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Tuberculosis - the continuing scourge of India

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Epidemiological picture of tuberculosis in India is complex with wide variation in the annual risk of infection and prevalence of disease. The concentration of the disease among younger age groups makes tuberculosis a major socio-economic burden in India. The disability adjusted life years (DALYS) is estimated to be around 63 and 46 lakhs of years of life lost in men and women respectively. The burden is likely to increase with HIV epidemic with an increase of cases with dual infection, increase in morbidity and mortality due to tuberculosis. Management of drug resistant tuberculosis is a major hurdle in tuberculosis control and is a major step in cutting the chain of transmission to those with HIV infection, AIDS and immunodeficiency. Development of new therapeutic modalities to address this problem are also urgently required. Poor patient compliance has been the reason for failure of many control programmes. Operational research studies conducted by the TRC have resulted in elucidation of socio-behavioural aspects of patients' which need further investigation for remedial measures. Studies to improve drug delivery and to measure the impact of health education and mass media on compliance are areas which need to be concentrated. Newer techniques such as DNA fingerprinting need to employed to improve knowledge of the patterns of transmission in communities. The impact of HIV infection on tuberculosis and the role of chemoprophylaxis in HIV infected individuals in high risk populations, children in close contact with newly diagnosed patients and HIV infected individuals need to be urgently explored. improved methods for diagnosis of *Mycobacterium tuberculosis* infection must await considerable advance in the understanding of basic immunology, mycobacterial antigenic structure and host-parasitic interaction.

Key words AIDS - BCG - case holding - case finding - controlled clinical trials - DNA finger printing - HIV - multi-drug resistance - operational research - tuberculosis

Tuberculosis has been identified globally as an important health problem and enormous research has been carried out all over the world on the operational, applied and basic aspects of tuberculosis control with special emphasis on epidemiology, with primary objective of monitoring the trend of the disease by effective surveillance and to find effective preventive strategies in the form of chemoprophylaxis and immunoprophylaxis[1]. Several aspects of tuberculosis such as the epidemiology, immunology and pathogenesis still remain unclear while there have been no new drugs for the management of the disease in the last two decades. However, there has been a global resurgence of interest in tuberculosis due to the HIV/AIDS epidemic and the WHO and other agencies have launched a massive research programme to combat the disease.

Prevalence of infection

The tools to measure both infection and disease have remained relatively unchanged for decades. Our current knowledge about infection is based on the tuberculin test which requires well trained personnel and is affected by cross-reactions with other myco-

bacterial infections and BCG vaccination. Multiple risk factors that are associated with the development of the disease have been identified although the natural history of the disease is poorly understood.

The epidemiological situation in India does not appear to have changed significantly over the years since the First National Sample Survey of 1955-58 (ICMR-Tuberculosis in India. A sample survey special reprint series No. 34, Delhi, ICMR, 1-21). A few small scale studies of district population conducted in the rural and peri-urban areas around Bangalore and a longitudinal study with 6 rounds conducted from 1961 to 1981 in 22 villages around Bangalore provide good data on small populations[1]. Similar information is available from the BCG trial population in Chingleput district of Tamilnadu[2].

The National Sample Survey did not include tuberculin skin tests and the annual risk of infection could not be measured directly at that point in time. The prevalence of infection based on tuberculin testing has been shown to be age dependent in the earlier studies carried out by Ukil and Benjamin[3,4] who also showed that, contrary to popular belief tuberculosis was common in rural areas. Frimodt-Moller[5] found that the infection rates in Madanapalle to be 10, 21 and 31 per cent at the ages of 10, 20 and 30 yr respectively. Similar observations have been made in skin test surveys conducted in Dharmapuri district, Tamilnadu and Anantapur district, Andhra Pradesh[6]. These surveys done between 1983 and 1984 showed that the prevalence of infection in children 0-9 yr was 10.1 and 10.4 per cent respectively. In the Chingleput BCG study area. the overall prevalence among all age groups was 50 per cent (54% in males and 46% in females)[2].

