

CONTROLLED STUDY OF THE EFFECT OF SPECIFIC TREATMENT ON BACTERIOLOGICAL STATUS OF 'SUSPECT CASES'

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Introduction

The WHO Expert Committee on tuberculosis in its eighth report defined a 'Case' of pulmonary tuberculosis from the epidemiological point of view as a person suffering from bacteriologically confirmed disease. All other possible sufferers from tuberculosis were classified as 'suspect cases'. These 'suspect cases' are recommended to be investigated and followed up without specific anti-tuberculous treatment. Under National Tuberculosis Programme (NTP) in India, 30% of pulmonary tuberculosis patients are confirmed bacteriologically and the remaining 70% are being diagnosed as active tuberculosis on the basis of X-ray examination (Quarterly NTP Reports, National Tuberculosis Institute (NTI) 1977). In developing countries, 75-85% of pulmonary tuberculosis patients on specific therapy are such 'suspect cases' only (Olakowski, 1974). The question whether it would be correct to treat radiologically active sputum negative tuberculosis patients or to keep them under observation assumes national importance from the clinical, operational, economic and community health point of view. In an attempt to have a clear picture of the issue, a study was designed to follow up two randomly selected groups of 'suspect cases' attending a tuberculosis centre with symptoms — one put on specific treatment, the other on placebo for one year — and determine the comparative incidence of breakdown with bacillary disease or unequivocal radiographic progression during the period.

Plan and Conduct of the Study

Patients

All patients admitted to the study were residents of Bangalore City Municipal Corporation area and had reported to Lady Willingdon Tuberculosis Demonstration and Training Centre (LWTDTC) with symptoms. They had an abnormal shadow on a chest photofluorogram, read as pulmonary tuberculosis (TBP) by the Medical Officer of LWTDTC, a negative direct smear result of one supervised spot specimen of sputum, were aged 12 years or more, had either received no anti-tuberculous chemotherapy at all or had received it for not more than two weeks

and were considered to be physically fit to attend the clinic for out-patient treatment.

The intake of study patients commenced in June 1975, and lasted upto November 1976. In all, the treatment for 4,160 new patients was initiated in LWTDTC of whom 457 who fulfilled the criteria of eligibility were admitted to the study. By a random allocation process, 228 were prescribed the INH + Thioacetazone ('TH') regimen and 229 the Placebo ('P') regimen.

Treatment regimens

The 'TH' regimen consisted of INH 300 mgm and Thioacetazone 150 mgm supplied as two tablets, each containing 150 mgm of INH and 75 mgm of Thioacetazone, to be self administered at home daily in a single dose after the evening meal.

The 'P' regimen consisted of calcium gluconate tablets with an inert dye that appeared exactly like the tablets of INH and Thioacetazone of the 'TH' regimen, to be consumed in the same way as the 'TH' regimen.

The drugs were collected by the patient or his representative every month from LWTDTC.

The study was carried out double blind, neither the patients nor the investigating personnel knew which regimen the patient was receiving.

All patients admitted to the study were allocated by a randomisation scheme to either 'TH' or 'P' regimen. Serially numbered covers each containing 12 packets bearing the same number as that of the cover, sufficient for one year treatment were prepared by the Statistical Section of NTI as per random allocation. All precautions were taken to avoid mixing at the time of packing. These covers were assigned to the eligible patients in the serial order in which they were admitted to the study. The identification particulars of each patient were entered on the cover allotted to him. At each monthly drug collection, care was taken to pick out the correct cover by checking the particulars in the Identity Card of the patient with those entered on the cover. After

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Verifying the correctness of the identity, a packet of drug was taken out and issued to the patient.

Investigations on admission to the study

On admission to the study another supervised spot specimen of sputum was collected for direct smear, culture, as well as identification and sensitivity tests of positive cultures at NTI laboratory. The initial photofluorograms which were classified as TBP by the Medical Officer at LWTDTTC, were read separately by the Superintendent of LWTDTTC and a Senior Medical Officer from NTI (Study Readers). In case of disagreement between the two, an umpire reading was done by a third senior reader.

