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Tuberculosis prevalence survey in Kashmir valley

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A tuberculosis prevalence survey was conducted in about 18,000 persons in Kashmir valley situated about 1650 m above the mean sea level. All persons were tested with 3 IU of PPD-S and 10 units of PPD-B. Persons aged 5 yr and above were X-rayed (70 mm X-ray), and from such persons whose photofluorograms were interpreted as abnormal two specimens of sputum were collected and bacteriologically examined. In addition, a large X-ray of the chest was taken for children aged 0-4 yr who had reactions of 10 mm or more to PPD-S. They were then clinically examined by a paediatrician, taking into account all available data, for evaluation for any evidence of tuberculosis. The results of the survey showed that the prevalence of non-specific sensitivity (59%) in the Kashmir valley is significant. The prevalence of tuberculous infection was 38 per cent. The prevalence of culture positive tuberculous patients (3 per 1000) and that of abacillary X-ray positive patients (14 per 1000) were found to be similar in the two sexes contrary to the usual experience of a higher prevalence among males. Results from studies of phage typing, susceptibility to thiophen-2-carbonic acid hydrazide (TCH) and virulence in the guineapig of strains obtained from patients diagnosed in the survey showed that most of these strains belonged to phage type A, were resistant to TCH and were not of low virulence. Regional variations in the prevalence rates were seen, the- problem of tuberculosis appeared to he more in the Baramulla district as compared to Srinagar and Anantnag districts. A comparison of results obtained from the present survey with those obtained from the BCG trial in Chingleput (Tamil Nadu) revealed that the tuberculosis situation in the two areas was quite different.

In a survey of the distribution of non-specific sensitivity in several parts of India it was observed that populations in villages situated at heights of 1200 m or more above mean sea level had a markedly lower prevalence of non-specific sensitivity than that in villages situated in the plains which had a high prevalence of non-specific sensitivity[1,2]. A similar finding had earlier been reported by Bates *et a1*[3]. However, in such areas of low prevalence of non-specific sensitivity very little is known about the pattern of tuberculous infection and disease. In order to obtain more

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information in this regard, a pilot survey for tuberculosis was conducted in the Kashmir valley, situated about 1650 m above mean sea level. The objective of the survey was to obtain estimates of the prevalence of tuberculous infection, non-specific sensitivity and tuberculosis disease in all age groups.

While designing the BCG trial it was considered necessary to obtain information on the protective effect of BCG vaccination in an area with low prevalence of non-specific sensitivity in addition to the study in Chingleput[4], where non-specific sensitivity is highly prevalent. Thus, identification of a population with low non-specific sensitivity and information on tuberculous disease and infection in such a population would also help in planning such a study.

Material & Methods

The Kashmir valley consists of three districts : Srinagar, Baramulla and Anantnag. The survey was confined to the rural population (excluding boat population) and a simple random sample of villages was selected from each of the three districts in such a way that the size of the sample selected from each district was in proportion to the total population of the district. However, as it was thought desirable to include an urban area in the survey, Pantchok, a semi-urban area, on the outskirts of Srinagar town, was also included. In all, 7,679 persons from 11 villages in Srinagar district, 5,769 persons from 9 villages in Baramulla district and 5,307 persons from 9 villages in Anantnag district constituted the study population. Thus, the total population included for the survey was 18,755. Of these 18,311 constituted the *de jure* population and are considered for analysis. The locations of the 29 villages included for the survey are shown in Fig. 1.

