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THE RISK OF TUBERCULOSIS INFECTION IN TUNISIA

DIRECTION DES SOINS DE SANTE DE BASE, TUNIS

THE RISK OF TUBERCULOSIS INFECTION IN TUNISIA

Results of a National Tuberculin Survey[1]

INTRODUCTION

Surveillance of the incidence of tuberculosis provides direct estimates of the problem and of its variation in the course of time. However, this method is only applicable if case finding and notification of cases are perfect. In most developing countries this method would be unreliable and therefore a method is preferred that consists of determining the annual risk of infection through periodic tuberculin surveys. The annual risk of infection is directly proportional to the tuberculosis incidence of smear-positive tuberculosis in adults and of tuberculous meningitis in young children (1). The procedure allows comparisons to be made between countries and in the same country to survey the trend of the problem.

Accordingly, Tunisia, in cooperation with WHO, had carried out a survey between October 1959 and February 1960. This survey had shown that among children aged 5 to 9 years the annual risk of infection was 3.02% (2). In 1986 a new survey was carried out among children of about 6 years of age to determine the trend of the tuberculosis problem and to establish a basis for a permanent system of surveillance.

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[1] The survey was organized by the Direction des Soins de Santé de Base, Ministère de la Santé Publique, Tunis, Tunisia (Director: Dr M. Sidhom). The data were analysed and the report was prepared by the Unité de lutte antituberculeuse (Responsible Officer: Dr B. Haouari, Technical Assistant: Mr S. Ben Mansour). The survey received technical guidance from WHO (Mr H. ten Dam) and financial support from the Regional Office for the Eastern Mediterranean (EMRO), Alexandria, and from WHO, Geneva.

MATERIAL AND METHOD

Survey principle

Classically, this type of survey can only be undertaken in a non-vaccinated population (without BCG scars). However, in view of the considerable BCG vaccination coverage it was attempted to apply a method proposed for determining also the prevalence of infection in subjects already vaccinated (6). This method makes use of the fact that tuberculin sensitivity induced by BCG vaccination tends to decrease whereas sensitivity induced by tuberculosis infection remains stable and is relatively high. In view of this, BCG (re)vaccination would reinforce sensitivity remaining from a previous vaccination but would not modify sensitivity acquired from natural infection.

Sampling

To estimate the sample size the results of a partial survey carried out in 1980 (4) were taken into consideration. These results showed that the prevalence of infection at the age of 6 years was about 6%. At this level a simple random sample of about 2 000 pupils (not BCG vaccinated) would be required to obtain an estimate with 95% confidence limits that would be within 1% from the observed value (5). However, as it was decided to use cluster sampling, it was considered appropriate to double this sample size.

As furthermore the BCG vaccination coverage in Tunisia was estimated at about 75%, a sample of about 16 000 pupils was required to find among them 4 000 non-vaccinated pupils. The statistics relative to primary education (3) showed that there were 191 668 new pupils enrolled for the first grade of primary school, distributed over 3 214 schools. The required sample size therefore seemed ensured by including one tenth of all these schools.

In order to ensure national representativeness and to give each child the same probability of being included in the sample, one school in ten was randomly selected from the lists of schools for each region. All the classes of the first grade of the primary schools thus selected were included in the sample. In this way the total sample consisted of 320 clusters of unequal size. Although not very common, this way of sampling appeared more practical for field work than sampling by clusters of equal size. In any case, this procedure was more or less imposed because the proportions of vaccinated and non-vaccinated children were unknown.

Organisation of field work

The study population consisted of children in the first grade of primary school because this population was easy to cover. In Tunisia this population is representative of the total population of the same age because the proportion of children enrolled in primary schools is over 99% (3). The national school vaccination programme foresees systematic BCG vaccination for all the pupils in the first grade of primary school. To be able to complete the survey before the start of the national vaccination programme, 71 teams were identified among the experienced vaccinators of the national school vaccination programme; each team was composed of a tester/reader and a secretary. The teams were directed by 24 regional supervisors. Information sessions were organized for all the teams and equipment and supplies were distributed to them on those occasions. Beforehand, a practical guide and forms for recording the data had been prepared by the central team. For general supervision Tunisia was sub-divided into six zones for which national supervisors were designated.

