

OPERATIONAL RESEARCH STUDIES IN TUBERCULOSIS CONTROL CONTRIBUTIONS IN THE LAST TWO DECADES FROM TUBERCULOSIS RESEARCH CENTRE, SOUTH INDIA

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Operational research (OR) provides a scientific and methodical approach that would help to better monitor the TB control programme in addition to routine reporting system in existence. OR should always be closely connected with disease control activities. OR in TB is a public health imperative in this millennium in the wake of multi-drug resistance and HIV in many parts of the world.

India has been a pioneer in undertaking innovative investigations in the field of TB. Tuberculosis Research Centre (TRC), Chennai has a big share in contributing towards evolution of effective chemotherapeutic regimens for both pulmonary and extra-pulmonary TB and on important operational aspects of programme¹. Findings of various TRC studies revolutionized the TB control practices in India and around the world (Table 1).

Table 1. Landmarks in tuberculosis research from TRC/ICMR

| Year | Research findings |
|-----------|---|
| 1955 | National Sample Survey to estimate the burden of tuberculosis |
| 1956 | Effectiveness of domiciliary treatment |
| 1958 | Need for direct observation of treatment |
| 1964 | Effectiveness of intermittent chemotherapy |
| 1974 | Lack of effectiveness of BCG vaccine in preventing adult TB |
| 1974 | Evolved effective shortcourse chemotherapeutic regimens |
| 1983-2002 | Various operational research studies |

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Similarly National TB institute (NTI) Bangalore contributed by voluminous research towards understanding of TB control in 1960s and 70s². The National Tuberculosis Programme, launched in 1962, was based on path-breaking epidemiological and sociological studies by NTI Bangalore and indeed, became a blue print for the control of tuberculosis in other developing countries of the world also³. In National Tuberculosis Programme (NTP) TB services were integrated into the general health services. ICMR Expert Committee evaluated NTP in 1975 and highlighted poor case-finding activity, poor defaulter retrieval system, non-availability of sufficient trained staff and inadequate supervisory activities⁴. According to a mathematical model with the case finding, case holding and chemotherapy efficiency of 30%, 35% and 75% respectively, it was estimated that less than 8% of patients were successfully treated under NTP⁵. The scenario did not change even after introduction of almost 100% effective Short-course chemotherapeutic regimens in the programme. In 1993, a review by Government of India / WHO / SIDA highlighted the operational constraints faced by NTP. RNTCP was built upon some of these lessons⁶. The challenge in implementation of RNTCP is to achieve sustainable programme objectives. Thus there is a need to study interventions that would enhance effectiveness of TB control measures.

TRC for more than 2 decades has been working on many aspects of the programme to identify or develop appropriate strategies for successful implementation of the programme. The issues addressed are listed in Table 2. A bird's eye view of these studies is given in this report.

Table 2. Areas investigated under Operational Research

a. Estimating the burden of illness

1. Prevalence of disease and infection during 15 years
2. Surveillance of drug resistance in TB in Tamil Nadu state
3. Socio-economic impact of tuberculosis on patients and their families
4. Socio-economic impact of parental TB on children
5. Usefulness of community surveys
6. Molecular epidemiology of TB in a rural area

b. Methods to improve case-finding and case -holding

1. Identification of task forces for TB case-finding in rural, tribal and urban areas
2. Influence of initial and repeated motivation on treatment compliance
3. Assessment of address card system acceptability and efficiency

c. Behavioral studies

1. Sample survey of awareness of tuberculosis and action taking behaviour of tuberculosis suspects in the community
2. Care seeking behaviour of tuberculosis suspects in the community
3. Sample survey to assess the knowledge of TB in a rural community initially and after health education
4. Assessment of knowledge of TB among educated public
5. Health seeking behaviour of tribals
6. Factors for delay by patients & at the level of the health system in the diagnosis of TB
7. Identification of reasons for "lost" cases in two districts in NTP
8. Association of tobacco smoking and TB

d. Evaluation of programme

1. Feasibility of introducing SCC under the existing NTP in 18 districts in India
2. Evaluation of different DOT providers RNTCP
3. Status of patients started on treatment in the programme in the follow up period after completing chemotherapy

in TB is of great importance for planning, monitoring and evaluation of TB programme. Reliable data on the subject are few in developing countries with heavy burden of disease.