The survey was conducted from June to November 1978. The procedures adopted were briefly as follows. A complete census of each village was taken by a house to house visit and all persons registered. The left shoulder of each person was examined for the presence or absence of a BCG scar. Each person was administered two tests, one with 3 IU of PPD-S and the other with 10 units of PPD-B, on the mid-dorsal aspect of the two fore-arms allocated randomly. After 72 h, the transverse diameters of the indurations were measured, without knowledge of the order in which the two tests had been allocated to the two forearms. and recorded. At the time of testing, all persons aged 5 yr and above were offered an X-ray examination of the chest by 70 mm miniature photofluorograms. The X-ray films of the chest were read, independently, by two readers. All those persons showing X-ray abnormality in the lung or any part of the chest indicative of tuberculosis, pulmonary or otherwise, were eligible for sputum examination. From such persons, two samples of sputum-a supervised spot specimen and the other an overnight specimen–were collected and subjected to bacteriological examination by fluorescent microscopy and culture. In addition, bacteriophage typing, thiophen-2-carbonic acid hydrazide (TCH) susceptibility[5] and virulence in the guinea-pig[6,7] of *Mycobacterium tuberculosis* strains isolated in the study were also carried out. All the bacteriological examinations were carried out at the Tuberculosis Research Centre, Madras.

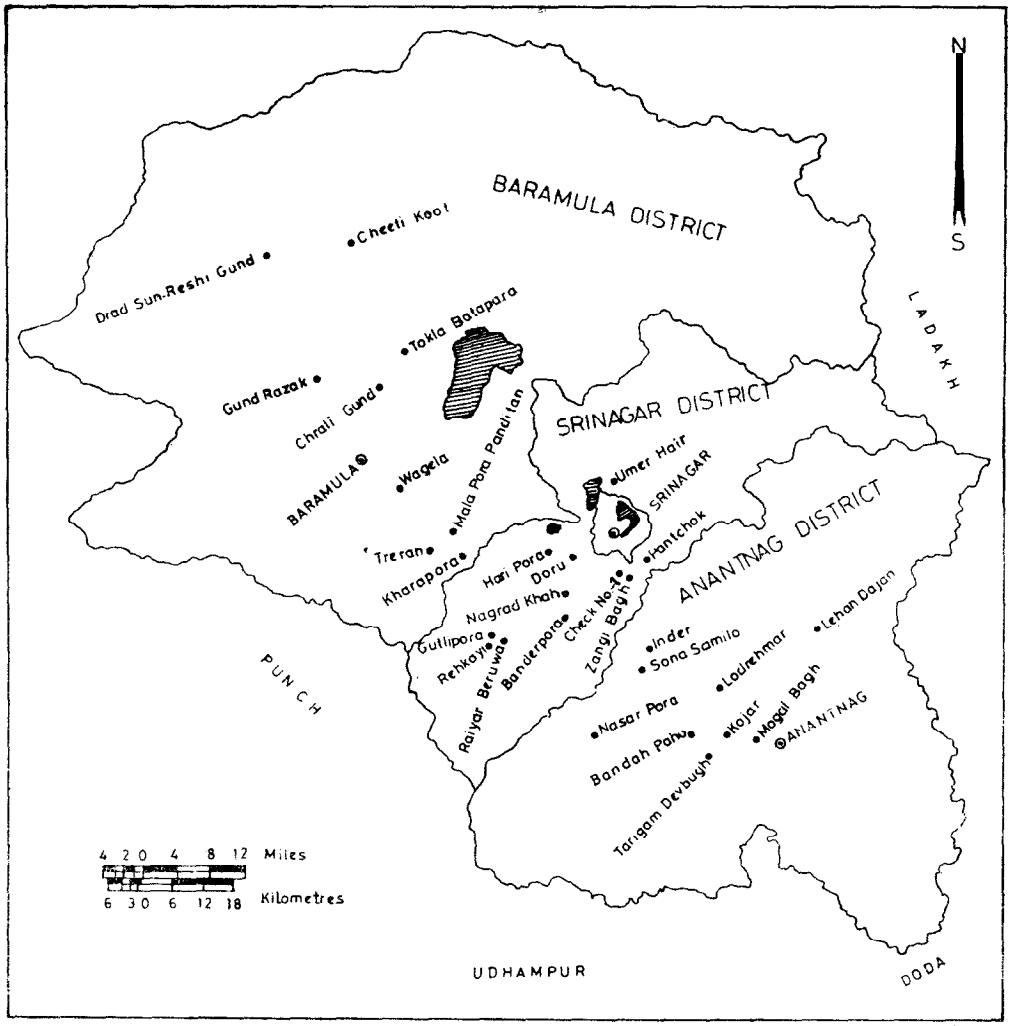

Fig. 1. Map showing locations of the selected villages.

