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Problems in Defining a " Case " of Pulmonary Tuberculosis in Prevalence Surveys*

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An analysis of data from two successive tuberculosis prevalence surveys (conducted at an interval of 18 months) in a random sample of villages in Bangalore District, South India, has shown that the term " a case of pulmonary tuberculosis " does not represent a single uniform entity, but rather embraces cases of several types, differing considerably in their mortality experience, tuberculin sensitivity, results of X-ray and sputum examinations, and in the reliability of their diagnosis.

The status at the first survey of the cases found at the resurvey and that at resurvey of those found at the initial survey give an indication of changes with time. Such changes show considerable differences for the various types of cases and provide another dimension to study the differences among them. The authors consider that, in spite of the great need and importance of a single straightforward definition of a case, no such definition is suitable for all situations; there is no other option but to continue to use more than one definition.

Although, theoretically, finding a single bacillus in the sputum should be adequate proof of pulmonary tuberculosis, it is shown that finding of a few bacilli, 3 or less, is probably far too often due to artefacts and should not be the basis for a diagnosis.

The findings also well bear out the notion that positive radiological findings, in the absence of bacteriological confirmation, indicate, not pulmonary tuberculosis, but only a high risk of the disease. Direct microscopy appears to be a consistent index of disease but, in community surveys, has the limitations of missing a substantial proportion of cases and of adding some false cases. The extent of these limitations, so far as symptomatic patients in a community tuberculosis control programme are concerned, remains to be investigated.

INTRODUCTION

Strange though it may seem, there is no generally accepted definition of the term " case of pulmonary tuberculosis ". Yet, despite the many difficulties involved in its establishment, such a definition is of fundamental importance. Comparisons of epidemiological data from different sources and estimation of the impact of control programmes are difficult, even confusing, without such a definition. Official figures on the prevalence of tuberculosis in most countries, in the absence of an agreed definition, may not be comparable. A definition is of importance in clinical medicine too, especially for comparison of results of various chemotherapy regimens. Even in an outstanding research programme, the term " definite cases of pulmonary tuberculosis " has not been sharply defined; both sputum-positive and sputum-negative cases have been included (Great Britain, Medical Research Council, 1963). On the other

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hand, the WHO Expert Committee on Tuberculosis (1964) has stated:

" The Committee believed that it was essential first to agree on a definition of a ' case ' of tuberculosis. It was decided that, from the epidemiological point of view, a ' case ' of pulmonary tuberculosis means a person suffering from bacteriologically confirmed disease. Acceptance of this definition would lead to the provision of statistical information that would be internationally and intranationally comparable, and would establish the basis for notification to the public health authorities. All other possible sufferers from tuberculosis, i.e., those in whom the disease has not been confirmed bacteriologically, would be classified as ' suspect cases ' and would remain so classified unless or until the presence of tubercle bacilli or some other etiology was established."

The main purpose of this paper is to focus attention on the difficulties of defining a case on the basis of bacteriological and X-ray examination and the tuberculin test. Data from two surveys in the same villages in Bangalore District, South India, carried out by the National Tuberculosis Institute, form the basis of the study. Changes in the status of a case from the first survey to the second, and the status at the first survey of cases found at resurvey, provide another dimension further to highlight the problem.

METHODS AND MATERIAL

SURVEY AND RESURVEY PROCEDURES

A simple random sample of 119 villages from among the 734 villages in 3 taluks of Bangalore District, South India, was surveyed from May 1961 to January 1963 and resurveyed after an average interval of 18 months. A further simple random sample of 14 of the remaining villages was surveyed from February 1963 to July 1963 and resurveyed after an average interval of 9½ months " in order to study changes after a shorter interval ". In none of these taluks had mass tuberculin testing or BCG vaccination previously been carried out. Survey techniques have been described in detail earlier (Raj Narain et al., 1963). Briefly, the relevant procedures adopted were as follows.

After a complete census, the entire population was offered a tuberculin test with 1 TU of RT 23 in 0.1 ml phosphate buffer containing 0.005% Tween 80. At the time of testing, both shoulders of each person were examined to identify those vaccinated elsewhere. The longitudinal diameter of induration to the tuberculin test was recorded after 3–4 days. As explained earlier (Raj Narain et al., 1963), all indurations of 10 mm or more were reported as positive.

All persons 5 years or more of age were offered a 70-mm photofluorogram of the chest at the time of the 1-TU test. The X-ray films were read independently by two readers. (Extracts from the code followed for X-ray reading are given in the Annex.) For pictures read as C or D (active or possibly active tuberculosis) by only one of the readers, a third reader recorded his readings with full knowledge of the previous readings.

All those with any kind of abnormality found by either reader, but not those with pulmonary calcification only, were eligible for sputum examination. Those with unsatisfactory photofluorograms or those who could not be X-rayed owing to physical disability were also eligible. In addition, all those eligible for sputum examination at the first round were also eligible for the examination at the resurvey regardless of their X-ray reading. Two samples of sputum, one " spot " (expectorated under direct supervision) and the other " overnight " (expectorated during the night or early morning), were collected. Each sample was examined independently. A smear was stained and examined first by fluorescence microscopy, destained and examined again by the Ziehl-Neelsen technique. Each sample was cultured on 2 slopes of Löwenstein-Jensen medium without potato starch, after homogenization with 4% sodium hydroxide. All positive cultures were identified by subculturing and observing growth at room temperature, rate of growth at 37°C, production of pigment in the dark and after exposure to light, peroxidase and catalase reactions and niacin production (the last test was introduced as from January 1962). On all positive cultures, sensitivity studies against several concentrations of isoniazid, streptomycin and *p*-aminosalicylic acid (PAS) were also carried out. Only those cultures considered to be of the human type have been reported as positive, but the term " sputum-positive " includes all cases, even those found positive only by direct smear (by fluorescence microscopy or by Ziehl-Neelsen staining) and not by culture.

The resurvey (or the second round) was started in November 1962 with similar techniques except

TABLE 1

DE JURE POPULATION[a] AND PERCENTAGE COMPLETING VARIOUS EXAMINATIONS AT ROUNDS I AND II IN 133 VILLAGES

Sex	*De jure* population	Percentage who had 1-TU test read	X-ray examination		Sputum examination	
			No. eligible	Percentage examined	No. eligible	Percentage examined
			Round I			
Males	37 733	81.5	32 126	86.7	3 791	90.3
Females	35 956	86.4	30 407	87.1	3 537	90.9
Both sexes	73 689	83.9	62 533	86.9	7 328	90.6
			Round II			
Males	37 978	75.5	32 225	83.0	6 535	84.2
Females	36 256	81.0	30 514	82.5	6 549	87.2
Both sexes	74 234	78.2	62 739	82.8	13 084	85.7

[a] Including those with BCG scars, definite or doubtful.

that the tuberculin test was given at a different site.

A third round, not reported here but referred to in passing below (page 720), was conducted after an average interval of 1½ years from the second round.

No treatment could be offered to patients diagnosed during the first survey. Not many facilities for treatment were available in the area. A history of treatment from all sputum-positive cases diagnosed initially was collected at the time of resurvey by the census takers of the survey team and, some 2–3 months later, by trained sociological investigators. No history of treatment was recorded at the initial survey.

STUDY POPULATION AND COVERAGE

Permanent residents, including those who were temporarily away at the time of registration, constitute the study population (*de jure* population). Table 1 shows the percentage of those who completed various examinations in the 133 villages at the 2 rounds. The coverage for 1-TU testing and reading was somewhat better for females than for males, but attendances for X-ray and sputum examinations did not show much difference between the two sexes. The coverages in respect of the different age-groups are not shown in the table. About 5% to 10% more of those below 15 years than those above this age, in each sex, completed the 1-TU test in the first round; in the second round, the coverage for the test among younger age-groups was even better, by over 15%. In all, 2328 persons at Round I and 2803 at Round II with a BCG scar (definite or doubtful) have been excluded from the analysis in order to confine the study to those with no previous BCG. These included 8 sputum-positive cases, and 19 sputum-negative X-ray cases at Round I and 6 and 20 respectively at Round II.

The criteria for eligibility for sputum examination were liberal in order to find the maximum number of sputum-positive cases. Of those X-rayed, 13% at Round I and 25% at Round II were eligible for sputum examination and sputa were collected from 91% of these at Round I and from 86% at Round II (Table 1).

METHODS OF ANALYSIS

The cases found during the initial survey were classified into different subgroups according to the results of the tuberculin test, X-ray and sputum examination. These results have been considered independently.

Definitions and abbreviations of some of the terms used are listed below:

Term	*Abbreviation*	*Definition*
Definite-positive on culture	C+	20 or more colonies grown in at least one culture tube from either of the 2 samples.
Scanty-positive on culture	C(+)	1–19 colonies grown in any culture tube, but not C+.

Negative on culture	C−	No growth in any tube in 8 weeks.
Definite-positive on microscopy	M+	At least 4 and quite often many more bacilli seen on any smear by any technique.
Scanty-positive on microscopy	M(+)	1–3 bacilli seen on a smear after a search for 10 minutes, but not M+.
Negative on microscopy	M−	No bacilli seen after a search for 10 minutes in any smear by any technique.
X-ray case	R+	Category C or D (see Annex) by any 2 readers.
Doubtful X-ray case	R(+)	Category C or D by 1 reader only and not confirmed by third reader.
Other X-ray abnormalities	Ro	Category A or B (see Annex) by at least 1 X-ray reader; may be negative by the other.
X-ray negative	R−	Negative by both readers.

For the various groups of cases from the first survey, the status at resurvey has been used to add a further dimension for bringing out differences among them. The cases found on resurvey were similarly classified and their status at the time of the first survey was studied in order to view the differences from a different angle.

FINDINGS

CLASSIFICATION OF SPUTUM-POSITIVE CASES INTO 4 MAIN GROUPS

In the material studied, there were 267 sputum-positive cases in Round I and 270 in Round II, 75 being common. As a result of the correlation between the culture and microscopy results in Table 2, these sputum-positive cases can be divided into 8 different groups, but over 90% at either round fall into the following 4 types:

1. C+ M+ cases: Definite-positive on culture as well as microscopy, constituting 26%–28% of the cases.
2. C+ M− cases: Definite-positive on culture but negative by microscopy, constituting 16%–17% of the cases.
3. C(+) M− cases: Scanty-positive on culture but negative by microscopy (22%–25%).
4. C− M(+) cases: Negative on culture but scanty-positive by microscopy (23%–25%).

Comparatively, the first type was the largest, the second the smallest and the other two of similar size. The second and third types together comprised all those positive on culture *only*, and of these about 60% were scanty-positive on culture.

TABLE 2

CORRELATION BETWEEN CULTURE AND MICROSCOPY RESULTS FOR SPUTUM-POSITIVE CASES AT ROUNDS I AND II IN 133 VILLAGES [a]

		Round I				Round II			
		Culture			Total	Culture			Total
		C+	C(+)	C−		C+	C(+)	C−	
Microscopy	M+	*75*	4	7	86	*69*	—	10	79
	M(+)	12	5	*60*	77	11	3	*66*	80
	M−	*46*	*58*	—	104	*43*	*68*	—	111
	Total	133	67	67	267	123	71	76	270

[a] See text-tabulation above for explanation of the abbreviations used. The 4 main types of cases (see text above), constituting over 90% of the total, are shown in italics.

TABLE 3
SEX DISTRIBUTION OF THE 4 TYPES OF SPUTUM-POSITIVE CASES AT ROUNDS I AND II IN 133 VILLAGES

	C+ M+		C+ M−		C(+) M−		C− M(+)	
	Males	Females	Males	Females	Males	Females	Males	Females
Round I								
Number	61	14	38	8	38	20	31	29
Sex ratio (females per 100 males)	23.0		21.1		52.6		93.5	
Round II								
Number	55	14	32	11	36	32	34	32
Sex ratio (females per 100 males)	25.5		34.5		88.9		94.1	

The 4 types are discussed further to illustrate that the sputum-positive cases, far from being a uniform group, show a great variation even among themselves.