*Follow up examination**

All the patients were followed up by X-ray and single spot sputum examination at the end of 2nd, 4th, 6th, 9th and 12th month. At 12th month an additional specimen of sputum was also collected. The follow up examinations were carried out within one week prior to or after the due date. All sputum samples were examined by direct smear culture as well as identification and sensitivity tests of the positive cultures. The follow up X-ray readings were done jointly by the study readers and in case of disagreement or if definite progression of disease was recorded by both, an umpire reading was made by the third senior reader, whose reading was taken as final. The comparisons made were in respect of both the initial and the immediate previous follow up photofluorograms.

Day-to-Day management

At the time of initiation of treatment, each patient was motivated as detailed in the manuals of District Tuberculosis Programme (DTP). If the patient failed to attend LWTDTTC for drug collection, defaulter actions were taken as per DTP procedures. The drug regimen prescribed to a patient was not altered during the study period. After the 12th month follow up, the patients were referred to LWTDTTC for further management as per routine of the DTP procedures.

If a patient needed referral to a general hospital for conditions other than tuberculosis, he was excluded from the study and all necessary assistance was given.

On follow up examination results, whenever a patient became sputum positive or if the X-ray revealed definite progression of lesion as read by two readers and confirmed by a third umpire reader, he was excluded from the study and transferred to LWTDTTC for further management without any undue delay. The drug covers of all

such excluded patients were sent back to NTI Statistical Section.

Maximum coverage was attempted for all follow up examinations. Sputum samples were either collected at home or at LWTDTTC when the patients came for X-ray examination. Maximum of 3 visits to the patients' home were made within the period specified for each follow up examination. All patients who failed to attend for follow up examinations, were visited irrespective of whether the patient was on 'TH' or 'P' regimen except those who were dead or excluded.

During the follow up, the patients were questioned for any additional anti-tuberculous treatment which they might have taken from another source and was recorded in detail.

Initial Findings

Table 1 reveals that of the total 457 'suspect cases', 144(31.5%) were found bacteriologically positive—49(10.7%) by direct smear and 95 (20.8%) by culture alone on second sputum sample.

The study readers agreed with the initial TBP readings of the Medical of LWTDTTC in 342 (74.8%) patients. Of the remaining in which there was no agreement, 13(2.8%) proved bacteriologically positive in the second sample. Nevertheless, on second sputum sample, out of these 342, 129(37.7%) were found to be sputum positive—46(13.5%) by direct smear and 83(24.2%) by culture alone.

Plan of Analysis

As per random allocation and the initial status of the patients, the study population was divided into six groups (Fig. 1).

Group A and D were cases, found by direct smear on second sputum sample or by culture and therefore usually are not diagnosed in the service programme. These were excluded from further analysis. Group C and F were sputum negatives read as TBP by the Medical Officer of LWTDTTC as well as the study readers and are considered as the 'Main Analysis Group'. Groups B and E were sputum negatives not read as TBP by the study readers and were considered under 'Subsidiary analysis Group'.