Trends in the prevalence and incidence of tuberculosis in South India

The burden of illness was measured with respect to trends in prevalence and incidence of disease and annual risk of TB infection (ARTI) during 15 years (1969-1985)⁷. The trends in the prevalence and incidence of tuberculosis in this part of South India has shown that the prevalence of tuberculosis and annual risk of TB infection (2%) showed little or no decrease during 15 years; prevalence of culture positive TB was highest in 1973-1975 survey , 890 / 100,000 and showed a significant steady decline by 2.3% per annum and was 694 / 100,000 in 1984-1986. But with reference to smear positive TB there was no consistent pattern; it was highest 511 / 100,000 in 1973-1975 and it was 428 / 100,000 in 1984-1986. Similar findings have been reported earlier from 3 epidemiological studies from India. The largest initiated in a rural population of 60,000 in 1961 in Bangalore district

STUDIES ON ESTIMATING THE BURDEN OF ILLNESS

Measurement of the burden of illness included estimating the prevalence of the disease, prevalence of infection, surveillance of drug resistance , assessment of socio-economic burden, and utilization of molecular epidemiological tools to obtain information on the mechanism of transmission of disease in the community. information on epidemiological trends

showed no change in prevalence of disease over a 5-year period⁸. Another study in 20-25 thousands rural populations in Tumkur district showed no change in prevalence of infection or disease over a 12-year period in 1961-1973⁹. A recent study from New Delhi showed no change in prevalence in 30,000 population over 30 year period¹⁰ (1962-1991) and no change in incidence over 15 year period (1962-1977)¹¹. Epidemiological trends are essential for evaluation of the performance of the programme

Reliable information on the levels of drug resistance at periodic intervals is essential to formulate treatment policy for the nation. However National surveys of drug resistance are prohibitively expensive and logistically difficult considering the many constraints faced, including the large size of the country. The levels of drug resistance provide an epidemiological indicator to assess the extent of resistant bacterial transmission in the community. This also serves as a useful parameter in the evaluation of current and past chemotherapy programmes.

Surveillance of drug resistance in tuberculosis in the state of Tamil Nadu

Surveillance of drug resistance in an entire state of Tamil Nadu was undertaken using internationally accepted standardized methodology¹². Drug resistance surveillance has shown gradual increase in initial drug resistance over the years in Tamil Nadu; the proportions of resistance to H, R and HR were 15.4%, 4.4% and 3.4% respectively in newly detected patients.

Surveillance of drug resistance in tuberculosis in two districts of South India

Drug resistance surveillance under taken in North Arcot district had shown that the proportion of MDR TB in newly diagnosed patients had marginally increased over the last 10–15 years (2.5- 2.8%)¹³. Also NTI reported that HR resistance was 1.36% in urban DTC and 3.42% in rural PHI¹⁴. These findings suggest that drug resistance needs to be monitored continuously in the programme. The only way to prevent emergence of resistance to rifampicin and isoniazid is to adhere to direct observation of treatment strictly in the programme.

Socio economic impact of tuberculosis on patients and family in India

TB affects the most productive age group and the resultant economic cost for society is high. We tried to document the economic impact (out of pocket expenses) of TB on patients and their families¹⁵. The findings were that the average total cost was Rs 5986 per patient amounting to about 13,000 crores a year for the Country, even though the treatment and diagnosis were offered free of cost to patients.

Socio economic impact of parental tuberculosis on children

In addition 11 % of children dropped out of school on account of parental illness and 20% of the children had to take up jobs in order to supplement income especially if the father had TB¹⁶. Thus TB has the potential to impede the development of both individuals and society. These findings may help policy makers, potential donors and health planners to develop new approaches for effective promotion of TB control.