SEX DISTRIBUTION OF THE 4 TYPES OF SPUTUM-POSITIVE CASES

Table 3 shows the number and ratio of these 4 types of sputum-positive cases for each sex, separately for the two rounds. The sex ratio (females per 100 males) almost consistently increased from 23 for the first type to 94 for the fourth type, for Round-I cases; a similar trend was seen in Round-II cases. The distribution among the different age-groups was fairly similar for each type of case and the trend for the sex ratio was also generally the same for each age-group (not shown in the table).

For a proper interpretation of the sex variation it is necessary to consider how often these types of cases were found among the total whose sputum was examined for each sex at each round (Table 4). Cases with definitely positive cultures (C+ M+ and C+ M−) occurred much less frequently among females ($P<0.01$), while C− M(+) cases occurred almost equally often in the two sexes. This was also true of the different age-groups (not shown). The equal frequency for C− M(+) in the two sexes suggests errors or other factors, the frequency of which is almost equal in males and females.

TABLE 4
PREVALENCE OF 4 TYPES OF SPUTUM-POSITIVE CASES AS PERCENTAGE OF THOSE WHOSE SPUTUM WAS EXAMINED IN THE TWO SEXES AT ROUNDS I AND II IN 133 VILLAGES

	Number sputum examined [a]	C+ M+	C+ M−	C(+) M−	C− M(+)
Round I					
Male	3 293	1.85	1.15	1.15	0.94
Female	3 127	0.45	0.26	0.64	0.93
Round II					
Male	4 913	1.12	0.65	0.73	0.69
Female	5 231	0.27	0.21	0.61	0.61

[a] Excludes those with a BCG scar, definite or doubtful.

TABLE 5

RESULTS OF X-RAY EXAMINATIONS (AS PERCENTAGE) FOR 4 TYPES OF SPUTUM-POSITIVE CASES, AND BY SEX, AT ROUNDS I AND II IN 133 VILLAGES [a]

X-rays status [a]	C+ M+	C+ M−	C(+) M−	C− M(+)	C+ M+ and C+ M−		C(+) M−		C− M(+)	
					Male	Females	Males	Females	Males	Females
Round I										
R+	90.7	67.4	51.7	6.7	81.8	81.8	57.9	40.0	9.7	3.4
R(+)	4.0	6.5	17.2	15.0	5.1	4.5	15.8	20.0	22.6	6.9
Ro and R−	5.3	26.1	31.1	78.3	13.2	13.7	26.3	40.0	67.7	89.7
Total [b]	100.0 (75)	100.0 (46)	100.0 (58)	100.0 (60)	100.0 (99)	100.0 (22)	100.0 (38)	100.0 (20)	100.0 (31)	100.0 (29)
Round II										
R+	89.7	60.0	43.5	1.7	83.5	60.9	56.3	30.0	3.1	—
R(+)	1.5	2.5	6.5	3.3	—	8.7	3.1	10.0	—	7.1
Ro and R−	8.8	37.5	50.0	95.0	16.5	30.4	40.6	60.0	96.9	92.9
Total [b]	100.0 (68)	100.0 (40)	100.0 (62)	100.0 (60)	100.0 (85)	100.0 (23)	100.0 (32)	100.0 (30)	100.0 (32)	100.0 (28)

[a] See text-tabulation on pages 703-704 for explanation of the symbols used.
[b] Figures in parentheses show the number X-rayed.

X-RAY RESULTS FOR THE 4 TYPES OF SPUTUM-POSITIVE CASES

The results of X-ray examination for the 4 types of sputum-positive cases are shown in Table 5 separately for the two rounds. The left half of the table shows that the proportion of R+ cases consistently decreased from about 90% in the first type to 6.7% in Round I and from about the same figure to 1.7% in Round II in the fourth type, while the proportions of Ro and R− cases consistently, and of R(+) cases generally, increased for both rounds from the first to the fourth type. Substantial proportions of sputum-positive cases of the last 3 types did not show radiological evidence of active disease (especially the fourth type, where over 90% were not R+ cases).

Comparison between males and females in the right half of Table 5 again shows an interesting difference. Except for the definite-positive cultures of Round I, the females had a smaller proportion of X-ray cases, being significantly less ($P<0.05$) in Round II for C+ and C(+) cases. Further, the proportion of cases considered as R− or Ro was generally greater among females, the differences being quite large in some instances. This may be due to the comparatively greater difficulty in reading the X-ray pictures of females, as also reported earlier (Raj Narain et al., 1963). It may also be seen that the proportion of R− and Ro cases was much higher at Round II for all categories of cases except the culture-positive cases in males, in which the proportion of X-ray cases remained more or less the same. This lower proportion of X-ray cases is referred to later (see page 708).

TUBERCULIN-TEST RESULTS FOR THE 4 TYPES OF SPUTUM-POSITIVE CASES

Table 6 shows the size of tuberculin reactions for the 4 types of sputum-positive cases. The one salient finding is that, among the C− M(+) cases, 56% in Round I and 46% in Round II had an induration of 9 mm or less and may not be considered as infected; the mean induration was 9.3 mm in Round I and 12.7 mm in Round II as compared with 22 mm to 26 mm for the other 3 types which are culture-positive (bottom row of Table 6). This again emphasizes that C− M(+) may not be real cases. It is interesting to note that a small proportion of even C+ M+ cases were also tuberculin-negative (5.5% in Round I and 1.6% in Round II), as were 8.1% of C+ M− cases of Round II. Among definite-positives on culture, the proportion having

TABLE 6

TUBERCULIN REACTIONS (AS PERCENTAGE) FOR THE 4 TYPES OF SPUTUM-POSITIVE CASES AT ROUNDS I AND II IN 133 VILLAGES

Induration to 1 TU (mm)	Round I				Round II			
	C+ M+	C+ M−	C(+) M−	C− M(+)	C+ M+	C+ M−	C(+) M−	C− M(+)
0–4	4.1	–	3.6	45.7	–	2.7	5.3	30.5
5–9	1.4	–	3.6	10.2	1.6	5.4	8.8	15.3
10–14	6.8	2.3	1.8	13.6	3.3	8.1	8.8	10.2
15+	87.7	97.7	91.0	30.5	95.1	83.8	77.1	44.0
Total [a]	100.0 (73)	100.0 (44)	100.0 (56)	100.0 (59)	100.0 (61)	100.0 (37)	100.0 (57)	100.0 (59)
Mean induration (mm)	22.3	26.2	24.1	9.3	25.0	22.3	22.2	12.7

[a] Figures in parentheses show the number tuberculin tested and read.

10-mm–14-mm reactions was even greater than that with reactions of 0 mm–9 mm, and the percentage with negative reactions would be doubled if a reaction of 15 mm or more were to be considered as evidence of infection (as suggested by Raj Narain, 1968).

Though this is not shown in the table, among the culture-positive cases females had a greater mean induration and a larger percentage had reactions of 15 mm or more than males. This is in line with the higher frequency of large reactions in females which has also been reported earlier (Raj Narain et al., 1963, 1966a). A similar sex difference in reactions to PPD-S and PPD-G has also been observed (Wijsmuller et al., 1968).

COMBINED X-RAY AND TUBERCULIN-TEST RESULTS FOR SPUTUM-POSITIVE CASES

Theoretically all or nearly all sputum-positive cases should show evidence of disease on X-ray examination and should be tuberculin-positive, but only 55% of the sputum-positive cases of the first round and 50% of the second round were R+ cases. The percentage of R+ cases is reduced to 53 and 48 respectively, if tuberculin positivity [1] is also considered. Of the sputum-positive cases, 14% in Round I and 16% in Round II were neither X-ray cases nor tuberculin-positive. By far the major source of this incompatibility comes from the C− M(+) group of cases. (For details, see Appendix Tables 1 and 2.)

On the basis of either culture or direct-microscopy results 4 groups of sputum-positive cases are chosen to illustrate interesting variations with regard to their X-ray and tuberculin results.

1. M+ cases: Among these, 80% were both X-ray cases and tuberculin-positive in each round, while 2% in Round I and 6% in Round II were neither X-ray cases nor tuberculin-positive.

2. C+ cases: Among these, 78% in Round I and 76% in Round II were both X-ray cases and tuberculin-positive, while none and 2% respectively were neither X-ray cases nor tuberculin-positive.

3. C(+) M− cases: Among these, 51% in Round I and 44% in Round II were both X-ray cases and tuberculin-positive, while 4% and 13% respectively were neither X-ray cases nor tuberculin-positive.

4. C− M(+) cases: Among these, 14% in each round were both X-ray cases and tuberculin-positive, while 42% and 36% respectively were neither X-ray cases nor tuberculin-positive.

Of the total sputum-positive cases found in the survey, only less than one-quarter were definite-positives on direct smear and were also X-ray and tuberculin-positive. Even definite-positives on culture which were compatible with X-ray and tuberculin

[1] Hereafter and unless otherwise specified, for the purpose of calculating percentages sputum-positive cases for whom tuberculin-test results are not available are considered to be tuberculin-positive if the majority of the cases in their category are tuberculin-positive; similarly, they are considered to be tuberculin-negative if that is the condition of the majority of cases in their category.

TABLE 7
TUBERCULIN STATUS OF SPUTUM-NEGATIVE R+ AND R(+) CASES IN ROUNDS I AND II IN 133 VILLAGES

X-ray status	Round I		Round II	
	Total test read	Percentage tuberculin positive [a]	Total test read	Percentage tuberculin positive [a]
D[b] by 2 readers	45	64.4	30	56.7
D[b] by 1 reader, C[b] by the other	74	58.1	46	71.7
C[b] by 2 readers	394	62.4	207	72.9
X-ray, i.e., R+, cases	513	62.0	283	71.0
D[b] by 1 reader only	20	50.0	11	54.5
C[b] by 1 reader only	709	50.1	241	61.0
Doubtful X-ray, i.e., R(+), cases	729	50.1	252	60.7

[a] With induration ⩾ 10 mm.
[b] See Annex for definitions of categories C and D.

results formed only about one-third of the total sputum-positives found. The incompatibility is reduced, but not very much, if the C− M(+) cases are excluded from the total.

SPUTUM-NEGATIVE CASES WITH X-RAY EVIDENCE OF ACTIVE DISEASE

The percentage who were tuberculin-positive among those with radiologically active disease (Category C and D as defined in the Annex) but with negative sputum is given in Table 7. The percentage tuberculin-positive was significantly higher at each round ($P<0.05$) among the R+ cases than the R(+) cases. The proportions of positives were not significantly higher among cases regarded as active with a greater degree of probability (D by 2 readers for R+ cases or D by 1 reader for R(+) cases); in fact, these were less than for C by 2 readers or C by 1 reader in Round II. Though this is not shown in the table, in all subgroups the percentage positive at the 10-mm level was less among females.

The difference in the X-ray readings at the two rounds should be noted. In Table 7, the sputum-negative R+ and R(+) cases at Round II were fewer by 42.5% and 65% respectively than at Round I. This happened in spite of the fact that one reader was the same throughout the 3-year period and that the new second reader, who took over half-way through Round II, was a trained medical officer and was accepted as a reader only after a number of trial readings conducted to ensure a high order of consistency both with himself and with the original readers. Among the sputum-positives of Round II, there were smaller proportions of R+ or R(+) cases and higher proportions of X-ray normals or non-tubercular cases than among those of Round I (Table 5). This could possibly mean that there was underreading at Round II. That this reduction in the proportion of cases is not due to the change in criteria for eligibility for sputum examination was shown by similar findings in tables made after excluding the extra persons who were eligible for sputum examination at Round II (see Methods and Material, above).