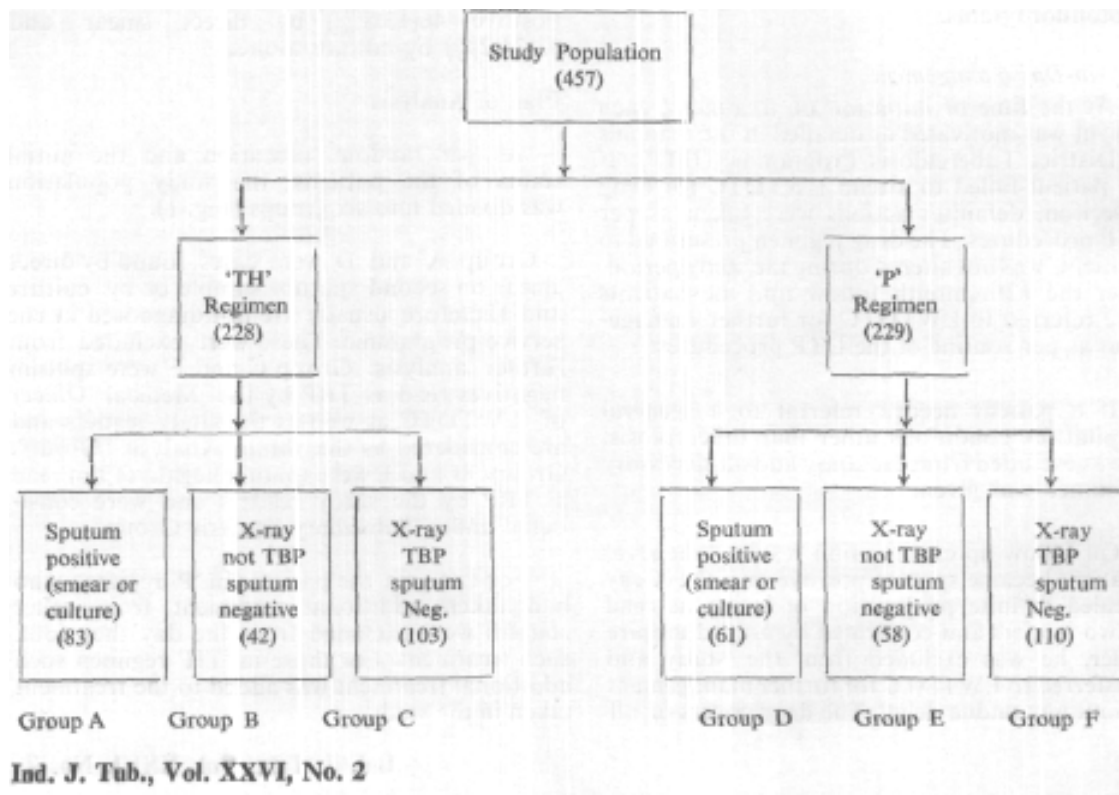
For analysis, the patients in 'P' regimen who had taken additional treatment from other sources were excluded from the day they took such treatment. For those in 'TH' regimen such additional treatment was added to the treatment taken in the study.

Table 1

Initial X-ray Status by Study Readers and Second Sample of Sputum Results.

X-ray reading	Second sample sputum result				
	Negative	Culture only positive	Direct smear only positive	Direct smear culture positive	Total
Pulmonary Tuberculosis	213	83	8	38	342
Lesions requiring observation	50	6	—	—	56
Non-tubercular	31	4	—	—	35
Normal	19	2	1	—	22
Not available	—	—	—	2	2
Total	313	95	9	40	457

Fig. 1

Distribution of Study Population by Analysis Groups

Main Analysis Group

Both the groups were similar in regard to age, sex, extent of disease and duration of symptoms (Table 2).

Table 2

Distribution of the patients in the main analysis group by their initial conditions

	Group C 'TH' (103)		Group F 'P' (110)	
	No.	%	No.	%
<i>Age</i>				
12—24	22	21.4	15	13.6
25—44	44	42.7	60	54.5
45 +	37	35.9	35	31.8
<i>Sex</i>				
Male	67	65.0	64	58.2
Female	36	35.0	46	41.8
<i>Radiological status</i>				
Zones : 1—2	49	47.6	54	49.1
3—6	54	52.4	56	50.9
Cavity : Cavity	20	19.4	18	16.4
No cavity	83	80.6	92	83.6
<i>Symptoms Status</i>				
Cough : <2 weeks	2	1.9	—	—
2—7 weeks	47	45.6	40	36.4
8 + weeks	52	50.5	66	60.0
No cough	2	1.9	4	3.6

The coverages at the follow up examinations at each predetermined time for both the groups were also similar and ranged from 69.7% to 84.8% in group 'C' and from 72.6% to 88.2% in group 'F' at various follow ups.