The DOTS strategy recommends screening of TB suspects at the health facilities as the primary mechanism for detecting TB. Recently there has been a renewed interest in active case detection as a part of expansion of DOTS strategy in high prevalent areas¹⁷.

Role of community surveys to detect tuberculosis patients in high prevalence areas

A unique opportunity was available to examine the value of active case finding in a rural area where cases were also detected at the health facilities. We tried to ascertain the usefulness of active case-finding for TB by Community surveys¹⁸. The

study findings were that Community surveys were of little help in reducing the spread of tuberculosis even in high prevalence settings, as they identify cases, which were less symptomatic and less infectious and also 80% of these cases had already consulted a governmental or private health-care provider for seeking relief of symptoms. Considerable resources were required by community surveys in: identifying new cases; motivating less symptomatic patients to start treatment; and persuading non-adherent patients to resume treatment. A community survey also has the potential to increase the risk of emergence of drug resistance by adding to the number of incompletely treated cases. Even without changing patient behaviour or additional resources for prohibitively expensive community surveys, case detection rates above 70% can be achieved by active and effective screening of patients with chest symptoms who voluntarily seek medical care. Hence active case finding is not necessary for TB control.

Molecular Epidemiology of TB in a rural area

A novel study on molecular epidemiology; restriction fragment length polymorphism analysis was undertaken on clinical isolates from TB patients treated under DOTS strategy has shown that majority of these patients were due to reactivation¹⁹. Therefore sustained TB control measures are needed to reduce the bacillary load in the community.

STRATEGIES TO AUGMENT CASE-FINDING AND CASE HOLDING COMPONENTS

Utilization of

- a) traditional birth attendants (DAIS) in rural area,

- b) literate tribal youth volunteers in tribal area &
- C) male student volunteers in an urban area for TB case –finding and drug delivery/ defaulter retrieval (motivation) of TB patients.

In order to augment case-finding and case-holding components of the programme, different task forces were utilized in various geographical areas; traditional birth attendants (DAIS) in rural areas²⁰, tribal literate youth volunteers in tribal area²¹ and male student volunteers in city²².

Role and acceptability of DAIS in a rural community

These task forces were chosen depending on the strength, availability and acceptability by the community²³. All these task forces were found to be very efficient in detection of TB cases in the community, transportation of sputum specimens with proper labeling and also in anti-tuberculous drug supply after a short period of training. This finding is in conformity with that reported by Jagota *et al* on utilization of traditional birth attendants for administering drugs under direct supervision for the entire 6 months in the PHI and the treatment completion rates, conversion rates and cure rates improved significantly. These task forces can be effectively utilized as DOT providers in respective areas. These task forces serve as excellent models of community participation.

Influence of initial and repeated motivation of patients on treatment adherence

Treatment default and premature discontinuation of treatment continue to be major constraints for the successful implementation of the NTP and

has always been an important topic for research. In order to assess the influence of motivation in improving patient compliance, a study was conducted at three taluka hospitals, in Tamil Nadu²⁵. Results have shown that treatment completion rate improved among patients who had initial and repeated motivation. These findings are similar to that reported from NTI, Nepal and an NGO from Bombay²⁶⁻²⁸. This study has highlighted the importance of initial counseling and motivation of patients in improving treatment adherence in programme.

Feasibility of an address card system for obtaining accurate address in programme

There are inherent problems in keeping track of TB patients till they complete treatment, as the period is 6-8 months. In addition, recording of addresses incorrectly is common in the programme. Obtaining accurate address of patients is crucial for retrieval of defaulters during treatment. A novel method of feasibility of utilizing address card system for obtaining accurate address of rural patients under programme conditions was examined²⁹. An address-card on which patient's home address is asked to be recorded by a person knowing for sure the patient's address, was investigated for acceptability and efficiency. This system was acceptable and found to be useful. This finding is similar to that reported by Radhakrishna et al where the acceptability was 96% and accuracy was 85% among urban patients³⁰. This system can be easily introduced in the programme.