Incidence of infection

In the Chingleput study the incidence of infection which was measured in the placebo treated group was 1.75, 2.4 and 4.03 per cent in the 1-4, 5-9 and 10-14 yr age groups respectively at the end of 4 yr of the study[2]. A longitudinal survey conducted by the National Institute of Tuberculosis, Bangalore[7], has provided information on the annual risk ofinfection of 3.2 per cent. In contrast the three surveys over a 15 yr period, using tuberculin testing conducted in Chingleput district, Tamilnadu, have not shown decreasing trends in annual risk of infection and estimates have been 1.7 per cent in 1969, 1.93 per cent in 1979 and 1.73 per cent in 1984[8].

Prevalence of disease

Passive case finding is the mainstay of-case finding in most developing countries. This relies heavily on sputum examination by smear and culture, chest radiography and tuberculin skin testing. The prevalence of disease in the BCG trial area as seen by culture positivity with one sputum sample was 404/ 100,000 (598 for males and 205 for females)[2]. Studies of prevalence of disease conducted over several rounds of the longitudinal study of the National Tuberculosis Institute (NTI), Bangalore, in the surrounding areas have shown that the overall prevalence of smear and culture positive tuberculosis has apparently remained constant[9]. But there has been a marked decline in smear positive tuberculosis and this is attributable to different screening methods used in the 1984-86 survey than in the previous rounds. This could have resulted in the increase in the number of smear negative culture positive cases detected.

In surveys I to IV conducted by NTI, the entire population over 5 yr of age was X-rayed and those with suspicious X-ray had sputum bacteriology done. However, in the 1984-86 survey, the population (10-44 yr of age) had skin tests and those with positive reaction 10 mm with PPD had sputum bacteriology done while the entire population over 45 yr of age had sputum bacteriology done. Thus, sputum bacteriology was performed on a much larger population in this recent survey. The decline in smear positive prevalence closely parallels the decline in annual risk of infection measured in the same population lending support to the hypothesis that in the area around Bangalore tuberculosis has been declining[6]. Contrary to the finding of NTI surveys in Bangalore area, the Tuberculosis Research Centre (TRC) surveys on small scale in the districts of North Arcot in Tamilnadu and Raichur in Karnataka States have shown total bacteriological prevalence of 430 and 1090 per 100,000 respectively[10]. The sputum examination in these surveys was conducted using Ziehl Neelsen stain and fluorescence microscopy on two

samples of sputum. and culture examination. These small scale studies illustrate the wide range of prevalence rates within India with potential for the occurrence of extremely high annual risk of infection in some areas such as Raichur district.

Thus, epidemiological picture of tuberculosis in India is of a complex nature with wide variation in the annual risk of infection and prevalence of disease. Hence it is felt essential that the level of risk of infection state-wise be determined in order to understand the epidemiology of tuberculosis in the Indian context and to monitor the control programme by well designed surveillance studies. The National Sample Survey and the Tuberculosis Research Centre surveys have clearly brought out the age distribution of the disease and its concentration among the younger age groups which are considered as the most productive segment of the population similar to the situation in most developing countries. The unique age-distribution of tuberculosis makes it as a major socio-economic burden in India.

Tuberculosis and women

It would be wrong to assume that tuberculosis is only a major health problem for men over 30 yr of age rather than for women although epidemiological studies show higher rates of this disease in men[6]. The National Sample Survey of 1955-58 and the longitudinal survey around Bangalore and more recent district surveys have shown that the problem of tuberculosis in women is considerable in their reproductive age of 15-44 yr. There are an estimated 70.000 deaths each from tuberculosis in the age group 15-44 yr[6].

Mortality

The mortality rates in tuberculosis as made out from published evidence of the first 4 surveys for 1961-68 have been between 69.2 and 95.4 per 100,000 and in subsequent V and VI surveys in 1977 and 1981 was estimated to be 41 per 100,000. The estimate made by sample registration system 1988 is around. 400,000 deaths per year from tuberculosis and shows an increasing trend with age[11]. These may be crude numbers; probably underestimates of the real mortality rate.