Case breakdown

The effect of treatment is measured by noting the incidence of breakdown with bacillary tuberculosis or unequivocal radiological progression observed during the treatment period of one year. All the patients in group C who broke down had collected more than 80% of the due drugs

upto the point of breakdown. In Group F, those who had taken anti-tuberculous treatment in between from outside source during the study period were excluded from the analysis from the day the anti-tuberculous treatment was taken. There were 9 such patients.

In Group C, 13 (12.6%) and in group F, 30(29.7%) broke down either with bacillary disease or radiological progression. The difference is statistically significant.

Radiographic progression without sputum positivity occurred among 2(1.9%) in group C and in 9 (89%) in group F.

In Group C, 11(10.7%) and in group F 21 (20.8%) became bacteriologically positive. Further, of the total breakdowns, in group C, among 13 cases, 8(61.5%) and in group F, among 30 cases, 22 (71.3 %) broke down in the first 4 months (Table not given).

Relative risk of breakdown

The relative risk (Armitage, 1973) is the ratio of the risk of incidence of case breakdown between untreated and treated groups studied. It is calculated by the ratio ad/bc where:

a = No. of cases broke down in group F

b = No. remained 'suspect cases' in group F

c = No. of cases broke down in group C

d = No. remained 'suspect cases' in group C

The relative risk so calculated was 2.9 (Table 5). Further, it was 4 in the age group 45 years and above and in males. There was a trend of increasing risk as the age advanced. This, however, failed to attain significance. Similarly, it increased with the increasing extent of the disease. The extent of the disease appeared to be a more important factor than presence or absence of cavitation.

Radiological Behaviour

The radiological assessment was done by comparing the photofluorograms of all the follow up examinations. A patient was eligible for radiological assessment if his photofluorograms of 12th month follow up and 3 other follow ups were available.

The eligibles of both the groups behaved in a similar way. In Group C, 15 (25.4%) and in group F, 9 (17.3%) cleared completely. Probably some of these lesions which cleared quickly were non-tuberculous in nature. Another 14 (23.7%)

Table 3

Coverages far follow up examinations

Month	Group C — TH (103)			Group F P(110)		
	*Eligible	Followed up	Coverage	*Eligible	Followed up	Coverags
2	98	80	81.6	102	90	88.2
4	92	78	84.8	86	74	86.0
6	90	67	74.4	76	61	80.3
9	89	62	69.7	73	53	72.6
12	85	69	81.2	70	57	81.4

*Exclusion: Deaths and excluded patients upto the month.

Table 4

Radiographic Progression and Sputum Postivity in C and F groups during the study period

	Group C TH (103)		Group F P (101)	
	No.	%	No.	%
Direct smear and or culture positive	5	4.9	4	4.0
Culture only Positive	6	5.8	17	16.8
Radiographic Prog- ression only	2	1.9	9	8.9
Total	13	12.6	30	29.7

in group C and 11 (21,2%) in group F showed continuing improvement which perhaps is indicative of self-healine process. The remaining 30 (50.8%) in group C and 32 (61.5%) in group F remained stationary. These were inactive lesions which usually are tuberculous in nature. All in all, both the groups appeared to contain a mixture of active and inactive tuberculous and non-tuberculous lesions. Most of these patients probably did not require the specific treatment.

Subsidiary Analysis Group

In group B (TH' regimen), 2 (4.8%) and in group E ('P' regimen), 8(14.5%) broke down. The breakdown rate as compared with C and F groups is much lower. Here it may be recalled that the study readers read these groups as non-TBP. It confirms the probable more over reading by the programme reader in these groups.