At the level of each cluster (school) the work was carried out in two stages:

- a first stage during which each child was examined for the presence of a BCG scar, the size of each scar was measured, a tuberculin test was given and read (three days later) and a new BCG vaccination was administered;

- a second stage, three months later, during which the scar of the second vaccination was measured and a new tuberculin test was given and read.

All measurements (in mm) as well as the age and the sex of the pupils were recorded on a pre-prepared form for each class. The tuberculin used was RT23 with Tween 80 and the dose was 2 TU. The BCG was freeze-dried, supplied by the Pasteur Institute of Tunis, in a concentration of 1 mg/ml with 3 to 7 million viable units per ml. Tuberculin as well as BCG were administered by strict intradermal injection in a dose of 0.1 ml.

Constraints

The survey was carried out between January and May 1986. Among the 320 schools randomly selected initially, 65 had already been visited by the teams of the national school vaccination programme. Since the survey protocol required a tuberculin test before revaccination these schools could not be included in the sample. It was possible to replace 52 of them by selecting the schools that preceded or superseded on the regional list of schools. This reduced the sample to 307 schools and to 16 438 pupils. Application required several visits of the teams and certain pupils were absent at one or more of the visits. In total this happened to 2 345 pupils. Thus 14 093 pupils remained for whom it was possible to obtain the complete set of data.

It was found that this study population comprised 3 821 pupils without a BCG scar and 10 272 pupils with a BCG scar.

RESULTS

Since the analysis of the results must be carried out separately for the non-vaccinated and the vaccinated pupils and since in this study the absence or the presence of a scar was the only available indicator of the vaccination status, it has been attempted to verify whether the absence of a BCG scar concords with the absence of vaccination. Figure 1 shows the distribution of the diameters of the BCG scars observed at the beginning of the survey. The distribution of the measurable scars appears "normal" and moreover between this distribution and the column of "0" reactions there is a clear antimode (at 1 mm), which means that the subjects without a scar belong indeed to a distinct population and therefore, very probably, were not vaccinated.

FIGURE 1. DISTRIBUTION OF DIAMETERS OF BCG SCARS AT THE START OF THE SURVEY

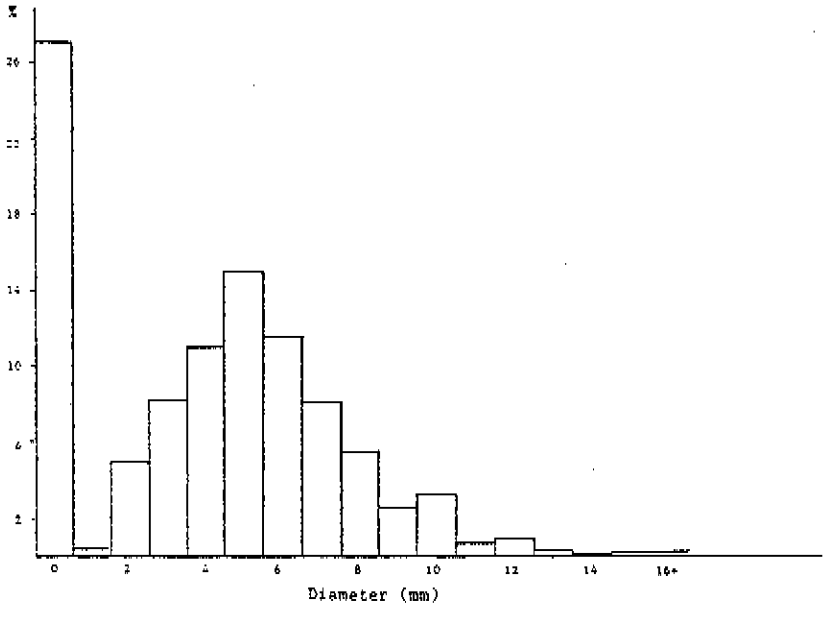


FIGURE 2. DISTRIBUTION OF TUBERCULIN REACTIONS TO 2 TU OF RT23 + TWEEN AT THE START OF THE SURVEY AMONG PUPILS WITHOUT BCG SCAR