BEHAVIOURAL STUDIES

TB Awareness studies in community, among educated public and tribal community and action taking behaviour of TB suspects in community

DOTS strategy recommends passive case finding at the health facilities as the primary mechanism of case finding in the programme. This is based on scientific evidence that TB suspects would seek care on their own for relief of their symptoms in the community. For this, the community should be aware of TB and its symptoms. Studies on the awareness on TB and action taking behaviour of TB suspects provide important clues for the planning of TB control programme. Hence care seeking behaviour of TB suspects and their awareness of symptoms were investigated on two occasions with an interval of about 10 years³¹⁻³². A sample survey in rural, urban and metropolitan areas was undertaken to identify the tuberculosis suspects and collect data on their action taking behaviour. The salient findings of the first study were that more than 80% of the symptomatics were aware, and more than 90% had contacted health facilities of which one half were governmental. The second study findings were that 80% of urban participants and 63% of rural participants had sought care, 93% within one month of onset of symptoms. Fifty percent of the participants who did not seek care felt that their symptoms were not severe. There has been no appreciable change in the behaviour of TB suspects over a period of 10 years. Earlier studies from NTI had reported that 96% of patients were aware, 74% were symptomatic and 49.5% of bacillary TB patients sought care and many of them at multiple agencies³³⁻³⁴.

Awareness of TB among educated public (college students, teachers, Bank employees, Clerical staff) was undertaken to find out whether awareness would be different from that of community³⁵. The educated were aware of the cause and symptoms and diagnostic tools of TB but unaware of sputum disposal and the duration of treatment. Hence health education on all

aspects TB is essential even for educated community.

This finding is substantiated by the findings of another study of assessment of knowledge about TB among nurses by Neeta Singla *et al*; only 41 % of nurses working in the TB ward and 11 % of the general hospital nurses had a satisfactory level of awareness³⁶. Paramedics and especially nurses are an integral part of any health care system. TB treatment is domiciliary for majority of patients but a few patients may require hospital admission. The nurses in the hospital are not only involved in management of patients and administration of the wards but they are also responsible for providing health education and also for clarification of doubts to patients and their families. Hence the programme managers should plan to train nurses on all aspects of TB. Poor knowledge of nurses may be a big hindrance in running the programme.

Tribal communities are quite different in all aspects from other communities due to their traditional and cultural background. A study was undertaken to assess the health seeking behaviour, preference of health facilities and awareness of TB among tribals of Andrapradesh³⁷. Only 44% of 429 tribals had heard of TB. The available government health facilities were acceptable to the tribals. They were in favour of modern medicine compared to native medicines.

Findings from the above awareness studies confirm that TB suspects are aware of TB and majority seek care either at governmental facilities or private health system within one month.

Role of health education methods in improving awareness on TB

The role of health education in improving awareness of TB has also been studied.

Knowledge of TB in a south Indian population initially and after health education was assessed in a rural area³⁸. After obtaining knowledge about TB, the community was educated about important aspects of TB by pamphlets, film shows, exhibitions, role-plays, group activities and public meetings. After 2 years, interview of the original respondents had shown that their knowledge on various aspects of TB had improved. This study highlights the efficiency of various health education methods used.

Risk factors for “patient delay” and “health system delay” in the diagnosis of TB

Delay in diagnosis of TB causes spread of infection in the community and is associated with a higher risk of mortality. TB diagnosis can be delayed when patients postpone seeking care until much after the onset of symptoms (patient delay) or when health providers take more time than required to diagnose patients seeking care (health system delay). Studies were undertaken to identify factors for patient and health system delays³⁹. The patient delay was greater if the patient had initially consulted a government provider, resided at a distance >2 km from a health facility and was an alcoholic. Factors associated with health system delay were: first consultation with a private provider, alcoholism and patients residence >2 km from a health facility. Studies conducted elsewhere have reported other factors like education lasting <9 years and lack of knowledge about tuberculosis associated with longer patient delays⁴⁰⁻⁴¹. Culturally appropriate messages should be developed to increase public awareness about chest symptoms and availability and location of free TB diagnostic Services. Effective partnership with private providers and their active involvement in the programme is mandatory.