Deaths

The patients in groups E and F who took treatment from other sources and those excluded from the study due to sputum positivity or radiological progression etc. were not followed up from the date of occurrence of that particular event. The comparison of deaths in both the groups was, therefore, not possible. However, a total of 15 patients died during the study period, of whom 6 died in the very first month of admission into the study. The deaths in those put on 'TH' and 'P' regimens were 10 and 5 respectively.

Discussion

Under NTP, in District Tuberculosis Centres (DTC), treatment is offered both to those confirmed by microscopy on single sputum specimen and those suspected to have active tuberculosis on X-ray evidence on single 70 mm photofluorogram but where sputum on direct microscopy is negative. Nagpaul *et. al.* (1974) reported that of all the diagnosed cases in a clinic situation, 43% are 'suspect cases'. There can be variation

Table 5

Relative risk of case breakdown in relation to age, sex, initial, extent of disease and cavitation

Particulars	Group C — TH			Group F — P			Relative risk
	No. observed	Case breakdown		No. observed	Case breakdown		
		No.	%		No.	%	
<i>Age:</i> 12—24	22	3	13.6	15	3	20.0	1.6
25—44	44	7	15.9	53	18	34.0	2.7
45 +	37	3	8.1	33	9	27.3	4.2
<i>Sex :</i>							
Male	67	9	13.4	59	22	37.3	3.8
Female	36	4	11.1	42	8	19.0	1.9
<i>Cavity Status:</i>							
Cavity	20	3	15.0	17	5	29.4	2.4
No cavity	83	10	12.0	84	25	29.8	3.1
<i>No. of zones:</i>							
1—2	49	9	18.4	50	15	30.0	1.9
3—6	54	4	7.4	51	15	29.4	5.2
Total	103	13	12.6	101	30	29.7	2.9

from clinic to clinic but a large number of patients do receive treatment on X-ray evidence of the disease alone, in all the DTCs in the country. What proportion out of these 'suspect cases' are true cases requiring treatment and in what proportion the shadows are non-tuberculous or caused by inactive tuberculosis who do not need specific anti-tuberculous therapy is a dilemma for which conflicting views are expressed (Nair 1974; Bordia, 1974).

From the findings of this study, it can be seen that among the 'suspect cases' attending a DTC of their own, with symptoms, more than

30% are genuine cases who are missed in the programme conditions as neither the second sputum sample examination is done nor the culture facilities are available there. Of the remaining, another 30% developed bacillary disease or progressive radiological lesions if treatment was not offered. Similar results have been reported by other workers also (Frimodt Moller, 1965; Krishnaswamy, 1976). In a DTC, therefore, among all the 'suspect cases' read as 'TBP' by the programme reader, nearly half are genuine cases who need specific treatment. Of the other half who remain sputum negative on direct microscopy, the radiological assessment of the eligible

Table 6

Comparative Radiological Behaviour of C and F group patients during the study period

	Group C(TH)		Group F(P)	
	No.	%	No.	%
Regression leading to clearance	15	25.4	9	17.3
Continuing Regression	14	23.7	11	21.2
Stationary	30	50.8	32	61.5
Total	59	99.9	52	100.0
Not eligible*	44		58	

*Not fulfilling assessment criteria, breakdowns upto 12th month, deaths, etc.

patients showed that lesions of nearly half of them remained stationary, a quarter cleared up completely and in another quarter there was progressive improvement even if the treatment was not offered. It cannot be said with certainty that shadows in all or none of them were etiologically tuberculous. Perhaps they were a mixture of both. Some of them must be inactive cases of pulmonary tuberculosis although it is difficult to prove it unequivocally and objectively on single X-ray interpretation. Nevertheless, most of these patients did not require specific anti-tuberculous treatment.

The risk of case breakdown was three times higher in the untreated, was more in males and in higher age group. It was directly related to the extent of the disease.