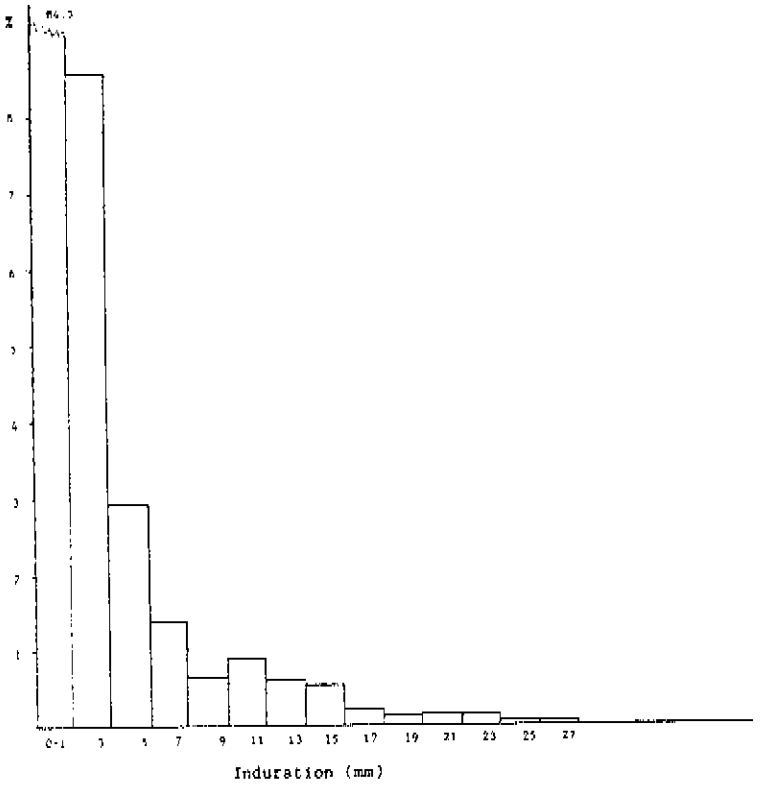
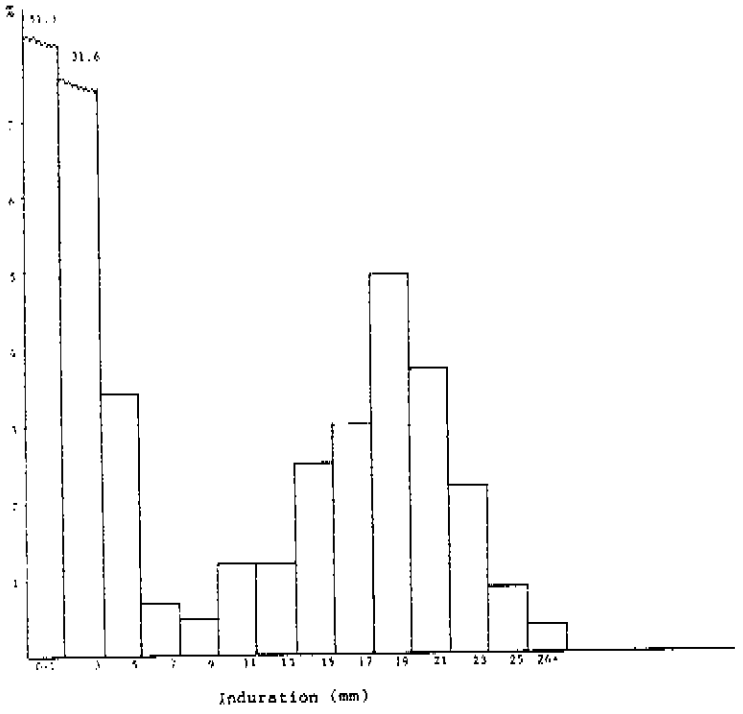


FIGURE 3. DISTRIBUTION OF TUBERCULIN REACTIONS AMONG CHILDREN 5-9 YEARS OLD TO 1 TU OF RT23 + TWEEN (1960)