Burden of illness

The socio-economic impact of the disease in the community in India needs to be looked into since the disability adjusted life years (DALYS) is estimated to be in the order 62.8 and 45.6 lakhs man-years of life lost in men and women respectively[12].

The burden of illness due to tuberculosis has hardly shown any decline and it is likely that it will be increased by the HIV epidemic with an alarming rate of increase of cases with dual infection to be followed by an increase in morbidity and mortality due to tuberculosis. To add to this complex situation. irregular and inadequate chemotherapy as a result of poor drug compliance by patients, difficulties in management of multidrug resistance tuberculosis and relapse of the disease coupled with a low efficiency of the control programme could add to the existing problem. It may be worthwhile mentioning that rationalization of prescription practice of anti-tuberculosis drugs by practitioners of medicine is essential for the efficient management of tuberculosis.

Tuberculosis in industries

As in other countries tuberculosis has been seen in areas with rapid industrialization and urbanization in India. There have been several surveys of tuberculosis among workers engaged in dusty occupations. An increased occurrence of tuberculosis was seen in the pottery and ceramic industries. However, there was no increase among those working in the coal and steel industries. Higher rates of occurrence were seen among *bidi* workers and cotton mill workers[13].

Drug resistance

Management of drug resistant cases of tuberculosis is a major problem for the practitioners of medicine and programme managers in tuberculosis control. It has been estimated that the initial drug resistance (primary and acquired) to INH in patients seeking treatment is as high as 30 per cent in North Arcot district in Tamilnadu and Delhi; and in those who remain bacteriologically positive after chemotherapy it is estimated to be around 78 per cent in North Arcot district, Tamilnadu[14]. Added to the problem of INH resistance is the appearance of rifampicin resistance which is of the order 2-4 per cent in newly

diagnosed cases and up to 16-30 per cent among treatment failures[14]. An estimate of drug resistance is of utmost importance in the epidemiology and control of the disease since the treatment programme needs to be modified for effective management of the disease. More importantly, this will also help to cut the chain of transmission of drug resistance tuberculosis to the vulnerable individuals especially those with HIV infection and AIDS and others with immunodeficiency.

The National TB control programme and its impact

Management of pulmonary tuberculosis was revolutionised in the mid fifties by the advent of domiciliary chemotherapy established by the Tuberculosis Chemotherapy Centre (TCC, Madras) now known as Tuberculosis Research Centre (TRC), with proven efficacy. This was the need of the hour when there were approximately 1.25 million infective pulmonary tuberculosis cases prevalent in the country with only about 30,000 beds in the sanatoria. The Government of India having been convinced with reliable results obtained by the well planned and executed controlled clinical trials by the Centre, considered integration of the National Tuberculosis Programme in the primary health care system to tackle the problem of pulmonary tuberculosis which was equally distributed in the urban and rural settings. The Programme was drawn up with excellent user-friendly protocols and manuals for health workers. The regimens of treatment which were investigated at the Centre and elsewhere in the world using streptomycin, PAS or thiacetazone and isoniazid initially for 2 months followed by 10, months of double drug combination of PAS or thiacetazone and isoniazid proved nearly 80 per cent efficacious under the clinical trial conditions[15]. However, there were failures of the regimen to the extent of approximately 20 per cent due to initial drug resistance and relapses. Earlier attempts at prevention of poor drug compliance by patients led to the evolution of supervised administration of streptomycin and isoniazid on a twice weekly basis for 12 months which was again a signal contribution of the TRC, Madras. This was found as efficacious as the daily unsupervised regimens (self-administered) of treatment. However the major setback for these regimens of treatment for a period of a year has been poor treatment adherence by patients with an unacceptable rate of 25-30 per cent of patients completing treatment under the programme conditions[16].