In addition, in order to obtain information on the prevalence of tuberculosis in children aged under 5 yr, on the day of reading, a large X-ray of the chest was taken for all children aged 0-4 yr who showed a reaction of 10 mm or more to PPD-S. These children were examined clinically by a Medical Officer and a paediatrician for evidence of tuberculosis including previous history of tuberculosis and family history of tuberculosis. In cases where further investigations were indicated (e.g., gland biopsy) these were carried out.

Results

Study population and coverages obtained : The population studied and coverages

obtained for various examinations are shown in Table I, by age and sex. High coverages were obtained uniformly in all age groups and both sexes, with overall coverages ranging from 84-98 per cent for tuberculin testing, X-ray, sputum and clinical examinations.

Prevalence of BCG scars : The area under study is covered by the mass BCG vaccination programme. BCG scars were seen in 4 (2613 examined), 17 (2492 examined), 37 (4645 examined), 29 (4169 examined) and 7 (2968 examined) per cent in the age groups 0-4, 5-9, 10-24, 25-44 and 45 + yr, respectively. For all ages, the proportion of persons with BCG scars was 22 per cent.

Persons with a BCG scar were also included for the analysis except for the estimation of prevalence of infection and non-specific sensitivity.

Prevalence of infection : The distribution of children aged 0-14 yr by size of reaction to PPD-S is shown in Fig. 2. It can be seen from the Fig. that the distribution is bimodal and the dividing line between the uninfected (left hand distribution) and the infected (right hand distribution), although not very sharp, is around 12 mm.

Table I. Coverages obtained for various examinations by age and sex

Age group (yr)	Sex	Popn. regd. *(de jure)*	No. test-read	No. X-rayed	Sputum		Clinical exam.	
					No. elig.	No. exam.	No. elig.	No. exam.
0-4	M	1410	1288	–	–	–	51	43
	F	1372	1268	–	–	–	56	47
5-9	M	1303	1236	1233	10	10	–	–
	F	1302	1216	1223	5	5	–	
10-24	M	2621	2310	2390	19	17	–	
	F	2438	2209	2251	24	24	–	
25-44	M	2477	1994	2137	67	65	–	–
	F	2186	1991	2026	90	89	–	–
45+	M	1889	1657	1726	187	182	–	
	F	1313	1224	1240	150	148	–	—
Total	M	9700	8485 (87)	7486 (90)	283	274 (97)	51	43 (84)
	F	8611	7908 (92)	6740 (93)	269	266 (99)	56	47 (84)
Grand total		18311	16393 (90)	14226 (92)	552	540 (98)	107	90 (84)

Figures in parentheses show coverage (%) obtained; -Not eligible for examination

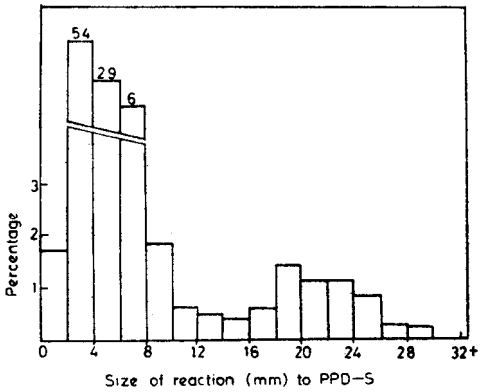

Fig. 2. Distribution of 5892 children aged 0-14 yr by size of reaction to PPD-S.