CHANGES WITH TIME

Changes in status of Round-I cases at Round II and of Round-II cases at Round I are taken to indicate changes with time. For this purpose, cases from only 119 villages, which were surveyed at an interval of 18 months, have been considered.

It has been shown that the sputum-positive cases found in the survey fall into a large number of subgroups when the results of culture, microscopy, X-ray and tuberculin test are considered (Appendix

TABLE 8

STATUS AT ROUND I OF DIFFERENT CATEGORIES OF SPUTUM-POSITIVE CASES AND OF SPUTUM-NEGATIVE X-RAY AND DOUBTFUL X-RAY CASES FROM ROUND II IN 119 VILLAGES

Category No. and status at Round II	Number of cases [a]	Bacteriological status at Round I			Radiological status at Round I		
		Number examined	Percentage C+	Percentage C− M−	Number X-rayed	Percentage R+	Percentage Ro and R−
Sputum-positive cases							
1. C+ M+ or M(+)	68	50	58.0	26.0	59	72.9	25.4
2. C+ M−	35	25	20.0	52.0	34	44.1	47.1
3. C(+) M−	53	31	25.8	54.8	46	41.3	52.2
Subtotal (1+2+3)	156	106	39.6	40.6	139	55.4	39.6
4. C− M(+)	51	20	—	100.0	48	2.1	93.9
All sputum-positive cases [b]	235	149	30.2	53.7	214	40.2	54.7
Sputum-negative R+ cases							
5. Tuberculin +	183	124	8.1	84.7	159	64.8	29.6
6. Tuberculin −	72	39	—	100.0	59	45.7	45.7
Subtotal (5+6)	255	163	6.1	88.3	218	59.6	33.9
Sputum-negative R(+) cases							
7. Tuberculin +	141	81	1.2	95.1	120	20.0	67.5
8. Tuberculin −	92	34	—	97.1	77	6.5	79.2
Subtotal (7+8)	233	115	0.9	95.7	197	14.7	72.1

[a] Cases whose sputum was not examined at Round II have been excluded.
[b] Includes sputum-positive cases not included in the first 4 categories.

Tables 1 and 2). Similarly, Table 7 shows some subgroups of the sputum-negative cases with X-ray evidence of active disease, which could be further subdivided into tuberculin-positives and -negatives. To illustrate variation in changes with time only 8 categories of " cases " are shown in Tables 8 and 9. Categories 2 and 3 include most of the additions by culture, category 2 being definite-positive, C+, and category 3 scanty-positive, C(+), on culture. Category 4 consists of C− M(+), i.e., the doubtful group of cases. Categories 5 and 6 represent sputum-negative R+ cases and categories 7 and 8 sputum-negative R(+) cases. The status of these categories of Round-II cases, as seen at Round I, is shown in Table 8, while the status of the same categories of Round-I cases, as seen at Round II, is shown in Table 9.

Status at Round I of different categories of Round-II cases in 119 villages (Source of cases)

Table 8 shows the bacteriological and radiological status at Round I of the 8 categories of cases in Round II in 119 villages. For bacteriological status, the percentages of C+ cases and of those negative by culture and smear at Round I are shown. For radiological status at Round I, the percentages of R+ X-ray cases and of those with no X-ray evidence of active disease (Ro or R−) are given.[1]

Sputum-positive cases. The most striking finding is that category-4 cases, C− M(+), were all sputum-negative 18 months earlier and that nearly all (94%) had no radiological evidence of disease. About 60% were tuberculin-negative at the earlier round (not shown in the table).

Cases in the first category, C+ M+ or M(+), had significantly higher proportions ($P<0.01$) of definite-positives on culture and of X-ray cases at the earlier round than did cases in categories 2 or 3. The percentage of those with no X-ray evidence of active disease was also significantly ($P<0.05$) less. The differences between categories 2 and 3 were rather small. This could indicate that those categories, both additions by culture, were rather similar and probably included a large proportion of new cases in their early stages.

Within each of the first 2 categories, those who were X-ray cases and tuberculin-positive at Round

[1] The percentage of C(+) and the doubtful group (C− M+) for bacteriological status and of R(+) for radiological status have not been shown in Tables 8 and 9, but can be calculated by subtracting from 100 the sum of the above two percentages given in the tables.

TABLE 9

STATUS AT ROUND II OF DIFFERENT CATEGORIES OF SPUTUM-POSITIVE CASES AND OF SPUTUM-NEGATIVE X-RAY AND DOUBTFUL X-RAY CASES FROM ROUND I IN 119 VILLAGES

Category No. and status at Round I	Mortality at Round II			Bacteriological status at Round II			Radiological status at Round II		
	No. of cases [a]	Number followed up	Percentage of deaths	Number examined	Percentage C+	Percentage C− M−	Number x-rayed	Percentage R+	Percentage Ro and R−
Sputum-positive cases:									
1. C+ M+ or M(+)	76	72	34.7	42	57.1	33.3	42	78.6	21.4
2. C+ M−	43	41	19.5	31	35.5	45.2	32	59.4	34.4
3. C(+) M−	55	51	9.8	41	34.1	48.8	40	55.0	37.5
Subtotal (1+2+3)	174	164	23.2	114	43.0	42.1	114	64.9	30.7
4. C− M(+)	52	49	2.0	43	—	100.0	43	2.3	93.0
All sputum-positive cases [b]	239	224	17.4	168	29.8	58.9	166	47.0	48.2
Sputum-negative R+ cases:									
5. Tuberculin +	276	258	4.3	215	6.0	88.4	203	46.3	43.3
6. Tuberculin −	167	157	7.6	127	0.8	97.6	122	35.2	55.7
Subtotal (5+6)	443	415	5.5	342	4.1	91.8	325	42.2	48.0
Sputum-negative R(+) cases:									
7. Tuberculin +	288	276	4.0	236	1.3	96.6	224	4.6	83.5
8. Tuberculin −	267	249	6.0	208	—	99.0	195	3.6	89.2
Subtotal (7+8)	555	525	5.0	444	0.7	97.7	419	4.5	86.2

[a] Cases whose sputum was not examined at Round I have been excluded.
[b] Includes sputum-positive cases not included in the first 4 categories.

II consistently showed larger proportions which were C+ and X-ray cases in the earlier round (not shown in Table 8 but shown in Appendix Table 3). The differences, however, were significant only for the percentages of X-ray cases ($P<0.05$). Though these significant differences could be expected because radiological status was a distinguishing criterion, it is interesting to record that a significantly higher proportion of those found at Round II to be sputum-positive and radiologically active (categories I, III and IV in Appendix Table 3) had been X-ray cases at Round I than had been sputum-positive cases.

Sputum-negative R+ cases. The sputum-negative R+ cases have been presented in 2 categories—tuberculin-positive and tuberculin-negative (categories 5 and 6, Table 8). Compared with the tuberculin-positives, none of the tuberculin-negatives was bacteriologically positive at the earlier round and a smaller number had radiological evidence of disease. In both respects the differences were statistically significant ($P<0.05$). It is possible to have further categories based on X-ray reading (see Appendix Table 3); suffice it to say here that the sputum-negative X-ray cases also do not represent a uniform population.

It may be added that about 10% of the tuberculin-negative cases at Round II were tuberculin-positive 18 months earlier (not shown).

Sputum-negative R(+) cases. The sputum-negative R(+) cases (categories 7 and 8, Table 8) show a similar difference between the tuberculin-negatives and the tuberculin-positives, and these can also be further subdivided according to the X-ray readings, as shown in Appendix Table 3. The same lack of homogeneity is seen.

Status at Round II of different categories of Round-I cases in 119 villages (Fate of cases)

Sputum-positive cases. Only 2% of the C−M(+) cases, for which the diagnosis has already been shown to be quite suspect, had died by the time of the resurvey 18 months later (Table 9). This mortality rate is lower than for any other category of cases and in its crude form is not much different from the general death rate. Besides, those in this category who were followed up were all bacteriologically

negative 18 months later and 93% showed no evidence of any radiologically active disease.

The first category in Table 9 showed a significantly higher mortality ($P<0.01$) and larger proportions which continued to be definite-positive on culture and to be R+ cases as compared with category 3 (differences with category 2 were not significant). Moreover, the indices considered in Table 9 consistently showed a more favourable change with time from category 1 to category 2 and from category 2 to category 3. The differences, however, failed to attain statistical significance, most probably owing to the small numbers available.

Further divisions of these 3 and other categories by X-ray and tuberculin status are shown in Appendix Table 4. Within each of the first 3 pairs, the status at resurvey of the cases that were R+ as well as positive to tuberculin was consistently more serious than that of those who were not both R+ and tuberculin-positive. The differences were highly significant ($P<0.01$) for both indices of radiological status within all 3 pairs. The proportion definitely positive on culture also differed significantly within the first pair ($P<0.01$) and within the second pair ($P<0.05$). These indices of bacteriological and radiological status showed similar variations when recalculated on the basis of the total number followed up in order to obviate the effect on them of higher mortality in any one category. The differences within the pairs were not significant with respect to mortality.

From the above analysis, it appears that the 3 categories of sputum-positive cases (all culture-positive) in Table 9 differ considerably in the seriousness of disease, and may also differ in the duration of the disease and possibly other aspects.

Sputum-negative R+ cases. For sputum-negative R+ cases (Table 9), there is no significant difference in mortality between the tuberculin-negatives and the tuberculin-positives. But from the tuberculin-positives 11.6% and from the tuberculin-negatives 2.4% became bacteriologically positive 18 months later, the difference being significant ($P=0.01$). Of the total R+ cases, 42.2% continued to be R+ cases 18 months later, while only 8.2% became bacteriologically positive.

Further categories of sputum-negative R+ cases based on the readings of the 2 readers (Appendix Table 4) show that the X-ray categories C and D (see the Annex) do not present any clear-cut difference between each other and the classification does not seem to serve a useful purpose.

Sputum-negative R(+) cases. Not much difference was seen between the fate of the tuberculin-positive and the tuberculin-negative R(+) cases (categories 7 and 8, Table 9).

On the basis of the foregoing observations on changes with time, some comments may be made:

(*a*) If a sputum-negative R+ case is tuberculin-negative, it would appear desirable, for practical purposes, not to consider it as a case of pulmonary tuberculosis.

(*b*) Among sputum-positive R+ cases, X-ray shadows persist longer than sputum positivity.

(*c*) Among sputum-negative R+ cases, as many as 60% were R+ cases 18 months earlier, while only 12% were then bacteriologically positive; 18 months later, 42% were R+ cases and only 8% were sputum-positive. Thus there were a large number of cases which were R+ but sputum-negative at both rounds.

Effect of treatment on the findings

Some of the changes with time, especially those shown in Table 9, could have been due to treatment taken by patients. The persons diagnosed as cases during the first round were neither informed about the diagnosis nor offered treatment, but some of them did seek treatment according to the normal behaviour pattern of cases in that area. Information regarding this was collected by interviewing the patients later (see Methods and Material, above). For those with sensitive strains and those in category C−M(+) at Round I, the distribution of the treated and the untreated cases according to their bacteriological and radiological status at resurvey is given in Table 10. Cases with resistant strains are omitted, as they are less likely to show the influence of the treatment available. Even those giving a history of 15 days' treatment have been considered as "treated" cases.