Prevalence of infection among children without a BCG scar

The distribution of the tuberculin reactions among the children without a scar at the first stage of the survey is shown in Figure 2. This distribution does not show a clear antimode that would make it possible to distinguish the infected from the uninfected population, contrary to what was observed during the survey in 1960 (Figure 3), when there was a distinct antimode at 8-9 mm. If this antimode is applied to the distribution found in 1986 it seems nevertheless possible to arrive at a reasonable estimate of the current prevalence of infection. Thus, among the 3 821 pupils without a scar, 109 would be considered positive which gives an infection prevalence for that group of 2.85% (see Annex 1). For this prevalence the confidence interval has been calculated according to the formula proposed by WHO (7). However, since the number of pupils per cluster differed largely (because the cluster size as well as the proportion of pupils without a scar was different for each cluster), a weighting factor has been introduced. Furthermore, as the sampling fraction (1/10) was rather high, also this fraction has been taken into consideration in the calculations. For the 95% confidence interval the formula finally used is the following:

$$I = p \pm 1{,}96 \sqrt{\frac{\sum \left(\frac{n_i}{\bar{n}_i}\right)^2 \left(p_i - p\right)^2}{k\,(k-1)} \left(1 - \frac{n}{N}\right)}$$

where
- I = confidence interval;
- p = proportion infected among the pupils without a scar;
- 1.96 = the factor used to arrive at a confidence interval of 95%;
- n_i = the number of pupils without a scar in cluster i;
- $\bar{n}_i$ = the mean number of pupils without a scar per cluster;
- p_i = proportion infected in cluster i;
- k = the number of clusters;
- n = the number of pupils included in the survey;
- N = the population from which the sample has been selected.

The calculations for these variables and for the pupils without a scar show the following values:

$p = 0.0285 \quad (= 2.85\ \%)$

$\bar{n}_i = 12.45$

$$\sum \left(\frac{n_i}{\bar{n}_i}\right)^2 \left(p_i - p\right)^2 = 11515.6699$$

$k = 298$ (307 - 9 void clusters):

$\frac{n}{N} = 0.1$ (1/10 of the schools)

so that $I = 2.85\ \% \pm 0.67\ \%$.

From the prevalence of infection the average annual risk $\left(\overline{ARI}\right)$ has been calculated according to the formula:

$\overline{ARI} = 1 - pn_i^{1/\bar{a}}$ when

pn_i = the proportion of uninfected children

(= 1 - 0.0285 = 0.9715)

$\bar{a}$ = mean age (= 6.39). Thus

$\overline{ARI} = 1 - 0.9715^{1/6.39}$

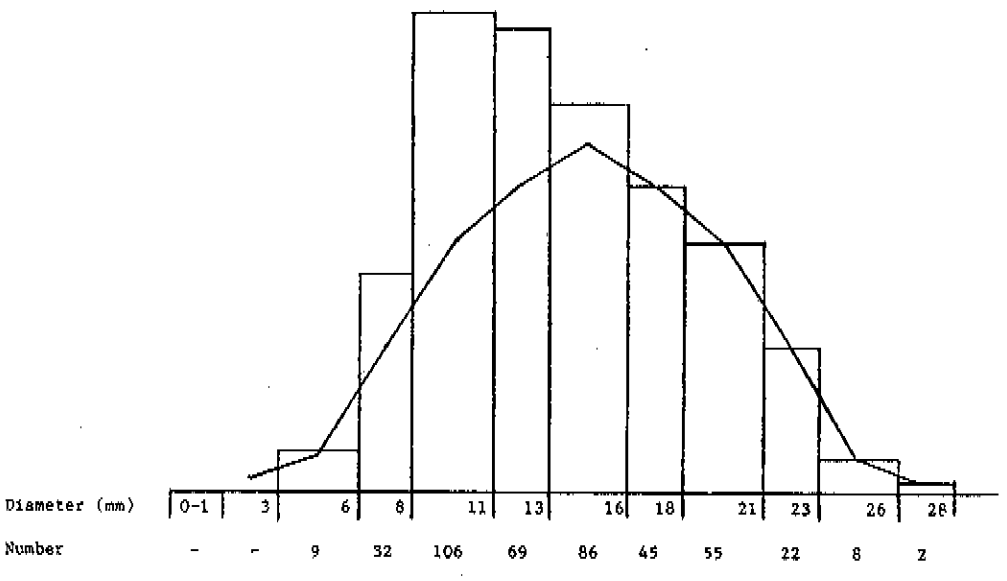
$= 0.0045$ or 0.45%.