The crux of the issue is whether to treat or not to treat the whole group of 'suspect cases' read as 'TBP' by a programme reader. The problem is to be viewed from the point of view of human suffering, epidemiological implications, operational feasibility of alternative approaches and the resources involved. If the treatment is initiated, about less than half of the 'suspect cases' who do not require anti-tuberculous therapy, are unnecessarily put on treatment. It would not only mean wastage of the resources,

delay in the diagnosis of their real ailment, but will also expose these patients to psychological trauma, sociological impediments and hazards of toxicity of the drugs. On the other hand if specific treatment is not offered the genuine cases who constitute more than half of the total 'suspect cases' and who really need the treatment for their suffering, remain unattended. Apart from the question of ethics, it may not be a desirable practice from the epidemiological point of view. In a community study, similar breakdown rates are reported by Gothi et al (1978) on short-term follow up of untreated persons with radiologically active, sputum negative tuberculosis. The results of the longitudinal survey in Bangalore district (Gothi et al. 1978) had revealed that although overall annual incidence of the disease among the persons who were not sputum positive but were judged active or probably active in previous rounds was 26.04 per thousand, yet if the whole group which forms 1.5% of the entire population is treated, 26.6% of the new cases will be prevented. It is, however, difficult to find out this group. Nevertheless 'suspect cases' form a vulnerable group which cannot be taken lightly and left as such without treatment,

The problem, however, is how to pin-point the 'suspect cases' who need the treatment. This is an extremely difficult task. About two-third of the case breakdown recorded in this study was through culture positivity. It is neither possible nor desirable to provide the culture facility in the DTCs for obvious reasons. The additional yield of sputum positive cases on direct microscopy by second specimen collected on two different days is well known (Nagpaul et al 1974). The adoption of such a procedure, however, is operationally difficult in programme conditions. The collection of the second sample on the same day appears to be operationally more feasible. In this study direct smear examination of second spot specimen on the same day had confirmed 10% of the 'suspect cases' as true cases. The second specimen was however examined in a different laboratory. The extent to which this has validity remains to be confirmed. The introduction of this procedure in the programme as a routine, therefore, might help in making definite diagnosis to that extent.

To eliminate most of the non-tuberculous cases, two procedures could be adopted. The first one is to improve the technique of X-ray reading. In this study, when the treatment was not offered, there was a case breakdown of only 15% among group 'E' which was not read as 'TBP' by the expert study readers against 30% in group 'F' where there was agreement of reading between the programme reader and the study

readers. It appears that most of the patients who do not need treatment fall in this group. It may be mentioned that the study readers missed 3% of the genuine cases. Improved technique of X-ray reading, therefore, cannot totally avoid the over-readings. Nevertheless it will certainly narrow down the margin of error. May be that the readings are required to be standardised or may be that exploration of computer technology for proper interpretation of various types of shadows is needed. The possibility of its applicability in the long run consistent with the resources and its availability at various levels should not be lost sight of.

The second procedure could be to put the 'suspect cases' on non-specific therapy and observe them for 3-4 months through repeated sputum examinations. In this study 70% of the total breakdowns occurred in the first 4 months. It would therefore be advantageous to adopt this procedure. Since the risk is more in males, in higher age group and in patients with extensive lesions, such patients, therefore could particularly be kept under strict observation. The operational feasibility of such a measure, however, requires to be studied in depth.

Conclusion

The conclusion which can be drawn from the study is that of all the 'suspect cases' read as 'TBP' in a DTC, who are bacteriologically not confirmed on one spot specimen, about 30% are genuine tuberculosis cases at the very outset and if treatment is not offered, another 20% breakdown with bacillary disease or radiological progression during the period of one year — a major portion in the first 4 months. Only one third of these true cases could be diagnosed if direct smear examination of second sample of sputum is introduced as a routine in the programme.

It would perhaps be appropriate to treat 'suspect cases' both from the clinical and epidemiological point of view. Due precautions should be taken to eliminate the non-tuberculous and inactive cases, as far as possible, from the pool of 'suspect cases' put on treatment in the programme.

Efforts should be made to improve the technique of X-ray reading. No immediate technology, however, is available to narrow down the margin of error.

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