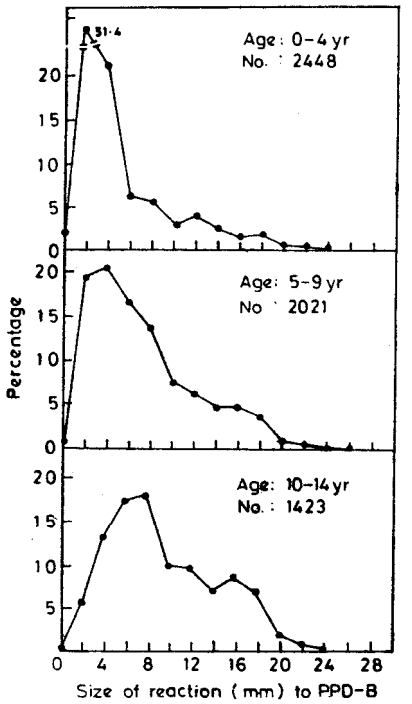

Fig. 3. Distribution of children by size of reaction to PPD-B.

Therefore, 12 mm was taken as a limit for defining 'reactors' to PPD-S.

The overall prevalence of infection was 38 per cent. The prevalence of infection rose rapidly, for both sexes, from the youngest age-group up to the age-group of 45-54 yr and then almost levelled off (Table II). At this age, over 85 per cent of males and over 75 per cent of females were infected. The prevalence of infection was about equal in both sexes up to the age-group 15-19 yr and thereafter lower among females than among males.

Prevalence of non-specific sensitivity : The distribution of children in three age-groups 0-4, 5-9 and 10-14 yr, by size of reaction to PPD-B is shown in Fig. 3. The distributions showed no clear separation between the uninfected and the infected even among children in the youngest age-groups. However, these distributions were skewed, the skewness starting around 10 mm. Therefore, for defining non-specific sensitivity 10 mm was taken as the limiting point.

The overall prevalence was 59 per cent. The prevalence of non-specific sensitivity increased, in both the sexes, up to the age of 35 yr, by which age more than 95 per cent among males and more than 85 per cent among females were infected (Table III). The prevalence of non-specific sensitivity was lower among females after the age of 15 yr ($P < 0.01$). The slightly higher prevalence seen in females in the 0-14 yr age group was not statistically significant.

Prevalence of disease in subjects aged 5 yr and above:

Culture positive cases-The overall prevalence was 2.8 per 1000–2.6 per 1000 among males and 3.6 per 1000 among females ($P>0.2$). In both the

Table II. Prevalence of infection (≥ 12 mm to PPD-S) by age and sex

Age group (yr)	Males			Females		
	No. tested	No. of reactors	% (adj)*	No. tested	No. reactors	% (adj)*
0-4	1223	25	2	1225	31	2
5-9	1008	66	7	1013	63	7
10-14	757	101	15	666	85	13
15-19	365	87	26	455	107	25
20-24	295	113	42	315	101	34
25-29	343	196	59	366	164	44
30-34	308	222	73	407	219	54
35-44	736	572	77	685	442	63
45-54	711	606	85	559	430	76
55-64	615	536	87	372	296	79
65+	258	213	81	150	123	84
Total	6619	2737	42	6213	2061	33

*Proportion calculated after adjusting for the size of total (rural) population in each of the three districts, using the formulas :

$$P_{st}=\sum_{h=1}^{3}\frac{N_h P_h}{N}$$

where P_{st}=estimated proportion appropriate to stratified random sampling; P_h=proportion of reactors (or cases) in the sample; N_h=population in the district; N=total population in the three districts

sexes, the prevalence rates generally increased with age, with a steeper rise after the age of 44 yr (Table IV).