Prevalence of infection among children with a BCG scar

For this group of children, for which the effects of the BCG vaccination and of natural infection are confounded, the annual risk of infection has been calculated according to the method proposed by ten Dam and Hitze (6).

The correlation table of the tuberculin reactions before and after revaccination is shown in Annex 2. After elimination from this table of the cases which were obviously erroneous (cases with very small reactions after revaccination), it was attempted to reconstruct the distribution of pre-revaccination tuberculin reactions in children who were classified as infected (Figure 4).

FIGURE 4. RECONSTRUCTED DISTRIBUTION OF TUBERCULIN REACTIONS BEFORE REVACCINATION AMONG CHILDREN WITH A BCG SCAR CONSIDERED INFECTED



In order to correct a slight imprecision in the reading of the reactions (by many readers), this reconstructed distribution is shown in alternate columns of 2 and 3 mm induration. It is seen that the distribution is skewed, with relatively many small reactions. It has therefore been attempted to normalize the distribution starting from the right, as is shown by the superimposed curve.

On the basis of this reconstructed distribution the area that includes the infected has been determined on the correlation table. This, finally, made it possible to determine the infection prevalence for each cluster. The variables from which the prevalence of infection and its confidence interval have been calculated are the following:

$p = 0.03271$ or 3.271%

$\bar{n}_i = 33.459$

$$\sum \left(\frac{n_i}{\bar{n}_i}\right)^2 \left(p_i - p\right)^2 = 6682.72$$

$k = 307$

$\frac{n}{N} = 0.1$

Calculated as for the children without a scar, the prevalence of infection in the children with a BCG scar and its 95% confidence interval are $3.271 \pm 0.50\%$.

This prevalence is only slightly higher than the prevalence of infection found among children without a BCG scar (2.85%); the 95% confidence interval of the difference is 0.84%.

Using the same formula as before to calculate the average annual risk of infection: $\overline{ARI} = 1 - 0.9673^{1/6.39} = 0.0052 = 0.52\%$

The weighted average of the $\overline{ARI}$ is:

$$\frac{(3821 \times 0.045) + (10272 \times 0.0052)}{14\ 093} = 0.0050 \text{ being } 0.50\%$$

Average annual decrease of the annual risk of infection

The prevalence of infection found during the survey carried out in 1960 among children aged 5 to 9 years was 21%. This corresponds to an average annual risk of infection of 3.02%, or 0.0302. The weighted average annual risk of infection in 1986 is 0.005. The average annual decrease has been calculated according to the formula:

$$X = 1 - \left(\frac{R2}{R1}\right)^{1/T} \text{ when}$$

X = rate of decrease

R2 = $\overline{ARI}$ in 1986

R1 = $\overline{ARI}$ in 1960

T = number of years between the two observations = 26

$\frac{R2}{R1} = 0.16556$ $\frac{1}{T} = 0.038314$

so that X = 0.066584 or 6.6584%

DISCUSSION

The distribution of the diameters of tuberculin reactions before (re)vaccination (in pupils without a BCG scar; see Figure 2 and Annex 1) shows a high proportion of intermediate reactions (around the "cut-off" point of 9 mm). Inspection of the results according to the regions (Annex 3) shows that there are seven regions (Kasserine - Kairouan - Bizerte - Sousse - Sidi Bouzid - Gabes and Mahdia) where this phenomenon is relatively frequent. The absence of strong reactions in these regions, where the incidence of tuberculosis is among the highest in the country, could indicate that there has been under-reading of the tuberculin reactions. But the readings of the tuberculin tests in each region had been made by several teams so that systematic under-reading is not very probable. Furthermore, the same phenomenon had been observed during the survey carried out in 1980.