If treatment had an influence on sputum conversion, the percentage treated could be expected to be higher among those who became sputum-negative at the resurvey. This was not found to be the case. On the contrary, the proportion not treated was significantly higher among the sputum-negatives ($P<0.01$) than among those who continued to be positive. Even after excluding category 4, the differences remained significant by the χ^2 test ($P<0.05$). It may be argued that the C+ cases at resurvey had been advanced cases at Round I in whom sputum conversions could not be expected with the irregular

TABLE 10

BACTERIOLOGICAL AND X-RAY STATUS AT ROUND II OF THE TREATED AND NOT TREATED CASES WITH SENSITIVE STRAINS FOR DIFFERENT CATEGORIES OF SPUTUM-POSITIVE CASES FROM ROUND I IN 119 VILLAGES

Category at Round I	Sputum result at Round II								X-ray cases at Round I			
	Total		C–		C(+)		C+		Total		Those still X-ray cases at Round II	
	Treated	Not treated	Treated	Not treated	Treated	Not treated	Treated	Not treated	Treated	Not treated	Treated	Not treated
1. C+ M+ or M(+)	23	13	7	8	2	1	14	4	22	7	21	6
2. C+ M–	11	18	4	8	3	3	4	7	8	13	7	12
3. C(+) M–	10	27	4	13	–	7	6	7	7	12	7	10
4. C– M(+)	1	42	1	42	–	–	–	–	–	2	–	1
All cases [a]	48 (31.0)	107	18 (18.8)	78	6 (35.3)	11	24 (57.1)	18	39 (52.7)	35	36 (54.5)	30
All cases excluding category 4 [a]	47 (42.0)	65	17 (32.1)	36	6 (35.3)	11	24 (57.1)	18	39 (54.2)	33	36 (55.4)	29

[a] Figures in parentheses show the percentage treated in the group concerned.

treatment available. This may not be so because, assuming that category 1 is more advanced than category 2 and that category 2 is more advanced than category 3, it will be seen that out of 42 C+ cases at resurvey, only 18 belonged to category 1, while 11 were in category 2 and 13 in category 3 at Round I. It may be noted that the very argument itself implies that among sputum-positives there is a great variation, cases differing considerably from one another in the extent to which they become sputum-negative in the next round, a conclusion reached by the earlier analysis from a different angle.

The last four columns of Table 10 show the number who were also X-ray cases at Round I among the 4 categories of sputum-positive cases and those who were still X-ray cases at Round II. Most of the cases, whether treated or untreated, remained X-ray cases at Round II. Thus the treatment taken did not result in much radiological improvement either. The variation in the percentage of " treated " cases in the different categories in the second and third columns of Table 10 is interesting. Only 1 out of 43 cases followed up in category 4 had treatment. The number of " treated " cases exceeded that of the untreated cases (and considerably so) only in category 1, which had been positive on culture and smear. Even in this category, 13 out of 36 cases did not give a history of treatment and 8 of these 13 were culture-negative at Round II. In some, the absence of a history of treatment may represent a limitation of the interview technique or the result of late recording of history, but not in all cases can this be true. The steady decline in the proportion who sought treatment from category 1 to category 4 shows that these cases also differed a great deal in their urge to seek treatment.

The above observations on the influence of treatment on the findings, and the rather high sputum conversion rates among the untreated cases in the first 3 categories, show that in a substantial number of cases sputum became negative with some irregular treatment or even without any specific treatment. Thus it would appear that many of the cases, especially if they are negative on direct smear (namely, categories 2 and 3), may not pose a public health problem, as the duration of their sputum-positive status and their capacity to spread infection during this period could possibly be slight.

Some sex differences

Changes with time for males and females separately are shown in Table 11 for only 3 broad categories of cases. Part A of the table shows the status at Round I of Round-II cases; part B shows the status at Round II of Round-I cases. All differences

TABLE 11

COMPARISON OF CHANGES WITH TIME FOR MALE AND FEMALE CASES IN 119 VILLAGES [a]

	Sputum-positive cases, excluding C− M(+)		Sputum-negative R+ cases		Sputum-negative R(+) cases	
	Males	Females	Males	Females	Males	Females
A. Status at Round I of Round-II cases						
No. of cases at Round II	126	56	172	102	123	123
Bacteriological status at Round I						
No. examined	93	34	116	61	70	52
Percentage C+	*43.0*	*14.7*	6.9	4.9	2.9	—
Percentage C(+)	17.2	20.6	5.2	4.9	1.4	3.8
Percentage C−	*39.8*	*64.7*	87.9	90.2	95.7	96.2
X-ray status at Round I						
No. X-rayed	115	50	153	80	106	105
Percentage R+	*63.5*	*24.0*	63.4	53.8	16.0	10.5
Percentage Ro and R−	*32.2*	*68.0*	*26.8*	*42.5*	72.6	74.3
B. Status at Round II of Round-I cases						
No. of cases at Round I	139	48	256	201	336	239
No. followed up at Round II	131	44	242	187	318	223
Percentage dead	19.8	27.3	5.8	5.9	5.0	4.5
Bacteriological status at Round II						
No. examined	98	27	196	160	268	189
Percentage C+	43.9 (*34.7*)	25.9 (*17.9*)	6.1 (5.7)	1.3 (1.2)	0.7 (0.7)	0.5 (0.5)
Percentage C(+)	12.2 (9.7)	18.5 (12.8)	3.6 (3.3)	2.5 (2.3)	— (—)	0.5 (0.5)
Percentage C−	43.9 (34.7)	55.6 (38.5)	90.3 (84.3)	96.3 (90.0)	99.3 (93.7)	98.9 (94.0)
X-ray status at Round II						
No. X-rayed	98	25	196	141	248	182
Percentage R+	66.3 (*52.4*)	48.0 (*32.4*)	*51.5* (*48.1*)	*32.6* (*28.3*)	6.0 (5.7)	2.2 (2.1)
Percentage Ro and R−	30.6 (24.2)	40.0 (27,0)	*37.8* (*35.8*)	*59.6* (*55.3*)	88.7 (83.3)	90.7 (85.9)

[a] Figures in parentheses show the percentages relative to the number examined, after including the dead at Round II. Differences between the sexes that are significant at the 95 % confidence level at least are shown in italics.

between sexes which were significant at least at the 95% level of confidence are shown in italics.

Sputum-positive cases. The doubtful, C−M(+) (category 4), cases have been excluded from the sputum-positive cases. A smaller proportion of female than of male cases in Round II had bacteriological or radiological evidence of disease 18 months earlier (part A of the table); the differences in the proportion of those who were culture-positive, culture-negative, R+, or Ro and R− at Round I were significant. This could indicate that the development of the disease might have been more rapid among females. Part B of the table shows that, while the mortality was higher among sputum-positive

TABLE 12

X-RAY CASES (BY SEX) READ AS CATEGORY C OR D [a] BY EACH READER IN THE TWO ROUNDS AND PERCENTAGE CONFIRMED BY CULTURE OR BY THE OTHER READER IN 133 VILLAGES

	Round I				Round II			
	Reader 1		Reader 2		Reader 1		Reader 2	
	Males	Females	Males	Females	Males	Females	Males	Females
Total number of cases	726	418	583	386	365	205	358	205
Percentage [b] C+ or C(+)	*16.96*	*8.18*	*20.64*	*8.12*	*27.51*	*14.89*	*27.66*	*12.95*
Percentage confirmed by another reader	54.27	50.24	*73.76*	*61.40*	*78.90*	*62.93*	*80.45*	*62.44*

[a] See Annex for definitions of categories C and D.

[b] Percentages are calculated relative to the total number of cultures examined. Where the result for confirmation by bacteriology or by the other reader is significantly different between the sexes, the percentages are shown in italics.

females at Round II, only smaller proportions of the remaining cases were culture-positive or radiologically active after 18 months. The differences were not, however, statistically significant, most probably because of the small number of female cases and the exclusion of a higher proportion of dead among them. Calculations that included the deaths among the total followed up (figures in parentheses in the table) showed the same picture, but now the percentages of C+ cases and R+ cases were both significantly less among females. It could be that in females the disease takes a faster course, either for better or for worse. Unpublished provisional figures for the prevalence in Round I and the incidence from Round I to Round II of culture-positive cases show that the annual incidence was about a fourth of the prevalence among males and about half of the prevalence among females. This also would support the above observation, that the course of the disease may be faster among females. Though based on small numbers, the death rates show some interesting variations (not shown in the table). For females there were 11 deaths among 25 C+ cases as compared with only 1 among 18 C(+) cases. Such a large difference was not shown by male cases, with 22 deaths among 88 C+ cases and 4 deaths among 37(+) cases. This might explain why at any one round a smaller proportion of female than of male cases were definite-positives on culture (C+ cases) (Table 3). That infection among contacts was less for female cases (Raj Narain et al., 1966b) might have been, at least partly, due to the shorter duration of disease among them.

Sputum-negative R+ and R(+) cases. Sputum-negative R+ and R(+) cases in Table 11 also showed similar changes with time. Proportionately more of such female cases of Round II had been bacteriologically or radiologically negative in the earlier round, and among the cases of Round I a larger proportion became radiologically negative at Round II and a smaller proportion were bacteriologically positive. The differences were statistically significant for the radiological status only.

Other factors. If it is assumed that the diagnosis was suspect in a higher proportion of the cases in females, this could explain the "rapid changes" from round to round but would not explain the higher mortality among the sputum-positive cases at Round II. Similarly, although pregnancy and its hazards have not been analysed, these could explain the higher mortality but not the higher bacteriological and radiological negativity at Round II.

Apart from these sex differences in changes with time, other sex differences were:

(*a*) A lower prevalence of bacteriological cases was seen among females at Rounds I and II (Table 3).

(*b*) Smaller proportions of the bacteriological cases among females were also X-ray cases (Table 5).

(*c*) A lower prevalence of X-ray cases in females was noted at each of the two rounds (Table 12).

(*d*) Significantly smaller proportions of C or D cases for each reader were confirmed bacteriologically in females (Table 12).

(*e*) Confirmation by the other reader or the umpire of cases in category C or D read by any one reader was also less frequent among females (Table 12). These differences were statistically significant except for cases by one reader in Round I. Similar

findings were reported earlier (Raj Narain et al., 1963). It could be that a larger proportion of X-ray cases constituted a doubtful group among females. In addition, more rapid changes in the evolution of disease among females have been suggested from Table 11. Assessment of the relative extent and effect of these two factors would need further work.

(*f*) The age distribution of cases in the two sexes was also significantly different. Whether in category C+ or in category C(+) (or in both together), the proportion of female cases less than 45 years of age was significantly greater ($P<0.01$) in each round than that of male cases.

Lastly, it may be stated that the lower prevalence of disease in females seen now and also reported earlier (Indian Council of Medical Research, 1959; Raj Narain et al., 1963) may be due, at least in part, to differences in the behaviour of the disease in the two sexes.

Diagnosis based on X-ray examination of those negative by direct microscopy

If, in view of the great variation seen even among sputum-positive cases, only culture-positives were to be considered as genuine cases of pulmonary tuberculosis, this would emphasize the importance of culture examination in the diagnosis of tuberculosis. In developing countries, facilities for culture are usually not available on any large scale and diagnosis is based on direct microscopy, followed, if possible, by X-ray examination of the smear-negatives. Some idea of the extent of overdiagnosis resulting from such X-ray examination can be obtained from the present findings, although there are many differences between the usual situation in developing countries and the study reported here. Many more cases were probably asymptomatic in the present material and direct microscopy was based on 2 sputum specimens, both being examined by 2 techniques of staining. Also X-ray diagnosis was based on the combined readings of 2 readers. Furthermore, the group of cases considered in Tables 13, 14 and 15—namely, direct-smear-negatives who were read as C or D by either of the two X-ray readers—would conform to what the report of the WHO Expert Committee on Tuberculosis (1964) treats as " suspect cases " only.

