±2.4	6.7±2.2	NS	6.1±2.2
Flavescin	145/222 (65%)		37/50 (74%)	73/102 (72%)		5/8 (63%)
	5.1±2.4	NS	5.2±2.2	5.8±2.5	NS	4.7±2.4
Chitin	210/222 (95%)		48/50 (96%)	100/102 (98%)		7/8 (88%)
	7.8±2.4	NS	7.6±1.8	7.8±2.3	NS	7.8±2.6
Leprosin A	206/222 (93%)		48/50 (96%)	98/102 (96%)		7/8 (88%)
	7.6±2.6*[4]	p<0.007	6.6±2.2	8.4±2.4*[4]	NS	7.6±1.9

Significant differences between those receiving BCG once, or twice, are indicated: *[1]: p<0.0001; *[2]: p<0.003; *[3] and *[4]: p<0.02.

Table 4. – Results for intermediate school children divided by two methods according to the likelihood of their being given BCG revaccination:

	Intermediate children not likely to be revaccinated						Senior children (1 scar)	
Tuberculin	>10 mm (31%)			largest	75%			
BCG scar sizes	6.9±2.0	mm		6.5±1.9	mm		7.3±2.1	mm
Gilvin	17/37	46%	p<0.03	29/62	47%	p<0.01	219/342	64%
Gordonin	16/16	100%	NS	29/39	74%	p<0.02	296/342	87%
Xenopin	54/76	71%	p<0.02	105/185	57%	p<0.000	280/342	82%
Flavescin	26/76	34%	p<0.000	54/185	29%	p<0.000	182/272	67%
Chitin	38/42	90%	NS	78/102	76%	NS	258/272	95%
Leprosin A	36/37	97%	NS	60/62	97%	NS	254/272	93%
	Intermediate children likely to be revaccinated						Senior children (2 scars)	
	Tuberculin<10 mm (69%)			smallest 25%				
BCG scar sizes	6.0±1.8	mm		5.7±1.8	mm		8.1±2.1	mm
Gilvin	19/57	33%	p<0.002	1/21	5%	p<0.000	44/71	62%
Gordonin	14/36	39%	p<0.000	4/13	31%	p<0.000	66/71	93%
Xenopin	58/170	34%	p<0.000	8/62	13%	p<0.000	65/71	92%
Flavescin	39/170	23%	p<0.000	8/62	13%	p<0.000	78/110	71%
Chitin	45/94	48%	p<0.000	10/34	29%	p<0.000	107/110	95%
Leprosin A	55/81	68%	p<0.000	11/30	37%	p<0.000	105/110	95%

The statistics shown are for differences between the intermediate and senior school children in each table (Fisher's exact text). Methods of division: 1) based on responses to tuberculin of less than 10 mm, or 10 mm and more; 2) based on the 25% smallest and 75% largest responses to tuberculin. The results obtained in senior school children according to whether they had one or two BCG scars are shown for comparison.

Discussion

No information is available on the effects of BCG revaccination at the age that it is performed in Kuwait, although there is some data on its effects after initial vaccination at birth. A recent report from Sri Lanka [7] included information suggesting that revaccination at the age of 10 yrs, after vaccination at birth, increased tuberculin positivity from about 15% to about 80% some 3 months later.

In Kuwait direct assessment of the effects of BCG revaccination was complicated because we studied a population in the relevant age group that was segregated already. One part of this population consisted of individuals who had responses to 2 tu of RT23 PPD of less than 10 mm, when they were 13 yrs old, and had been revaccinated with BCG (23%). The other part consisted of those who had reactions of 10 mm or more at that time and were not revaccinated. Thus, it was not possible to directly compare results for the senior children vaccinated once, with those for their juniors, and the tuberculin we used was not PPD. As described above, the results for the intermediate school children have been divided by 2 methods into those for children that might or might not expect to be revaccinated (table 4).

By applying to our tuberculin results for intermediate school children the criterion used for selection for revaccination based on responses to PPD of less than 10 mm, 69% would be revaccinated, which is almost certainly an over-estimate. By the method of assuming that the same proportion of intermediate school children would require revaccination as did the present senior school children when tested 5 yrs ago, the results for the 25% with the smallest tuberculin responses are shown separately in table 4.