Abacillary radiologically possiblei/probable cases–The prevalence of abacillary X-ray possible/probable cases (hereafter referred to as X-ray cases) has been estimated based on the readings of 70 mm photofluorograms. An X-ray case is defined as a person (abacillary) whose X-ray picture was interpreted as C or D (indicating possible or probable tuberculosis etiology respectively) by two readers. X-ray pictures interpreted as C or D by one of the readers only were submitted to a third (umpire) reader and persons for whom the X-ray pictures were then classified as C or D by the third reader are also considered as X-ray cases. The prevalence of abacillary X-ray cases is shown in Table V. The overall prevalence was 13.6 per 1000–13.3 per 1000 among males and 14.0 per 1000 among females (P>0.2). The

Table III. Prevalence of non-specific sensitivity (≥ 10 mm to PPD-B) by age and sex

Age group (yr)	Males			Females		
	No. tested	No. of reactors	% (adj)*	No. tested	No. of reactors	% (adj)*
0-4	1223	159	13	1225	175	15
5-9	1008	268	29	1013	313	33
10-14	757	330	46	666	313	47
15-19	365	236	68	455	281	63
20-24	295	235	82	315	221	72
25-29	343	302	90	366	280	78
30-34	308	287	94	407	332	82
35-44	736	697	96	685	589	87
45-54	711	668	95	559	485	87
55-64	615	582	95	372	312	84
65+	258	216	82	150	126	88
Total	6619	3980	61	6213	3427	56

* See foot-note under Table II

Table IV. Prevalence of culture positive cases by age and sex

Age group (yr)	Males			Females		
	No. X-rayed	No. of cases	Rate* per 1000	No. X-rayed	No. of cases	Rate* per 1000
5-14	2397	1	0.5	2209	3	1.5
15-24	1226	2	1.5	1265	2	2.1
25-34	1122	3	2.0	1149	4	4.8
35-44	1015	2	1.0	877	2	1.9
45-54	800	4	4.8	657	3	5.2
55-64	658	5	8.6	418	0	–
65+	268	3	12.4	165	4	23.0
Total	7486	20	2.6	6740	18	3.0

*See foot-note under Table II

Table V. Distribution of abacillary X-ray cases by age and sex

Age group (yr)	Males			Females		
	No. X-rayed	No. of cases	Rate* per 1000	No. X-rayed	No. of cases	Rate* per 1000
5-14	2394	1	0.2	2205	3	1.5
15-24	1221	3	2.8	1262	2	1.7
25-34	1117	7	6.0	1144	15	12.0
35-44	1010	14	10.5	872	17	18.3
45-54	794	13	17.6	652	16	25.1
55-64	648	30	47.3	415	24	63.6
65+	263	29	124.8	157	14	100.2
Total	7447	97	13.3	6707	91	14.0

*See foot-note under Table II

prevalence rates increased with age, in both the sexes, gradually up to the age of 54 yr, and more steeply thereafter.

Differences in the prevalence of infection, non-specific sensitivity and disease in the three districts : As the prevalence of infection, non-specific sensitivity and disease rates, by age and sex, obtained in Pantchok were similar to those obtained in the rest of the material from Srinagar district the two sets of data were combined.

Data on the prevalence of infection, non-specific sensitivity and disease is shown in Table VI, separately for the three districts. Minor variations in the prevalence rates for the three districts were observed. Thus, the overall prevalence of infection, for both sexes, was the highest in Baramulla district. This higher prevalence was confined to the age-group 5-34 yr among males and 5-24 yr among females. Considering the age-group 0-14 yr, the prevalence of non-specific sensitivity, for both males and females, was the highest in Anantnag district. The prevalence of culture positive cases was, in general, higher in the Baramulla district as compared to the other two districts. These rates are based on small numbers of cases. However, this difference was statistically significant ($P< 0.01$) among males but not among females.

The prevalence of abacillary X-ray cases was similar in all the three districts and the small differences that were seen were not statistically significant.