Table 13 shows, separately for either reader, the radiologically active cases of disease in the two rounds who were all either negative or scanty-positive on direct microscopy (in 119 villages only). The percentages of those who were culture-positive (definite or scanty) and of those confirmed radiologically by the other X-ray reader are also shown. The total number of such cases in Round I was 899 according to Reader 1 and 608 according to Reader 2; in Round II the number was 417 according to each reader. Even if the 7%–12% culture-positive cases among them are excluded, the number of such " suspect " cases remains high and it is important to judge their real significance.

Although, as noted, only 7% to 12% of these cases were positive on culture, radiological confirmation of one reader's results by the other varied from 48% to 79%. For cases classified as D (see Annex) the percentage confirmed by culture was doubled (except for Reader 1 in Round II) and radiological confirmation was higher still (86% to 99%), but these cases formed only about one-sixth or less of the total; the vast majority were classified as C. Even for category D, confirmation by culture did not exceed 26% and most cases remained unconfirmed.

Cavitary cases. Cases with cavity, doubtful cavity or no cavity as assessed by each reader at the two rounds are also shown in Table 13. The latter two categories did not differ much in respect of the proportion of culture-positives among them.

Those with cavity constituted less than 10% of the total cases and even among these the maximum percentage of culture-positives was 25% (minimum 6.9%). Thus a large majority of the cavitary cases were culture-negative, and even recording of a cavity does not remove the considerable doubt about the nature of " suspect cases ".

Changes with time in category C or D cases who were not definitely positive by direct microscopy. Table 14 shows the bacteriological and radiological status at Round I of cases which, at Round II, were not definitely culture-positive and were read as C or D (radiologically active). Only about 15% of either reader's cases were culture-positive in Round I but X-ray shadows were present in about 50% as R+ and in another 10% as R(+). As could be expected, larger proportions of those who were culture-positive than of those who were culture-negative had bacteriological and radiological evidence of disease in Round I. More of X-ray category D than of category C had evidence of disease 18 months earlier (not shown in Table 14); the difference was seen for both the culture-positives and the culture-negatives, but was not always statistically significant. Even among the more serious category D cases about

TABLE 13

X-RAY CASES READ AS CATEGORY C OR D [a] BY EACH READER (EXCLUDING THOSE DEFINITELY POSITIVE BY MICROSCOPY) IN THE TWO ROUNDS AND PERCENTAGE CONFIRMED BY CULTURE OR BY THE OTHER READER IN 119 VILLAGES

	Round I		Round II	
	Reader 1	Reader 2	Reader 1	Reader 2
Total no. of cases [b]	899	608	417	417
Percentage culture-positive	7.2	9.9	12.0	11.5
Percentage radiologically confirmed [c]	48.4	78.8	68.8	70.5
Category-C cases				
No.	777	534	346	351
Percentage culture-positive	5.9	7.7	12.1	9.7
Percentage radiologically confirmed [c]	42.5	76.0	63.3	66.7
Category-D cases				
No.	122	74	71	66
Percentage culture-positive	15.6	25.7	11.3	21.2
Percentage radiologically confirmed [c]	86.1	98.6	95.8	90.9
Cases by cavitary status				
Cavity				
No.	72	16	36	29
Percentage culture-positive	18.1	25.0	13.9	6.9
Doubtful cavity				
No.	196	22	74	32
Percentage culture-positive	9.2	9.1	13.5	12.5
No cavity				
No.	586	513	271	311
Percentage culture-positive	5.5	10.1	12.5	12.9
Other C or D cases (e.g., pleural effusion or hilar adenitis)				
No.	45	57	36	45
Percentage culture-positive	4.4	3.5	2.8	4.4

[a] See Annex for definitions of categories C and D.
[b] Excluding cases whose sputa could not be examined.
[c] Confirmed by the other reader or umpire.

85% had been culture-negative and about 40% had no radiologically active lesion in the earlier round (not shown). Thus 18 months earlier the vast majority of these were not cases by bacteriological criteria and only about 50% were R+ cases.

What happened to these cases 18 months later is shown in Table 15. Even including those who were culture-positive at Round I, only 11% of those considered radiologically active by Reader 2 at that time were culture-positive at Round II (7.2% definite and 4.1% scanty) and only 8% of those classed as C or D by Reader 1. More than half had no radiologically active disease at the resurvey (63.2% according to Reader 1 and 50.8% according to Reader 2). Again, deaths and persistence of bacteriological or radiological disease after 18 months were more frequent among culture-positives than among culture-negatives; for both parameters this was more marked among category D cases than among Category C cases (not shown in the table); the differences between the latter categories were not always statistically significant, probably owing to the small numbers involved. Again, even among category D, very large proportions were culture-negative after 18 months, but X-ray shadows persisted in over 50% (not shown in the table).

Changes with time according to cavitary status as assessed by either reader. The proportion which had been positive on culture 18 months earlier did

TABLE 14

STATUS AT ROUND I OF CASES READ AS CATEGORY C OR D [a] BY EITHER READER AT ROUND II WHICH WERE NOT DEFINITELY POSITIVE BY MICROSCOPY IN 119 VILLAGES

Bacteriological status at Round II	Number of cases	Bacteriological status at Round I				Radiological status at Round I		
		Number examined	Percentage			Number X-rayed	Percentage	
			C+	C(+)	C–		R+	Ro and R–
Cases read as category C or D at Round II by Reader 1								
Culture-positive	50	41	31.7	22.0	46.3	48	72.9	20.8
Sputum not examined	35	22	9.1	..	90.9	33	36.4	57.6
Culture-negative	367	232	5.2	4.7	90.1	314	47.5	43.3
Total	452	295	9.2	6.8	84.0	395	49.6	39.2
Cases read as category C or D at Round II by Reader 2								
Culture-positive	48	35	34.3	20.0	45.7	46	67.4	26.1
Sputum not examined	29	22	13.6	..	86.4	26	53.8	42.3
Culture-negative	369	221	5.0	3.6	91.4	317	46.7	42.6
Total	446	278	9.4	5.4	85.2	389	49.6	40.6

[a] See Annex for definitions of categories C and D.

TABLE 15

STATUS AT ROUND II OF CASES READ AS CATEGORY C OR D [a] BY EITHER READER AT ROUND I WHICH WERE NOT DEFINITELY POSITIVE BY MICROSCOPY IN 119 VILLAGES

Bacteriological status at Round I	Number at cases	Mortality at Round II		Bacteriological status at Round II				Radiological status at Round II		
		Number followed up	Percentage of deaths	Number examined	Percentage			Number X-rayed	Percentage	
					C+	C(+)	C–		R+	Ro and R–
Cases read as category C or D at Round I by Reader 1										
Culture-positive	65	60	13.3	48	39.6	16.7	43.7	47	80.9	17.0
Sputum not examined	59	52	3.8	36	5.6	2.8	91.7	32	31.3	68.7
Culture-negative	834	792	5.7	651	2.6	1.5	95.9	606	25.2	66.5
Total	958	904	6.1	735	5.2	2.6	92.2	685	29.3	63.2
Cases read as category C or D at Round I by Reader 2										
Culture-positive	60	57	14.0	43	44.2	18.6	37.2	41	87.8	9.8
Sputum not examined	54	48	4.2	28	10.7	3.6	85.7	33	36.4	60,6
Culture-negative	548	512	5.3	425	3.1	2.6	94.3	412	36.4	54.1
Total	662	617	6.5	496	7.2	4.1	88.7	486	40.7	50.8

[a] See Annex for definitions of categories C and D.

TABLE 16

COMPARISON OF CHANGES WITH TIME AMONG CASES READ AS CATEGORY C OR D [a] BY READER 1 OR READER 2 (EXCLUDING THOSE DEFINITELY POSITIVE BY MICROSCOPY) ACCORDING TO CAVITARY STATUS IN 119 VILLAGES

	Cavity assessed by Reader 1			Cavity assessed by Reader 2		
	Present	Doubtful	None	Present	Doubtful	None
Status at Round I of Round-II cases						
No. of cases at Round II [b]	36	74	271	29	32	311
Bacteriological status at Round I						
No. examined	28	55	179	23	27	193
Percentage C+	10.7	20.0	6.1	4.3	14.8	8.8
Percentage C(+)	3.6	5.5	8.4	—	3.7	7.3
Percentage C–	85.7	74.5	85.5	95.7	81.5	83.9
X-ray status at Round I						
No. examined	31	65	239	26	27	271
Percentage R+	77.4	78.5	42.3	69.2	81.5	48.7
Percentage Ro or R–	9.7	18.5	47.3	15.4	3.7	42.1
Status at Round II of Round I cases						
No. of cases at Round I [b]	72	196	586	16	33	513
No. followed up	67	191	556	15	19	481
Percentage of deaths	18.4	5.8	5.9	20.0	10.5	6.2
Bacteriological status at Round II						
No. examined	54	157	454	10	17	397
Percentage C+	11.1	7.6	3.7	20.0	5.9	6.8
Percentage C(+)	3.7	3.2	2.4	—	5.9	4.5
Percentage C–	85.2	89.2	93.9	80.0	88.2	88.7
X-ray status at Round II						
No. X-rayed	49	150	421	9	16	380
Percentage R+	79.6	39.3	19.2	77.8	81.3	41.6
Percentage Ro or R–	14.3	52.0	73.6	—	12.5	48.9

[a] See Annex for definitions of categories C and D.
[b] Excluding cases whose sputa could not be examined.

not differ significantly whether there was cavity, doubtful cavity or no cavity at all in Round II (upper half of Table 16). In fact, among the 29 cases with cavity assessed at resurvey by Reader 2, the proportion culture-positive was even smaller than for those without any cavity although more of the former than of the latter had been radiologically positive earlier. That most of these cavitary cases had been R+ cases 18 months earlier and yet did not show bacteriological evidence of disease in either round is surprising but may have its own significance.

The lower half of Table 16 shows that the 3 cavitary-status groups of Round I also did not differ significantly with respect to the proportion culture-positive 18 months later. The vast majority (over 75%) of these cavitary cases continued to be X-ray cases and yet most of them remained culture-negative. A large number of even cavitary cases which are not definite-positives on microscopy may not be cases of pulmonary tuberculosis, in spite of their continuing to show definite shadows judged as active tuberculosis on the X-ray film.

The results in Tables 14, 15 and 16 show rather

clearly that the vast majority of cases which were not definite-positives on microscopy but were diagnosed on X-ray evidence were not culture-positive cases of tuberculosis either at the earlier or at the later round. Thus most of these cases may not be considered as suffering from pulmonary tuberculosis.

DISCUSSION

The problem of defining a " case " of tuberculosis has engaged the attention of many research workers. Which of the large variety of cases described should be regarded as genuine cases of tuberculosis does not appear easy of solution. The WHO Expert Committee on Tuberculosis (1964) believed that " it was essential first to agree on a definition of a ' case ' of tuberculosis " and decided " that, from the epidemiological point of view, a ' case ' of pulmonary tuberculosis means a person suffering from *bacteriologically confirmed* [1] disease ". Further " the Committee emphasized that persons with chest *symptoms* [1] and with positive direct smears are *genuine* [1] ' cases ' ". This preference for direct microscopy is probably due to operational reasons, as this is the only method available on any large scale in the developing countries. The equal stress on symptoms and bacteriological confirmation is intended to emphasize the priority that the Committee felt should be accorded to cases with symptoms in view of the paucity of treatment facilities in the developing countries. Furthermore, the Committee stated that " if no culture facilities exist, tuberculin-positive ' suspects ' should be referred for X-ray examination, if possible ". The order of priority of the Committee for the definition of a case is, first and foremost, awareness of symptoms; second, direct smear; third, culture; and last, tuberculin test and X-ray.