Extensive experimental studies with highly bactericidal and sterilizing drugs such as rifampicin and pyrazinamide revolutionised the treatment of tuberculosis in the early 1970s. Applying the principles of chemotherapy based on sound scientific foundation regimens of treatment of shorter duration ranging from 5-8 months containing highly bactericidal drugs such as streptomycin, isoniazid, rifampicin and pyrazinamide were evolved by well designed and conducted studies at the TRC, Madras and elsewhere in the world by the British Medical Research Council (BMRC)[17-19]. These short course chemotherapy regimens were highly efficacious with very low relapse rates ranging from 1-5 per cent and were also found to be very useful in successfully treating patients with initial drug resistance to streptomycin and isoniazid.

The treatment regimens of 12 month duration and short course regimens of 6-8 months duration have been accepted for application under the NTP by the Government of India based on the proven efficacy of these regimens under controlled trial conditions.

The regimens of treatment with shorter duration of 6-8 months when applied under the existing conditions in the District TB Programme in India on a pilot scale in 18 districts were shown to improve the treatment adherence; 50-60 per cent of patients completing treatment compared to about 30 per cent with conventional 12 month regimens. However, this is not a panacea for tackling the major problem of treatment defaulters. Operations research studies conducted by the TRC and elsewhere have resulted in identifying sociological and behavioural problems in patients which need to be investigated to find out remedial measures and evolve suitable strategies. One such strategy could be the involvement of the community in the programme with its effective partnership in tackling this major health problem by establishing a link between the providers and beneficiaries of health in respect of tuberculosis. There is also need for health education of the community to create awareness of the disease and sensitisation to demand health care from the providers. A good programme needs good health services management

and the providers of health care either the Governmental or the non-Governmental Organisations should be efficient programme managers and as such training of health personnel at various levels should also be ensured. Basic orientation of health workers at the management and grass-root levels should also be considered by instituting continuing education programmes by experts at the state and district levels.

Although the NTP has been in operation for the past three or four decades there has been little impact on the epidemiology of the disease which could be attributed partly to the laxity in the management of the Programme, financial constraints and probably due to lower priority given to the Programme as compared to others. With the advent of HIV infection and AIDS and the projected heavy burden of the deadly disease in the population, the problem of tuberculosis in India could escalate many folds with 50 per cent of the population already infected with tuberculosis as evidenced by tuberculin positivity and an ARI (annual risk of infection) of 1.2 to 1.5 per cent among children below 5 yr[6].

It is therefore obvious that in spite of the fact that effective tools to tackle this major health problem are available, the disease has perpetuated for decades since the tools have not been put to proper use. Thus all efforts should be made to augment the efficiency of the programme in order to contain and control the disease. The revised tuberculosis control strategy that has been planned emphasises good treatment adherence of patients, with micro level planning and an attempt to decentralise at the district level to improve the efficiency at the peripheries in order to meet the requirements of health services at the primary health care level.

It is worth mentioning here that no programme would be worse than a badly managed programme since a badly managed programme would result in perpetuating the malady not to mention the financial drain on the national exchequer. Further, a badly managed programme could result in serious consequences such as increase of drug resistance tuberculosis especially the multidrug resistant forms (MDR-TB) which will incur a phenomenal amount of money for management of such patients; a burden that is felt even by the technically advanced countries with affluence.

Recommendations for research in tuberculosis in India

Research in the area of epidemiology should be focussed on the establishment of surveillance systems to monitor the change in transmission risk in selected communities and the risk factors for tuberculosis disease should be identified so that control measures may be modified or focussed. Newer techniques such as DNA 'fingerprinting' need to be employed to improve knowledge of the patterns of transmission in communities. The impact of HIV infection on tuberculosis and the role of chemoprophylaxis in HIV infected individuals also need to be urgently explored.