These studies highlight that the behaviour of the TB suspects and patients does not need to be changed but the health system's response to this behaviour must change suggesting that the responsibility is that of the health providers to "think TB" and diagnose them promptly.

Analysis of reasons for getting "lost" from programme

Reasons for stopping treatment prematurely and getting lost to the programme were investigated in two districts in Tamil Nadu and Karnataka⁴². The main reasons for stopping treatment or getting "lost" from Short-course chemotherapy (SCC) were abatement of symptoms (19%, 35%), adverse reactions 13-22% and lack of faith in diagnosis and treatment 10-27%. About 50% of patients who were "lost" had done so within 2 months. Hopewell from Peru had reported that 60% of patients were lost within 3 months⁴³. Seetha *et al* had also stated that about half the "lost" patients discontinued treatment at the second or third collection⁴⁴. The programme should include initial counselling and repeated motivation covering all these issues.

Association between smoking and TB

In almost all the countries, the TB notification rates were higher among males compared to females. In this context the association between smoking and TB was examined by a case control study⁴⁵. There appears to be a positive dose-response relationship between tobacco smoking and bacillary TB (OR 2.5). These findings reinforce that these issues should be addressed in health education programmes in the community. IEC activities need to be strengthened in programme.

EVALUATION OF PROGRAMME

Seven-year findings of SCC in 18 districts in India under NTP

Public health programme needs continuous monitoring and periodical evaluation to assess the programme performance, identify lacunae and to take appropriate corrective measures. We undertook 3 important studies to evaluate the programme performance. A feasibility and acceptability study of introducing SCC in 18 districts with a population of 40 million under the existing NTP in India was undertaken⁴⁶. Cohort analyses had shown that the treatment completion rate was 51 %-55% for Short-Course Chemotherapy. Even though it was feasible to introduce SCC, additional efforts have to be made for further improvement of case finding and case holding. A report published from NTI on the impact of SCC on the operational efficiency of programme had shown that PHIs showed increased efficiency in new sputum examination performance, number of TB patients diagnosed and number of bacillary cases detected⁴⁷. These findings suggest that decentralisation has happened. This is an encouraging finding.

Risk factors for default, failure, & death among TB patients in a DOTS programme

The second study was analysis of the risk factors associated with default, failure, and death, among tuberculosis patients treated in DOTS programme in South India⁴⁸. Higher default rates were associated with irregular treatment, being male, history of previous treatment, alcoholism, diagnosis by community survey and age ≥ 45 years. Multi-drug resistant tuberculosis patients were more likely to fail treatment. Higher death rates were independently associated with weight < 35 kg and history of previous treatment. To

prevent default, directly observed treatment should be made more convenient for patients. Community volunteers can be utilized for DOT closer to the residence of patients. Alcoholism has been reported as a risk factor for default in other studies as well. Better supervision, home visits and health education have been successfully used as interventions to reduce default⁴⁹⁻⁵⁴. To reduce mortality, the possible role of nutritional interventions should be explored among underweight patients.

Critical assessment of smear - positive PTB patients after chemotherapy in NTP

The third one was critical one time assessment of smear - positive pulmonary tuberculosis patients after chemotherapy in programme⁵⁵. The salient findings were that even among those who had taken less than 50% of their treatment, 56% were bacteriologically negative. However, inadequate or irregular chemotherapy resulted in over four times the mortality and about twice the rate of smear positivity as compared with those who had taken adequate chemotherapy. These findings strongly suggest that the community should be educated about the dangers of inadequate and irregular chemotherapy.