The BCG vaccination coverage in these regions is similar to that in the other regions. Only three regions are at sea level and four regions at higher altitude. Non-specific sensitivity (either induced by atypical mycobacteria or by BCG) therefore does not seem to be the obvious explanation for this observation. Nevertheless, if the method based on the correlation of pre- and post-vaccination reactions is applied to the children without a BCG scar (Annex 1), it is seen that many of the intermediate reactions to the first test have clearly increased after BCG vaccination, which does indicate that they are non-specific. It follows that the values found above for the prevalence and the annual risk of infection are probably overestimates.

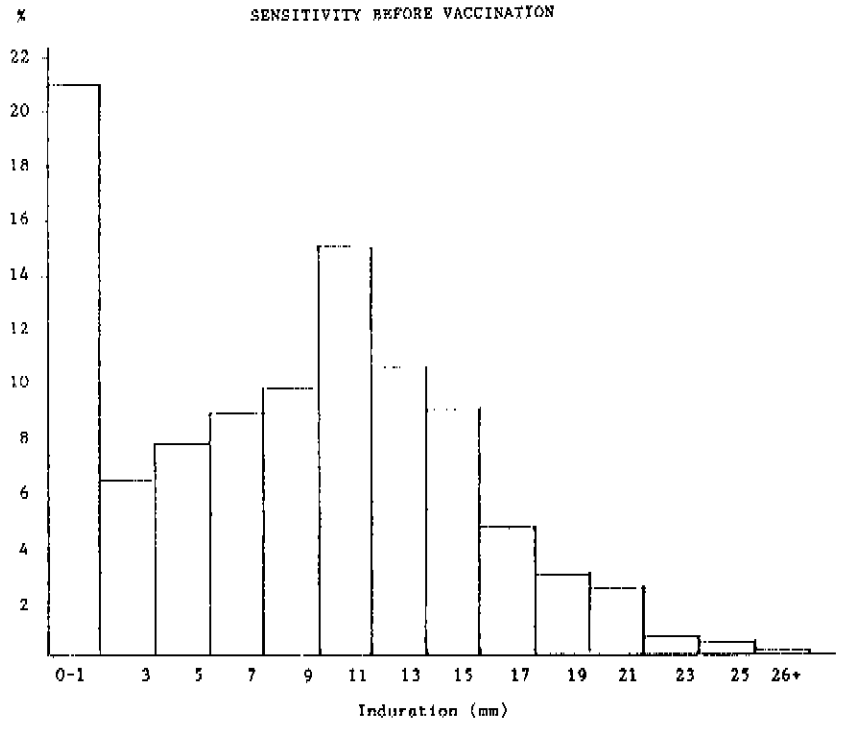
Even though the annual risk of infection in 1986 may have been overestimated there is a clear decrease, from 3.02% in 1960 to 0.50% in 1986. This decrease, strictly speaking, applies only to children of pre-school age and therefore to intrafamilial transmission of tuberculosis. Although this transmission plays a major role in the maintenance of the endemic, its decrease is not immediately followed by an identical decrease in the incidence of the disease in the adult population. The main reason for this is the existing large reservoir of infected persons. The increase in life expectancy favours the maintenance of this reservoir. On the other hand, it can already be observed that the acute forms of childhood tuberculosis such as meningitis and miliary tuberculosis are becoming rare. Not more than two cases of tuberculous meningitis were declared in 1985 and 1986.

The average decrease in the annual risk of infection has been 6.7% per year over a period of more than 25 years. This rate of decrease is appreciable and higher than in many countries in Africa and Asia, but it is inferior to that obtained recently in some limited surveys in other countries in the Eastern Mediterranean Region like in Bahrain (12%) in Kuwait (10%) and in Libya (12%), where it has become similar to that observed in western European countries (8). However, since the interval between the two surveys was more than 25 years, it may well be that the current rate of decline differs largely from 6.7%. To determine the present rate it is necessary to carry out a repeat survey in about 5 years (7).