Diagnosis (case-finding) : Passive case finding is the mainstay of case finding in most developing countries. This relies heavily on sputum examination by smear and culture, chest radiography and tuberculin skin testing. Improvement of case-finding programmes will require development of methods for estimating the coverage and efficacy of case detection in the community and to determine the principal factors influencing the coverage of case-detection, such as health education, training of health personnel. Attention should be given especially to technological improvements in existing diagnostic procedures for use during the period preceding the introduction of new technologies. The objectives are to increase sensitivity, specificity and technical simplicity without compromising cost-effectiveness and to adapt present technology for the increasing problem of diagnosing sputum smear-negative tuberculosis in HIV-positive individuals. Improved methods for diagnosis of *Mycobacterium tuberculosis* infection must await considerable advance in the understanding of basic immunology, mycobacterial antigenic structure, and hostparasite interactions. The objective is the development of a better *(i.e.,* simple, rapid, sensitive, specific, inexpensive) method for identifying persons harbouring viable tubercle bacilli, especially those most likely to develop clinically active disease.

Treatment and case-holding : Although efficacious regimens have been developed for the treatment of tuberculosis, poor patient compliance has been the

reason for the failure of many control programmes. Studies of options to the delivery of the intensive phase of therapy by evaluating the feasibility of directly observed therapy (DOT) in the initial intensive phase of short-course chemotherapy need to be explored. Studies to improve the patient compliance by use of calender packs, identifying patients who need to have supervised therapy, and the effect on compliance of personal health education and mass media are other areas which need to be explored. Studies to determine how, and quantify the extent to which, private physicians can be induced to participate in a National Tuberculosis Control programme through accurate diagnosis, appropriate regimen selection, and extended patient follow up as well as studies of the surveillance of primary resistance to isoniazid, streptomycin, rifampicin and ethambutol worldwide also need to be carried out. Development of new therapeutic modalities *(i.e.,* new drugs, drug delivery systems. and immunotherapy) to address the problem of increasing drug resistance and further shorten current therapy are also urgently required.

Prevention : BCG vaccination and preventive chemotherapy are currently used as preventive agents in tuberculosis. The role of BCG has been critically examined in several trials but the results at best have been equivocal. Efficacy and operational studies, including analysis ofcost-effectiveness to define the role of preventive chemotherapy in high-risk populations, especially children living in close contact with newly diagnosed patients and persons infected with HIV need to be carried out. In addition, studies of revaccination with BCG vaccine to assess this frequently performed but unproven intervention need to be explored.

Development of new forms of preventive therapy, e.g., new drugs, depot preparations, and immunotherapeutics need to be explored along with efforts to develop and test new tuberculosis vaccines, including basic studies of the immunology and microbiology of the tubercle bacillus. These studies should also include efficacy studies ofneonatal vaccination, studies of additives of BCG (e.g., killed *M. vaccae),* and continued studies of the safety of BCG vaccine in HIV infection.

Economic, social and operational research : The WHO has identified major socio-economic challenges and operational problems confronting national tuberculosis programmes[20]. These include studies of the economic and social impact of tuberculosis at the household, community and national levels, including analysis of differential impacts on socio-economic, ethnic and age groups. The development of a tuberculosis transmission model to illustrate the potential benefits of proposed tuberculosis control programmes at the national level will greatly help in planning control strategies. It is mandatory that surveys of tuberculosis should include estimation of prevalence of drug resistance also as a major component in order to monitor the control programme. The outcome of such studies could be the evidence of drug compliance by patients and prescription practices.

Accurate epidemiological information is needed through well planned and designed studies which are properly executed to yield reliable results. These studies need to be conducted by group of experts from various disciplines with a common protocol using reliable tools and application of proper methodology for collating and analysing the data collected. There is also a need to establish methodologies for surveillance which should be standardized and made user-friendly to be applicable throughout the country by any agency. These are considered important steps in epidemiology as it may be observed from the foregoing paragraphs of this paper that the epidemiology of tuberculosis presents a varied picture in different parts of the country attributed to the geographic location. socio-cultural milieu and economic strata.

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