Whichever method is applied, and taking ages into account, the results for all 7 reagents in the children unlikely to have been revaccinated are similar to those for the senior school children only vaccinated once, as shown in the upper half of table 4. The effect of the second BCG on those children likely to have been revaccinated can then be seen clearly in the lower half of the table. The effect is highly significant on responses to all of the reagents, whichever method is used to divide the intermediate children, and about twice that expected due to increasing age alone. There is, unfortunately, no direct evidence that additional protection from disease has been provided, since it was shown in the Medical Research Council BCG trial in the United Kingdom [8] that those without positive tuberculin responses after vaccination were just as well protected as those with. Nonetheless, the increase in tuberculin positivity, and the increase in category 1 responders [4, 6, 9] to group i, common mycobacterial, antigen (data not shown) suggests that the revaccination policy has been beneficial. In other words, the revaccinated children have an improved capacity to recognize environmentally encountered mycobacteria, which may well be a correlate of improved protective immunity [10].

Unfortunately the scar size of the first BCG was not measured in those who were revaccinated, but the mean scar size of senior school children only vaccinated once (7.5 mm in table 2) is larger than that of the intermediate school children (6.4 mm), which is larger than that of the junior school children (5.4 mm) [4]. The increase in scar size between the intermediate and senior school children suggests that revaccination was given to those with a small scar after their first vaccination and the data on scar sizes (table 4) provide supporting evidence for this. There is still a significant increase in scar size between those unlikely to be revaccinated at the intermediate school, and those found to have only one scar in the senior school. This must be due to a genuine increase in scar size with age [7], or to different scar-forming characteristics of the BCG batches used at different times.

The differences in scar sizes between the sexes amongst the senior children was particularly striking in our study, boys having significantly larger scars than girls after both 1 and 2 BCG vaccinations (table 2). There was also a tendency for boys to have larger skin test response sizes than girls, except for tuberculin to which the girls had larger responses. These differences were not noticeable in the younger age groups, suggesting that they might be due to sex-related changes in skin structure developing after puberty.

In conclusion, the evidence obtained from this study generally supports the continuation of the BCG revaccination policy in Kuwait, although we cannot be sure that it is associated with a real improvement in protective immunity from tuberculosis. This does not mean that the same conclusions can be applied to different situations, and similar studies should be carried out before adopting such a policy, especially in countries where BCG vaccination has not proved to be very useful.

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Revaccination au BCG: ses effets sur les tests cutanés chez les enfants des écoles supérieures au Koweit. M.A. Shaaban, M. Abdul Ati, G.M. Bahr, J.L. Stanford, D.N.J. Lockwood, I.C. McManus.

RÉSUMÉ: Par suite d'une politique adoptée au Koweit il y a plus de 20 ans concernant la vaccination par le BCG, les enfants sont vaccinés pour la première fois immédiatement avant de commencer les classes, et ceux qui ont une réponse inférieure à 10 mm d'induration à 2 unités de tuberculine RT23 PPD à l'âge de 13 ans sont revaccinés. Les effets de cette revaccination sur la positivité du test cutané ont été étudiés dans un groupe d'enfants d'écoles supérieures, âgés de 18 ans. Dans un groupe d'étude randomisé, l'on a trouvé 23% de sujets ayant reçu deux vaccinations BCG. La revaccination a entraîné une augmentation significative de la positivité à l'égard de la tuberculine et des 6 autres réactifs testés, augmentation bien plus importante que celle qu'on aurait attendue par suite du passage du temps seul chez les répondants faibles. Les cicatrices de la seconde vaccination au BCG étaient plus grandes qu'après la première et différentes selon le sexe, les cicatrices étant significativement plus grandes chez les garçons que chez les filles. Les garçons avaient également tendance à développer les réponses les plus importantes aux tests cutanés, à l'exception notable de la tuberculine, pour laquelle les filles avaient les réponses les plus marquées. Dans la plupart des cas, la réponse aux tests cutanés était plus importante après revaccination qu'après vaccination simple. En se basant sur cette étude, il est impossible d'être sûr que la revaccination améliore l'immunité protective, mais l'augmentation de la réactivité à la tuberculine et la mise en évidence d'espèces mycobactériennes environnementales pourraient être des preuves indirectes de cette conclusion.

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