As the number of children included in this study is large it is possible to evaluate the pre-school age programme and the immediate qualitative effect of BCG vaccination in schoolchildren. The distribution of BCG scars (Figure 1) shows that the pre-school age vaccination coverage attains 73%. The distribution of post-vaccination tuberculin reactions among the pupils without a BCG scar and without tuberculin sensitivity (reactions of 0-1 mm) at the

beginning of the survey is shown in Figure 5. It is seen that the reactions are normally distributed but that the mean is relatively low. The result of this is that 21% of the pupils have no sensitivity that can be revealed with a dose of 2 TU.

FIGURE 5. DISTRIBUTION OF POST-VACCINATION TUBERCULIN REACTIONS AMONG PUPILS WITHOUT A BCG SCAR AND WITHOUT TUBERCULIN SENSITIVITY BEFORE VACCINATION



The method of estimating the prevalence of infection in vaccinated children (6) has indeed made it possible to determine the cause of the tuberculin sensitivity represented by the relatively large reactions to the first test. For the smaller reactions this proved more difficult and it is therefore important to construct the distribution of reactions to the first test for the subjects provisionally classified as infected and to normalize this distribution if necessary. Utilization of a strong and "standardized" dose of BCG for the revaccinations no doubt will improve the effectiveness of the method.

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CORRELATION OF TUBERCULIN REACTIONS BEFORE AND AFTER REVACCINATION IN PUPILS WITHOUT A BCG SCAR

Post-vaccination reaction (mm)

Pre-vaccination reaction (mm)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30+	Total
0	641	18	119	82	111	135	140	138	159	150	332	141	206	127	133	150	69	79	56	34	60	16	15	6	8	9	1		1	1	5	3,140
1	7	3	10	4	3	7	5	1	4	4	10	1	1	3	2	3	3		1	2		1	1									76
2	13	2	13	3	11	8	11	6	12	5	19	10	18	9	8	11	9	4	5	4	3		2		1	2						187
3	14	4	17	4	6	5	7	5	2	6	14	4	10	4	7	9	6	2	4													130
4	5		6	6	5	3	5	2	6	4	9	3	4	6	5	3	1	2				2				1						78
5			2	1	1	1	2		3		5	2	2	5	3	5	1	1	1			1		1								37
6			1		2	1	0		3	5	5	1	1	3	2	1			2		2					1						30
7	1			1	1	1		0			5	1	1		1		2	2	1													17
8				2	1				0		1	2	2	2	1	2			1		2										1	17
9										0	1	3	1	1					1												1	8
10			2			3	1	1			0		4		3	7	2	3	1	1	1											29
11												0			1	1	1				1	1										5
12	1			1							1		1		4		1		2	1	1		1								1	15
13														2					2	1	2									1		8
14															1		1		2													4
15													1	1	1	4	1	3	2	1	1	1										16
16												1				1	0	1	1		1	1										6
17																		0	1									1				2
18																			0							1						1
19																				0	1		1									2
20											1								1		0	1		1	1							5
21																						0										
22																					1		1				1					3
23																								1								1
24																									0							
25																										1					1	2
26																											1					1
27																												0			1	1
28																													0			
29																														0		
30+																															0	
Total	682	27	170	104	141	164	171	153	189	174	403	149	252	163	172	197	97	97	82	44	76	24	21	9	10	15	3	1	1	2	8	5,821

ANNEX 2

CORRELATION OF TUBERCULIN REACTIONS BEFORE AND AFTER REVACCINATION IN PUPILS WITH A BCG SCAR

Post-vaccination reaction (mm)