Considering the widely different conditions in the world and even within the developing countries, the tremendous difficulties which the Committee must have faced in arriving at an agreed definition of a case and *applying it uniformly* can be imagined. Their order of priorities can be viewed in the light of the findings of the present paper. The large number of categories of cases that could be considered by the combined use of direct microscopy, culture, X-ray examination and tuberculin testing at any one time (e.g., in a prevalence survey) is evident from Tables 2–9. On top of these, if another factor—symptoms—is added as an essential ingredient in the diagnosis of a case, the situation will become further complicated, especially for surveys. This aspect, i.e., how much stress should be laid in the definition of the case on symptoms (or suffering), cannot be studied from the present material. A study of the changes with time, as in this report, provides another perspective which helps us better to understand most of these categories of cases and possibly their epidemiological and public health significance. Yet the problem of defining a case remains elusive and epidemiologists and public health workers have to be content with " working definitions ".

CORRELATION OF CULTURE AND SMEAR RESULTS

In Table 2, about 40% of the sputum-positive cases in either round were positive only by culture. About 10% of the M+ cases and about 80% of the M(+) cases were not confirmed by culture; of the total smear-positives about 45% were not confirmed by culture. In an earlier survey, in which a single sample of sputum was examined and by the Ziehl-Neelsen technique only (Raj Narain et al., 1963), 29% of smear-positives were not confirmed by culture. In tropical Africa 18 out of 108 (17%) of the direct-smear-positives were not culture-positive, while of the doubtfuls on microscopy 4 out of 72, or only 5.6%, were culture-positive (Roelsgaard et al., 1964). The different materials do show that the problem of lack of confirmation by culture of certain types of direct-smear-positives is not rare. The higher frequency of this lack of confirmation in the present report is due to the large numbers of the C− M(+) cases, which are discussed below.

A SALIENT FINDING: CASES CULTURE-NEGATIVE BUT SCANTY-POSITIVE BY SMEAR

One result stands out. Cases which were negative by culture but scanty-positive by smear—i e., C− M(+)—were mostly false cases. The evidence can be summed up as follows:

[1] Our italics.

(1) Each person eligible for sputum examination had 4 direct smear examinations—2 specimens, each of which was examined by 2 methods (Ziehl-Neelsen and fluorescence microscopy). The scanty-positives from any one of the 4 examinations were mostly negative in the other 3. The 4 examinations resulted in an almost 4-fold increase in the number of scanty-positives.

(2) A large proportion (80% or more) had no radiologically active disease at the time of diagnosis (Table 5) and about half were tuberculin-negative (Table 6).

(3) Examination 18 months earlier (Table 8) and 18 months later (Table 9) than the time of diagnosis showed absence of bacteriological or radiological evidence of disease in the vast majority. If this category of C− M(+) cases were to be regarded as genuine cases, it would have to be assumed that there are a considerable number of cases in the community which become infected and develop disease quickly, in the course of 18 months or less, or become cured equally quickly, about half of them not even showing any evidence of infection!

(4) Almost none of the cases had sought treatment (Table 10).

(5) Such cases, in contrast to C+ cases, were found with equal frequency in the two sexes (Table 4). If such cases were due to some kind of error, their distribution could be expected to be equal in the two sexes (see page 705).

(6) The mortality experience at the time of the resurvey is less than that of any other type of case, and in its crude form, does not appear to be much different from that of the general population (see page 710).

There were 60 C− M(+) cases among the 267 sputum-positives of Round I and 66 among the 270 of Round II (Table 2). Such positives could be due to staining of atypical bacilli or to artefacts. Items No. (1), (2), (4) and (6) above would suggest that the "1–3 bacilli seen" were mainly artefacts giving rise to errors. The theoretical probability distribution of these errors was worked out for each round. This expected distribution was not different from that in fact observed, showing that these cases were randomly distributed among those whose sputum was examined in the different age- and sex-groups. This would further suggest that the 3 or fewer acid-fast bacilli seen were mostly artefacts, even though the slides were examined by well-qualified and fully-trained technicians. Whatever its cause, the scanty-positive smear should not, by itself, be considered a basis for a diagnosis of tuberculosis. Theoretically the finding of a single bacillus should be proof positive of pulmonary tuberculosis, but in practice it would appear to have serious limitations. Further, where culture facilities are not available, it would appear necessary to disregard *all* scanty-positives by smear, because for every genuine case missed by this criterion a wrong diagnosis will be prevented in a much larger number (Table 2).

SMEAR-POSITIVE CULTURE-NEGATIVE (M+ C−) CASES

In addition to the scanty-positives by smear, there were 7 cases among the definitely positives by smear in Round I and 10 in Round II, in 133 villages, which were culture-negative (Table 2). Of these, 2 in each round were X-ray cases.

Among the 7 cases in Round I, 5 were negative on culture at Round II (this includes 1 definite-positive on direct smear at both rounds). Four had no radiological lesion of tuberculosis, active or inactive, at any round, not even at the third round conducted 1½ years after the second (see page 703). Only 1 was an X-ray case both at Round I and at Round III, but the sputum at Round II and even at Round III was negative. Of the remaining 2, 1, an X-ray case, died before Round II; the other, with no radiologically active lesion, migrated before Round II. Only the person who died had a history of treatment. History could not be recorded for the one who migrated.

Among the 10 cases at Round II, 8 were negative by culture and smear at Round I; 1 was culture-positive and the other smear-positive only. The one with positive culture continued to be positive at Round III also and gave a history of treatment. The one with positive smear was not examined at Round III. Seven of the remaining 8 were examined at Round III and were culture- and smear-negative. They had no history of treatment. These results indicate that even definite-positives on smear which are not confirmed by culture or radiology may be doubtful cases. However, the extent of this problem is not large, and, the numbers being small, even relatively few errors can play a large part.

TABLE 17

NUMBER OF SPUTUM-POSITIVE CASES ACCORDING TO SOME INDICES OF THE PREVALENCE OF PULMONARY TUBERCULOSIS IN 119 VILLAGES AND CHANGES WITH TIME AMONG THEM

	Direct-smear definite-positives: M+	Culture definite-positives: C+	All culture positives: C+ or C(+)	Sputum-positive X-ray cases
Cases at Round I				
Total cases	74	119	180	132
Direct-smear definite-positives	74	67	69	64
Status at Round II				
No. followed up	70	113	168	125
Percentage dead	32.9	29.2	22.6	26.4
No. of sputa examined	43	73	118	84
Percentage sputum-positive	65.1	61.6	57.6	64.3
No. X-rayed	42	74	118	82
Percentage X-ray cases	72.2	68.9	62.7	89.0
Cases at Round II				
Total cases	71	106	167	108
Direct-smear definite-positives	71	61	61	55
Status at Round I				
No. of sputa examined	53	77	116	82
Percentage sputum-positive	69.8	64.9	57.8	64.6
No. X-rayed	62	95	152	98
Percentage X-ray cases	67.7	63.2	57.2	77.6

SOME INDICES OF PREVALENCE OF PULMONARY TUBERCULOSIS

Not only is no uniformly acceptable definition of a case available, but even a suitable index for comparison or for estimation of the size of the infectious pool has not been defined. A good index must be based on reasonably certain diagnosis of the disease and simple enough to be applicable in different situations. In clinical medicine one has to be and can afford to be meticulous as regards diagnosis; a patient can be kept under observation (undiagnosed) for a considerable time. But in surveys, especially in developing countries, only one-time examinations are possible owing to the large numbers involved and the general paucity of diagnostic facilities. The report of the WHO Expert Committee on Tuberculosis (1964) states " the prevalence of pulmonary tuberculosis proved bacteriologically by microscopy of a single specimen is the best available index of the size of the infectious pool in the community ". Styblo (1964) has also suggested the same. In the light of our findings, this index should be confined to the direct-smear definite-positive cases—i.e., scanty-positives should be excluded.

Another index could be to regard culture-positives as cases of pulmonary tuberculosis. Should one differentiate between the scanty-positives and the definite-positives? The sex ratios in Table 3 for the scanty-positives are different. Also the possibility that some of these persons might have been atypical bacilli has been mooted (Raj Narain et al., 1968). In Table 9 the death rates were significantly lower for the group scanty-positive by culture; this could well be due to their being less advanced cases than those who were definite-positive by culture. There is not enough evidence to allow one not to regard those who are scanty-positive by culture as cases. However, the definite-positives by culture have also been considered as a separate index.

Another index could be to regard only those sputum-positive cases who were also X-ray cases as genuine cases. The diagnosis is more certain and the cases which might be missed by the use of this index may represent, to a certain degree, errors or limitations of bacteriological technique.

Changes with time are shown separately for each of these 4 indices in Table 17. Culture-positive cases are the most numerous and the direct-smear-

positives the least; apart from this, changes 18 months after or before the diagnosis do not help much in the choice of the most suitable index.

A suitable index should give comparable results when applied to different situations or communities. In each community the findings would be subject to many variables. However, the results obtained with 2 specimens of sputum, " spot " and " overnight ", for each case in a particular index would probably be subject to fewer variables and could be compared. The degree of consistency of results for the 2 specimens per case in each index could indicate the index that is likely to give the most comparable results. To test this, cases from both rounds were pooled, only those for whom results for both samples were available being taken into consideration. Of the direct-smear definitely positive cases in either sample, 64.8% were definitely positive by smear in both samples; while 54.9% of those definitely positive on culture in either sample were definitely positive on culture in both samples. When all culture-positives are considered, the proportion confirmed by both samples was nearly the same (56.2%). The differences are not statistically significant. It is somewhat surprising that, for all its crudity and simplicity, the direct-smear-positive index (of course, after deducting the scanty-positives) appears to be as good as any for giving comparable results by 2 different specimens of sputum. Besides, this is the only practical index for developing countries and, therefore, for any large-scale international comparisons. However, the index is not sensitive and is based upon less than half the total sputum-positive cases.

In conclusion, there does not appear to be much to choose among the 4 indices. Perhaps each could be used under different circumstances.

DIRECT-SMEAR-NEGATIVE X-RAY CASES

The reason for selecting this group is its importance in the National Tuberculosis Programme of India. Tables 13 to 16 have shown that most of the cases regarded as active cases of pulmonary tuberculosis on the basis of X-ray examination alone, after excluding those which are definite-positives by smear microscopy, were not in fact likely to have been cases of tuberculosis. Only about 10% (Table 13) of them were positive on culture. Even if all these culture-positive cases were symptomatic, and assuming that only 50% of the X-ray cases had symptoms (Sikand & Raj Narain, 1957), the proportion of " genuine " cases among them would have been only 20% at the most. Thus out of 100 cases which would be treated on the basis of an X-ray diagnosis but who were direct-smear-negative, some 80 would be likely to be subjected to treatment of uncertain value. Even among the 20 cases positive by culture only, about 8 would be likely to become sputum-negative without treatment (as seen in Table 15, 43.7% of such Round-I cases by Reader 1 and 37.2% of those by Reader 2 were culture-negative at Round II). Thus probably only 12 of the 100 such X-ray cases treated would really benefit from treatment. These findings strongly support the statement of the WHO Expert Committee on Tuberculosis (1964) that " those in whom the disease has not been confirmed bacteriologically would be classified as suspect cases and would remain so classified unless or until the presence of tubercle bacilli or some other etiology was established ". This statement may be applicable with greater force for female cases diagnosed on X-ray examination. By not treating such " suspect cases ", it might be possible to unearth disease due to other etiology and masquerading as pulmonary tuberculosis, because, although a large number of such cases in our material were not culture-positive either 18 months before or 18 months after the time of diagnosis, yet, as Tables 14 and 15 show, a very substantial proportion (40% to 60%) showed persistent X-ray evidence of disease at both points in time. Table 18 shows the number and percentage of such cases and of those that were tuberculin-negative at both rounds. Not only direct-smear definitely positive but also all sputum-positive cases have been excluded from that table. The number of such cases is fairly large, and 38 of them

TABLE 18

SPUTUM-NEGATIVE R+ or R(+) CASES WITH NEGATIVE TUBERCULIN REACTIONS AT BOTH ROUNDS, IN 119 VILLAGES

Radiological status	Total no. of cases	No. test-read with 1 TU at both rounds	Negative to 1 TU at both rounds	
			No.	%
R+ at both rounds	111	97	21	21.6
R+ at one round but R(+) at the other	45	41	7	17.0
R(+) at both rounds	28	25	10	40.0
Total	184	163	38	23.3

were tuberculin-negative at both rounds, including 21 who were R+ cases at each round. A well-equipped diagnostic centre and a long follow-up would appear necessary for understanding the nature of these radiographic shadows.