Drug sensitivity to isoniazid and streptomycin : Of the 38 patients with positive cultures, drug sensitivity results to both the drugs were available in 30 patients. Strains were regarded as resistant to isoniazid if the minimal inhibitory concentration (MIC) was more than 1 µg/ml and resistant to streptomycin if the resistance ratio (RR) was more than 4. Of the

Table VI. Prevalence of infection, non-specific sensitivity and disease separately for the three districts

Age group (yr)	Srinagar		Baramulla		Anantnag	
	Males exam.	Females exam.	Males exam.	Females exam.	Males exam.	Females exam.
Prevalence (%) of infection :						
0-4	518 (2)	517 (3)	361 (2)	371 (4)	344 (1)	337 (1)
5-14	710 (6)	695 (7)	570 (14)	519 (12)	485 (9)	465 (8)
15-24	270 (23)	303 (20)	178 (40)	253 (38)	212 (32)	214 (23)
25-34	259 (59)	296 (51)	216 (71)	260 (52)	176 (64)	217 (46)
35-44	321 (79)	250 (68)	221 (77)	246 (67)	194 (77)	189 (57)
45+	596 (87)	432 (79)	538 (84)	354 (78)	450 (86)	295 (79)
Total	2674 (39)	2493 (31)	2084 (45)	2003 (37)	1861 (41)	1717 (31)
Prevalence (%) of non-specific sensitivity :						
0-4	518 (14)	517 (14)	361 (9)	371 (11)	344 (16)	337 (19)
5-14	710 (29)	695 (35)	570 (30)	519 (30)	485 (46)	465 (48)
15-24	270 (63)	303 (58)	178 (78)	253 (76)	212 (77)	214 (62)
25-34	259 (86)	296 (77)	216 (93)	260 (80)	176 (93)	217 (82)
35-44	321 (93)	250 (84)	221 (96)	246 (86)	194 (96)	189 (88)
45+	596 (91)	432 (83)	538 (93)	354 (87)	450 (94)	295 (87)
Total	2674 (56)	2493 (52)	2084 (60)	2003 (56)	1861 (65)	1717 (60)
Prevalence (per 1000) of culture positive cases :						
5 +	3116 (2.2)	2728 (1.5)	2323 (5.2)	2191 (4.1)	2047 (0.5)	1821 (2.7)
Prevalence (per 1000) of abacillary X-ray cases :						
5 +	3101 (12.3)	2716 (12.5)	2305 (13.4)	2179 (13.3)	2041 (13.7)	1812 (15.5)

Rate is shown in parentheses

30 patients, 2 (7%) had strains resistant to both the drugs, 6 (20%) resistant to isoniazid only, and the remaining 22 (73%) had strains sensitive to both the drugs.

Bacteriophage typing, susceptibility to TCH and virulence in the guineapig : Studies of bacteriophage typing and susceptibility to TCH were undertaken for a total of 34 isoniazid sensitive strains, obtained from 22 tuberculosis patients in the study population. Of these, 31 strains from 20 (91%) patients were classified as of phage type A. One strain (from one patient) was of type B. The remaining patient, who had given two strains, had a mixed

pattern: one strain of type B and the other of type I. Of the 34 strains, 33 had an MIC of more than 20 µg/ml to TCH *(i.e.,* resistant to TCH), while the other had an MIC of 10 µg/ml. Strains from 17 of the 22 patients were also tested for virulence in the guineapig. Only in three cases the mean root-index of virulence was less than 1 (0.80, 0.94 and 0.98). In all other cases it was more than 1, the overall mean being 1.24 (range 1.04-1.55).

Prevalence of tuberculosis in children aged below 5 yr : Of the 2,556 children aged 0-4 yr and test-read for PPD-S, 107 children showed a reaction of 10 mm or more and were eligible for clinical examination. Of these, 90 were clinically examined by the medical officer and the paediatrician. A diagnosis of primary complex was made in 33 of the 90 children. No other forms of tuberculosis, glandular, bony, miliary or meningitis, were recorded. Thus, among children aged 0-4 yr, the prevalence of 'primary complex' was estimated to be 15 per 1000.