Pre-vaccination reaction (mm)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30+	Total
0	784	10	157	149	218	278	326	256	355	308	872	370	664	355	392	463	222	208	180	93	155	56	52	41	37	30	12	5	4	1	5	7,058
1	13	3	11	7	7	6	13	4	8	6	20	8	8	4	9	2	4	2	3	1												139
2	32	2	40	15	37	28	38	27	53	25	76	31	71	35	29	35	20	12	11	5	7	1	1		1	2						634
3	21	2	22	28	21	25	23	11	21	21	45	21	31	33	23	31	19	14	12	2	4	1	6	1	4	1						443
4	10	2	14	6	17	11	11	14	25	9	42	18	32	23	18	23	7	9	8	5	11	1	3	1		1					1	322
5	4		11	3	8	9	6	11	17	9	41	13	28	21	20	28	12	16	14	2	7	3	2	3		1					1	290
6	4		1	6	1	4	9	8	10	5	19	10	17	15	17	24	6	10	8	5	8	2	2	4	1	1			1			198
7	1		1	3	3	1	4	3	5	4	20	5	13	13	13	11	7	17	11	4	8	1	1	1	1	1			1		1	154
8	1		4	1	1	1	2	5	8	1	11	10	24	4	15	16	6	3	8	3	10	1	3	2	1	4		1				146
9			1		2	2		3	2	7	10	5	8	6	12	7	8	6	7	1	5		3			1			1	1	1	99
10	3		5	1		4	3	5	6	13	20	14	27	11	16	26	16	11	15	8	14	2	7	2	1	1		2			1	234
11				1		1				4	4	1	10	7	10	9	8	3	9	1	5	2	2	1								78
12	1				1		1	1	2	2	11	1	11	9	10	11	14	8	6	3	10	2	4	2	2	3	2				2	119
13						1		1	1		2	2	7	3	5	12	10	11	4	4	2		4	2	1	1						73
14									1		1	1	2	4	4	4	4	1	2	4	3	2	1	1	2	1	1		1			40
15	2				1				1	2	3	1	6		8	6	6	4	9	6	6	3		2	3	2	2				2	75
16												1	2	1	2	2	5	2	4	1	4			1			1		1		1	28
17							1				1		2	1	1	3	1	3	1		2	1			1		2				2	22
18										1	1			2	2	1	1		7		7		1	1	2	1		1	1		1	30
19																1	1		1	1		1		1		1		1				8
20					1				1		4		2	1	2	5	4		4		9		2	2	2	1		1	1		4	46
21																		1		2		0										3
22															1	2	3	1	1	1	2	1	2		1	1						16
23																		1		1	1	1	1	0	1							6
24	1																				2				0							3
25															1	1					2			1		1						6
26																											0					
27																			1				1					0				2
28																													0			
29																														0		
30+																															0	
Total	877	19	267	220	318	371	437	349	516	417	1,203	512	965	548	610	723	384	343	326	153	284	81	98	69	61	55	20	11	11	2	22	10,272

DISTRIBUTION BY REGION OF TUBERCULIN REACTIONS BEFORE REVACCINATION IN PUPILS WITHOUT A BCG SCAR

Diameter (mm)

Region	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Tunis	177	1	14	8	7	2	2	3	1			1	3	1		1	1		1		1		1	1		1	1		223
Sfax	194		4			1				1				2			1	1	1	1	1							1	208
Ariana	235		9	1	4		1	1	2				2	1	1	2													259
Nabeul	192		1	1							1			2															197
Kasserine	276	21	11	6	3	2	3	1	1	3	2	1			1		1				1								333
Kairouan	196	16	29	11	8	7	2	1	4		4		1			1		1											281
Bizerte	190	7	18	27	15	4	3	3	1		3		1	1		2													275
Monastir	94	16	21	12	3		1																						147
Sousse	48	1	5	1	2	2	2		1		1				1														64
Sidi B. Zid	250	1	7	5	4	1	2	1	3	2	4		2			1													285
Gabe's	171	1	3	14	5	12	9	5	1	2	12	1		1															237
Mahdia	106	1	12	10	8	2	2		1			1			1	1													145
Medenine	242				1	1	1				2		1			2							1			1			252
Ben Arous	47		8	8	2	1	1	1	2																				70
Jendouba	262				2	1	1	1																					267
Gafsa	146	17	22	9	3	2	1			1		1				1					1								204
Siliana	127		1	2	3			1		1			2	1	1	4	1			1	1		2						148
Beja	72	9	7	10	6	3	3				2						1				1								114
Kef	159	1	4	3				1																					168
Kebili	66		24	12	5		2	1								2													112
Zaghouan	66		1										3																70
Tataouine	80		1	1	1		2				1						1												87
Tozeur	50																												50
Total	3,446	92	202	141	82	41	38	20	17	10	32	5	15	9	5	17	6	2	2	2	6	0	4	1	0	2	1	1	4,199