CLASSIFICATION OF DISEASE

Classification of disease also appears to be in need of review. Classification into categories C and D, or even by radiological indication of cavity, does not appear to have much significance (Table 13). Classification of disease on the basis of bacteriology should be explored. An arbitrary and inadequate division of cases into " definite-positive " and " scanty-positive " on microscopy, and also, to some extent, on culture, has shown a promising possibility that merits further exploration.

SUGGESTIONS APPLICABLE TO THE NATIONAL TUBERCULOSIS PROGRAMME OF INDIA

So far as the National Tuberculosis Programme of India is concerned, we suggest that scanty-positives by smear should not be regarded as cases, and that sputum-negative X-ray cases should not be treated. A second sputum examination should be feasible and more convenient than prolonged treatment. These suggestions are also likely to be operationally welcome, as these can substantially reduce the considerable burden of treating sputum-negative X-ray cases.

CONCLUSION

In conclusion, it is not easy to define a case. Perhaps the term does not represent a single and uniform entity. The WHO Expert Committee on Tuberculosis (1964) has given one working definition, whose value for international comparisons and for research programmes is in need of further study, but how far it would be advisable to depend upon symptoms, at least to the degree envisaged by the WHO Expert Committee, for such comparisons or programmes cannot be commented upon from this material. For the present, there seems to be no other option but to use more than one definition of a case for assessing prevalence or incidence.

SUMMARY

Data from two successive surveys in a random sample of 133 villages (with population of over 70 000), undertaken by the National Tuberculosis Institute, India, have been utilized to illustrate some of the difficulties in defining a " case " of pulmonary tuberculosis for reporting the prevalence or incidence of disease. The entire population was tuberculin-tested with 1 TU of RT 23 at both rounds, and those 5 years of age and older were examined by 70-mm photofluorogram. Two sputum specimens (" spot " and " overnight ") were collected from those with any abnormality on X-ray as recorded by either of 2 independent readers. Both specimens were examined by fluorescence microscopy and the Ziehl-Neelsen technique and by culture. The direct-smear-positives were arbitrarily divided into 2 categories: those who showed 3 bacilli or less, and those who showed 4 bacilli or more. The culture-positives were also divided into 2 groups: those who had 20 or more colonies on any tube and those who had less than 20 colonies.

In the two rounds 267 and 270 sputum-positive cases respectively were found. In addition, 574 and 334 sputum-negative cases respectively were considered radiologically active by both readers. Similarly 816 and 292 cases were considered radiologically active by one reader only in the two rounds. In either survey, 26% to 28% of the sputum-positive cases were positive by both culture and microscopy, 39% to 41% by culture only, and 22% to 24% showed 1–3 bacilli on microscopy only.

Only less than one-fourth of the sputum-positive cases showed 4 or more bacilli on direct smear, radiologically active disease and a positive tuberculin test. Only about one-third of the total sputum-positives had 20 or more colonies on culture, radiologically active disease and a positive tuberculin reaction. About one-sixth of the total sputum-positives were neither radiologically active nor tuberculin-positive.

On the basis of the sputum, X-ray and tuberculin tests, cases can be divided into several widely varying categories. Salient findings for some categories are summarized in Table 19.

Cases diagnosed in the first round could not be offered treatment, nor were the medical facilities in the area adequate to influence the status after 18 months.

TABLE 19
SUMMARY OF SALIENT FINDINGS FROM SURVEY AND RESURVEY

Category of "cases"	Confirmation by other examinations at the same round	Status	
		18 months earlier	18 months later
Culture and microscopy positive	Over 90 % radiologically active and about 95 % tuberculin positive	About 25 % negative by culture and smear; an equal percentage not radiologically active	About 35 % died. Of the remainder, about 30 % negative by culture and smear; about 20 % not radiologically active
Positive by culture only	50 %–60 % radiologically active and 90 %–95 % tuberculin-positive	Over 50 % negative by culture and smear; an equal percentage not radiologically active	About 15 % died. Of the remainder, nearly 50 % negative by culture and smear; over 40 % not radiologically active
Culture negative and direct smear showing 1,2 or 3 bacilli	2 %–7 % radiologically active and 45 %–55 % tuberculin-positive	All negative by culture and smear; nearly 95 % not radiologically active	2 % died. All the remainder negative by culture and smear; over 95 % not radiologically active
Sputum negative but radiologically active as assessed by 2 readers	60 %–70 % tuberculin-positive	Nearly 90 % negative by culture and smear; about 40 % not radiologically active	About 5 % died. Of the remainder, over 90 % negative by culture and smear; about 60 % not radiologically active
Sputum negative but radiologically active as assessed by 1 reader	50 %–60 % tuberculin-positive	Over 95 % negative by culture and smear; over 85 % not radiologically active	5 % died. Of the remainder, 98 % negative by culture and smear; about 85 % not radiologically active

It is shown that those negative on culture and showing only 1, 2 or 3 bacilli on smear should not be regarded as cases of tuberculosis. Sputum-negative but radiologically active cases were also mostly false cases. Such cases should be kept under observation and not treated until a diagnosis is established. Even all the culture-positives cannot be considered a homogeneous group; those negative by direct smear showed self-healing of the order of 50% and had a lower mortality than those positive by direct smear. Analysis showed that the type of treatment available probably did not influence the conclusions.

The prevalence of sputum-positive disease among females was much lower than among males, and its course appeared to be faster among females, among whom both the mortality and the rate of cure were higher. The diagnosis by X-ray among females was found to be less reliable than that among males.

Among sputum-negative cases considered to be cavitary, about 85%–95% had been culture-negative 18 months earlier, though about 70%–80% of them were considered radiologically active. Eighteen months later, about 80%–85% were culture-negative but about 80% radiologically active. This persistence of cavitary disease with negative bacteriological findings raises the question of the nature and diagnosis of the latter. Better diagnostic facilities and longer observation are needed for an exact answer.

In view of the difficulty of giving a precise definition of a case of tuberculosis 4 indices have been suggested:

1. Cases definite-positive by direct smear;
2. Cases definite-positive by culture;
3. All cases by culture;
4. Sputum-positive cases which are radiologically active.

Each could be used under different circumstances. For the present there seems to be no option but to use more than one definition of a "case of pulmonary tuberculosis" for assessing prevalence and incidence of disease.

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RÉSUMÉ

L'analyse de données recueillies par l'Institut national de la Tuberculose (Inde) au cours de deux enquêtes successives portant sur plus de 70 000 habitants de 133 villages montre combien il est difficile de définir un « cas de tuberculose pulmonaire » afin d'évaluer la prévalence ou l'incidence de la maladie.

Dans chacune de ces enquêtes, on a soumis l'ensemble de la population à une épreuve tuberculinique et pratiqué un examen radiophotographique chez les personnes âgées de 5 ans et plus. Deux échantillons de crachats ont été recueillis chez les sujets qui présentaient des images radiologiques anormales (appréciées par deux examinateurs indépendants) et étudiés par examen microscopique direct et par culture. On a classé arbitrairement les sujets à examen direct positif en deux catégories selon que l'examen montrait la présence de 3 bacilles ou moins, ou de 4 bacilles ou plus. De même les sujets à culture positive ont été répartis en deux groupes suivant que le nombre de colonies dans l'un ou l'autre tube était supérieur ou inférieur à 20.

Les enquêtes ont permis de découvrir respectivement 267 et 270 sujets à expectoration bacillifère. En outre, 574 et 334 personnes chez lesquelles l'examen bactériologique était négatif présentaient, de l'avis des deux examinateurs, des lésions radiologiquement évolutives; pour 816 et 292 autres, un diagnostic identique n'a été posé que par un seul lecteur. Dans chaque enquête, 26 à 28% des cas bactériologiquement positifs l'étaient à la fois à l'examen direct et à la culture, 39 à 41% à la culture uniquement et 22 à 24% à l'examen microscopique direct uniquement avec présence de 1 à 3 bacilles.

Moins d'un quart des cas bactériologiquement positifs présentaient 4 bacilles ou plus à l'examen direct, des signes radiologiques de tuberculose évolutive et une réaction positive à la tuberculine. Chez moins d'un tiers d'entre eux, on notait 20 colonies ou plus à la culture, des lésions radiologiques et une réaction tuberculinique positive. Enfin, un sixième des cas ne montraient ni signes radiologiques d'évolution ni réaction tuberculinique positive.

Sur la base des données bactériologiques, radiologiques et des réactions tuberculiniques, on peut classer les cas en catégories très différentes dont certaines sont définies au tableau 19. L'observation des malades de chacun de ces groupes au cours des 18 mois séparant les deux enquêtes montre d'importantes variations d'évolution. Il faut noter qu'aucun traitement systématique n'a été appliqué aux cas diagnostiqués lors de la première enquête et que les moyens médicaux disponibles n'ont pu modifier leur état durant cet intervalle. On constate que les sujets négatifs à la culture et ne présentant que 1,2 ou 3 bacilles à l'examen microscopique direct ne devraient pas être considérés comme des cas de tuberculose. La plupart des sujets bactériologiquement négatifs mais présentant des images radiologiques d'évolution ne sont pas non plus de vrais cas. Ces personnes devraient être placées sous surveillance et ne recevoir aucun traitement avant que le diagnostic ne soit établi avec certitude. Même les cas positifs à la culture ne constituent pas un groupe homogène, les sujets négatifs à l'examen direct présentant un taux de guérison spontanée de l'ordre de 50% et une mortalité plus faible que les sujets à bacilloscopie positive. L'analyse des données montre que cette diversité d'évolution n'est probablement pas due à l'effet d'un éventuel traitement.

La prévalence des cas de tuberculose avec expectoration bacillifère a été beaucoup moins élevée dans le sexe féminin; l'évolution de la maladie y était également plus rapide, avec un taux de mortalité et un taux de guérison plus élevés. Chez les sujets de sexe féminin, la valeur diagnostique des investigations radiologiques a été moindre que chez les sujets de sexe masculin.

Parmi les sujets bactériologiquement négatifs considérés comme atteints de lésions cavitaires, 85 à 95% avaient présenté des cultures négatives 18 mois auparavant, bien qu'ayant été reconnus, dans la proportion de 70 à 80%, comme atteints de tuberculose évolutive à l'examen radiologique. Lors de la seconde enquête, 80 à 85% de ces sujets présentaient des cultures négatives et 80% d'entre eux environ montraient des signes radiologiques d'évolution. Cette association persistante de lésions cavitaires et de données bactériologiques négatives pose le problème de la valeur diagnostique de ce dernier type d'examen.

Les auteurs suggèrent de tenir compte de quatre indices pour évaluer la prévalence de la tuberculose pulmonaire: les cas chez lesquels l'examen microscopique direct, ou la culture, sont incontestablement positifs; tous les cas présentant des cultures positives; les cas à expectoration bacillifère avec lésions évolutives à l'examen radiologique. Chacun de ces indices pourrait être utilisé selon les circonstances. Il semble qu'actuellement on soit obligé d'accepter plus d'une définition d'un « cas » si l'on désire évaluer la prévalence ou l'incidence de la maladie.