Chest X-rays of 29 of the 33 children diagnosed as having primary complex by the paediatrician were independently read by a tuberculosis specialist who had no knowledge of the observations of the radiologist or the paediatrician; 23 (79%) were interpreted as normal or non-tuberculosis by the tuberculosis specialist. The corresponding figure for the radiologist was 17 (59%). Thus, of the 29 children diagnosed as primary complex in as many as 16 (55%) the diagnosis was not confirmed by either the radiologist or the tuberculosis specialist. Even among the remaining 13 children where either of them interpreted the X-ray as of tuberculosis etiology (inactive or possibly active), in only 5 cases did they agree on the diagnosis. These results suggest that the estimated prevalence of primary complex in children aged below 5 yr may be an overestimate.

Discussion

A sample survey to obtain estimates of prevalence of tuberculous infection, non-specific sensitivity and disease in Kashmir valley was carried out and the results obtained are reported. The prevalences increased with age. The prevalences of infection and non-specific sensitivity were more among males than among females. It is generally believed that the prevalence of non-specific sensitivity is very low in places at high altitudes. But the present survey showed that the prevalence of non-specific sensitivity in Kashmir valley is not insignificant. In the age-group 10-14 yr, nearly 50 per cent of the children showed a positive reaction to 10 units of PPD-B. Another significant finding of the survey was that the prevalence of culture positive cases and of abacillary X-ray positive cases among males were similar to those seen among females contrary to the usual experience that the prevalence of disease is 2 to 4 times higher in males than in females[4,8]. Results from studies of phage typing, susceptibility to TCH and virulence in the guineapig of strains obtained from patients diagnosed in the survey showed that most of these strains belonged to phage type A, were resistant to TCH and were not of low virulence.

Regional variation in the prevalence of infection, non-specific sensitivity and disease were observed in the three districts. Considering younger age-groups, prevalence of infection was maximum

in Baramulla district and that of non-specific sensitivity in Anantnag district. Considering the age-group 5+ yr, prevalence of culture positive cases was the highest in Baramulla district. These results suggested that the problem of tuberculosis was more in Baramulla district as compared to the other two districts.

The survey in Kashmir valley was conducted by the same field teams conducting the Tuberculosis Prevention Trial[4] in the Chingleput area and using similar techniques. A comparison of the results from the two areas showed that the prevalence of infection and non-specific sensitivity, among both males and females, were considerably lower in the Kashmir valley. In the Chingleput area ho differences were observed in the prevalence of non-specific sensitivity between males and females whereas in Kashmir, after the age of 15 yr, females had a lower prevalence than males. The prevalence of culture positive cases was also higher in Chingleput area. But in Chingleput area the prevalence in males was nearly 4 times higher than that in females whereas in Kashmir the prevalences in the two sexes were similar. As a result, the higher prevalence in Chingleput area was mostly confined to males. Most of the strains from Kashmir area which were tested were shown to be of phage type A, resistant to TCH and with a mean root-index of virulence of more than 1, whereas of 50 strains from Chingleput area (unpublished data), tested using similar procedures, 16 were of phage type A, 11 with an MIC of more than 20 μg/ml to TCH and 19 with a mean root-index of virulence of more than 1. Thus, the tuberculosis situation in the two areas appeared to be different. The differing ethnic characteristics, virulence of infecting organisms and immunological mechanisms as also environmental factors might have had a bearing on this difference.

One of the objectives of the study was to know whether Kashmir valley could be considered to represent an area with a low prevalence of non-specific sensitivity and therefore suitable for conducting a study on the protective effect of BCG. The present survey has shown that although the prevalence of non-specific sensitivity in Kashmir valley is lower than that in Chingleput district it is still high and Kashmir valley may not be a suitable area for the proposed BCG study. We do not know whether populations located at still higher altitudes are free from non-specific sensitivity. Even if they are, the size of such populations would be too small for a BCG-trial, apart from other operational difficulties.

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