ASSESSMENT OF TREATMENT AND DIAGNOSTIC PRACTICES OF PRIVATE MEDICAL SECTOR

In India, the private health sector has outgrown the public health sector and 80% of the qualified medical personnel in the country are in private sector⁵⁶. More than half of TB patients initially approached private practitioners (PPs) for treatment. Still PPs did not have a strong presence or defined role in NTP. Few studies have investigated the TB management practices of

private medical practitioners. There was a need to conduct similar studies in other parts of the country. Hence a study was conducted to find out the prescription practices for TB of medical practitioners including chest specialists and practitioners working in government programmes from all over India⁵⁷. This study was repeated after 5 years to find out the change in the prescribing patterns. The salient findings were that initially only 36% of practitioners prescribed proper SCC regimens in 1991. These findings are similar to that reported earlier from Bombay that PPs did not have adequate knowledge of proper treatment regimens for TB⁵⁸. However this proportions increased to 81 % when the study was repeated after 5 years in 1996 and the encouraging finding is that only SCC regimens were being prescribed. The main source of information was from books, journals, WHO periodicals & TB institutes.

Subsequently TB diagnostic and treatment practices of rural and urban private for-profit providers (allopaths) were investigated. Both rural and urban practitioners relied on chest radiographs for diagnosis, as they do not have reliable laboratories to perform sputum microscopy. Patients are treated with various regimens tailored to the patient needs. They prescribe but have no mechanism to monitor treatment adherence, defaulter retrieval and details regarding patients completing treatment. The heartening element of the study was that majority were willing to participate in the programme (TRC, unpublished).

A similar study was done at New Delhi among private practitioners from the area where RNTCP was field-tested⁵⁹. About 12% of the PPs advised sputum examination for the diagnosis. Only 20% of doctors emphasized the importance of regular treatment.

Findings from the above studies suggest that PPs need to be trained in RNTCP. Programme managers should collaborate with the PPs and develop a sustainable public-private model for the control of TB.

Role of private pharmacies in TB programme

In an other study dispensing practices of the pharmacies were studied. In most settings in India, private pharmacies dispense prescriptions for anti tuberculosis drugs, given by private practitioners. We assessed the dispensing practices for tuberculosis and knowledge on tuberculosis programme of 300 pharmacies⁶⁰. Doctors' prescriptions were for months but half the patients bought drugs one dose at a time, due to lack of funds, for self-administration. This practice might promote drug resistance. Majorities were willing to learn and contribute towards tuberculosis control. This study has shown that there is potential and a need to involve private pharmacies in tuberculosis control.

DESIGNING BETTER DIAGNOSTIC TOOLS

It is well known that the sputum smear microscopy has varying sensitivity for the diagnosis of acid-fast bacilli. Few attempts were made to refine the Ziehl-Neelson (ZN) staining procedure. All these procedures were double blind and used culture results as the "gold standard".

The sensitivity and specificity of 0.3% carbol fuchsin staining method for AFB was compared with that of the standard ZN staining method⁶¹. The sensitivity of the 0.3% ZN staining method was significantly lower than that of the standard method. The World Health Organisation's recommendation of 0.3% carbol fuchsin in the ZN staining needs to be reconsidered.

Secondly the sensitivity and specificity of the phenol ammonium sulfate (PhAS) sediment smear microscopy method was examined⁶². The sensitivity and specificity of the PhAS was comparable to the direct method. The PhAS method was better accepted by the laboratory technicians and safer but necessitates an overnight sedimentation, which delays reporting of results until 1 day after sputum collection.

A two-reagent cold staining method for detection of acid fast bacilli in sputum smears was also found to be as sensitive and specific as the Z-N method⁶³. However, large-scale multi centric studies in different climatic conditions need to be conducted to assess its efficacy in the diagnosis of pulmonary tuberculosis.

Washing of microscopic glass slides in dichromate solution has not been found to be beneficial⁶⁴.

Similarly processing of sputum samples in a refrigerated centrifuge does not improve the rate of isolation but resulted in rapid isolation of *M. Tuberculosis*⁶⁵.

CONCLUSIONS

All these studies have given an insight into the functioning and effectiveness of the programme. Some of the studies need to be repeated to draw firm conclusions. Policy makers, potential donors and Health planners may use the findings of these studies to develop new approaches towards more effective TB control. Even though the programme is based on scientific principles, the tools need to be evaluated periodically and refined in order to make them user friendly and also to optimise the available resources. Operational research studies are essential to develop sustainable strategies. This will enhance the success of the programme and make TB control a reality.

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