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Annex

EXTRACTS FROM THE CODE FOR THE READING OF X-RAY FILMS

READING OF X-RAY FILMS

All readings of X-ray films will be recorded on a separate form. Each form will clearly indicate the group number, group name, film-roll number, date of X-ray exposure, date of X-ray reading and the name of the reader. This is done to ensure complete independence of the two readings. Individual cards are not available to the readers at the time of reading.

X-RAY CODE

The X-ray code is based mainly on the code followed earlier (Indian Council of Medical Research, 1959). In all cases with an abnormality (except for calcification only) only one of the following categories is recorded:

O. *No abnormality.*

A. *Probably non-tuberculous :* All lesions considered of non-tuberculous origin.

B. *Probably tuberculous but inactive :* All scars and other healed lesions except calcifications (some doubtful shadows, if they are recorded at all, may be classified as inactive).

C. *Probably tuberculous, possibly active :* Lesion appearing to be of tuberculous nature but without a definite cavity and not extensive.

D. *Probably tuberculous and active :* The lesion appears to be of tuberculous nature, may be extensive, may be bilateral, or a definite cavity is present.

The last two categories (C and D) are grouped together as "radiologically active tuberculosis". (For the definition of an X-ray case used in this paper, see text.)

APPENDIX TABLE 1

COMPATIBILITY OF INITIAL X-RAY AND SPUTUM EXAMINATIONS AND TUBERCULIN TEST RESULTS FOR SPUTUM-POSITIVE CASES IN ROUND I IN 133 VILLAGES

Culture result	Direct-smear result	X-ray cases: R+				R(+), Ro and R− cases				Total
		Tuberculin-test result			Total	Tuberculin-test result			Total	
		Positive[a]	Negative	Not available		Positive[a]	Negative	Not available		
Positive: C+	Positive: M+	62	4	2	68	7	—	—	7	75
	Scanty-positive: M(+)	8	—	1	9	3	—	—	3	12
	Negative: M−	30	—	1	31	14	—	1	15	46
	Total	100	4	4	108	24	—	1	25	133
Scanty-positive: C(+)	Positive: M+	3	—	1	4	—	—	—	—	4
	Scanty-positive: M(+)	1	—	—	1	4	—	—	4	5
	Negative: M−	28	1	1	30	24	3	1	28	58
	Total	32	1	2	35	28	3	1	32	67
Negative: C−	Positive: M+	2	—	—	2	3	2	—	5	7
	Scanty-positive: M(+)	2	2	—	4	24	31	1	56	60
	Total	4	2	—	6	27	33	1	61	67
Grand total		136	7	6	149	79	36	3	118	267

[a] With induration ⩾ 10 mm.

APPENDIX TABLE 2

COMPATIBILITY OF RESULTS OF INITIAL EXAMINATIONS FOR SPUTUM-POSITIVE CASES IN ROUND II IN 133 VILLAGES

Culture result	Direct-smear result	X-ray cases: R+				R(+), Ro and R− cases				Number not X-rayed	Total
		Tuberculin-test result			Total	Tuberculin-test result			Total		
		Positive[a]	Negative	Not available		Positive[a]	Negative	Not available			
Positive: C+	Positive: M+	54	—	7	61	6	1	—	7	1	69
	Scanty-positive: M(+)	7	1	—	8	2	—	—	2	1	11
	Negative: M−	20	2	2	24	14	1	1	16	3	43
	Total	81	3	9	93	22	2	1	25	5	123
Scanty-positive: C(+)	Positive: M+	—	—	—	—	—	—	—	—	—	—
	Scanty-positive: M(+)	2	—	—	2	—	—	—	—	1	3
	Negative: M−	25	1	1	27	24	7	4	35	6	68
	Total	27	1	1	29	24	7	4	35	7	71
Negative: C−	Positive: M+	2	—	—	2	4	4	—	8	—	10
	Scanty-positive: M(+)	—	—	1	1	32[b]	26	1	59	6	66[b]
	Total	2	—	1	3	36	30	1	67	6	76
Grand Total		110	4	11	125	82[b]	39	6	127	18	270[b]

[a] With induration ⩾ 10 mm. [b] Includes 2 whose culture result was contaminated (1 male, 1 female).

APPENDIX TABLE 3

STATUS AT ROUND I OF DIFFERENT CATEGORIES OF SPUTUM-POSITIVE AND RADIOLOGICALLY POSITIVE AND DOUBTFUL CASES OF ROUND II IN 119 VILLAGES

Category No.	Status at Round II			Number of cases	Bacteriological status at Round I			X-ray status at Round I		
	Bacteriological	X-ray	Tuberculin		Number examined	Percentage definitely positive by culture	Percentage negative by culture and smear	Number X-rayed	Percentage X-ray cases	Percentage Ro and R– cases
	Culture / Microscopy									
I	+ / +	+	+	53	40	62.5	20.0	45	84.4	15.6
II	+ / + or (+)	±	±	15	10	40.0	50.0	14	35.7	57.1
	Subtotal 1 (1st pair)			68	50	58.0	26.0	59	72.9	25.4
III	+ / –	+	+	20	17	29.4	41.2	20	70.0	20.0
IV	+ / –	±	±	15	8	–	75.0	14	7.1	85.7
	Subtotal 2 (2nd pair)			35	25	20.0	52.0	34	44.1	47.1
V	(+) / –	+	+	22	15	33.3	60.0	20	70.0	25.0
VI	(+) / –	±	±	31	16	18.8	50.0	26	19.2	73.1
	Subtotal 3 (3rd pair)			53	31	25.8	54.8	46	41.3	52.2
VII	– / (+)	±	±	51	20	–	100.0	48	2.1	93.8
VIII	Other sputum-positive cases			28	23	13.0	73.9	27	29.6	63.0
	Total sputum-positive cases			235	149	30.2	53.7	214	40.2	54.7
	Total sputum-positive excluding category VII			182	127	35.4	45.7	165	51.5	43.0
IX	– / –	D by two	+	16	11	9.1	81.8	12	91.7	8.3
X	– / –	D by two	–	13	9	–	100.0	11	72.7	18.2
	Subtotal 4 (4th pair)			29	20	5.0	90.0	23	82.6	13.0
XI	– / –	C by one, D by the other	+	31	25	16.0	76.0	29	75.9	20.7
XII	– / –	C by one, D by the other	–	10	9	–	100.0	10	80.0	20.0
	Subtotal 5 (5th pair)			41	34	11.8	82.4	39	76.9	20.5
XIII	– / –	C by two	+	136	88	5.7	87.5	118	59.3	33.9
XIV	– / –	C by two	–	49	21	–	100.0	38	28.9	60.5
	Subtotal 6 (6th pair)			185	109	4.6	89.9	156	51.9	40.4
XV	Other X-ray cases (including sputum not examined)			43	31	9.7	77.4	36	58.3	27.8
	Total sputum-negative X-ray cases (including sputum not examined)			298	194	6.7	86.6	254	59.4	33.1
XVI	– / –	D by one	±	9	6	–	100.0	6	–	33.3
XVII	Sputum not examined	C by one	±	20	12	8.3	83.3	20	20.0	75.0
XVIII	– / –	C by one \ 7th	+	137	79	1.3	94.9	118	20.3	67.8
XIX	– / –	C by one / pair	–	87	30	–	96.7	73	6.8	82.2
	Subtotal 7			253	127	1.6	94.5	217	15.2	72.4
XX	Other radiologically doubtful (including sputum not examined)			14	7	–	100.0	14	–	85.7
	Total sputum-negative radiologically doubtful cases (including sputum not examined)			267	134	1.5	94.8	231	14.3	73.2
	Total sputum-negative cases with X-ray evidence of disease: R+ and R(+)			565	328	4.6	89.9	485	37.9	52.2

APPENDIX TABLE 4

STATUS AT ROUND II OF DIFFERENT CATEGORIES OF CASES OF ROUND I IN 119 VILLAGES

Category No.	Status at Round I			Number of cases	Mortality		Bacteriological status at Round II			X-ray status at Round II		
	Bacteriological	X-ray	Tuberculin		Number followed up	Percentage of deaths	Number examined	Percentage definitely positive by culture	Percentage negative by culture and smear	Number X-rayed	Percentage X-ray cases	Percentage Ro and R− cases
	Culture / Microscopy											
I	+ / +	+	+	57	54	35.2	32	71.9	18.8	32	100.0	..
II	+ / + or (+)	±	±	19	18	33.3	10	10.0	80.0	10	10.0	90.0
	Subtotal 1 (1st pair)			76	72	34.7	42	57.1	33.3	42	78.6	21.4
III	+ / −	+	+	29	28	21.4	21	47.6	33.3	21	90.5	9.5
VI	+ / −	±	±	14	13	15.4	10	10.0	70.0	11	..	81.8
	Subtotal 2 (2nd pair)			43	41	19.5	31	35.5	45.2	32	59.4	34.4
V	(+) / −	+	+	28	27	14.8	20	45.0	40.0	20	90.0	5.0
VI	(+) / −	±	±	27	24	4.2	21	23.8	57.1	20	20.0	70.0
	Subtotal 3 (3rd pair)			55	51	9.8	41	34.1	48.0	40	55.0	37.5
VII	− / (+)	±	±	52	49	2.0	43	..	100.0	43	2.3	93.0
VIII	Other sputum-positive cases			13	11	..	11	9.1	72.7	9	33.3	55.6
	Total sputum-positive cases			239	224	17.4	168	29.8	58.9	166	47.0	48.2
	Total sputum-positive excluding category VII			187	175	21.7	125	40.0	44.8	123	62.6	32.5
IX	− / −	D by two	+	25	22	13.6	16	6.3	87.5	17	82.4	..
X	− / −	D by two	−	14	14	21.4	10	..	100.0	10	100.0	..
	Subtotal 4 (4th pair)			39	36	16.7	26	3.8	92.3	27	88.9	..
XI	− / −	C by one, D by the other	+	33	31	3.2	24	8.3	83.3	22	72.7	18.2
XII	− / −	C by one, D by the other	+	24	24	12.5	19	..	100.0	16	75.0	12.5
	Subtotal 5 (5th pair)			57	55	7.3	43	4.7	90.7	38	73.7	15.8
XIII	− / −	C by two	+	218	205	3.4	175	5.7	89.1	164	39.0	51.2
XIV	− / −	C by two	−	129	119	5.0	98	1.0	96.9	96	21.9	68.8
	Subtotal 6 (6th pair)			347	324	4.0	273	4.0	91.9	260	32.7	57.7
XV	Other X-ray cases (including sputum not examined)			53	48	8.3	32	9.4	81.3	33	54.5	36.4
	Total sputum-negative X-ray cases (including sputum not examined)			496	463	5.8	374	4.5	90.9	358	43.3	46.9
XVI	− / −	D by one	±	18	18	5.6	17	..	100.0	13	38.5	38.5
XVII	Sputum not examined	C by one	±	48	43	2.3	28	..	100.0	29	3.4	96.6
XVIII	− / −	C by one \ 7th	+	280	268	4.1	229	1.3	96.5	219	4.6	84.5
XIX	− / −	C by one / pair	−	257	239	5.9	198	..	99.0	187	2.1	91.4
	Subtotal 7			603	568	4.8	472	0.6	97.9	448	4.5	86.8
XX	Other radiologically doubtful cases (including sputum not examined)			20	16	..	13	..	100.0	11	..	90.9
	Total sputum-negative radiologically doubtful cases (including sputum not examined)			623	584	4.6	485	0.6	97.9	459	4.4	86.9
	Total sputum-negative cases with X-ray evidence of disease: R+ and R(+)			1 119	1 047	5.2	859	2.3	94.9	817	21.4	70.6