Chapter - 5

An illustration of steps leading to epidemiological estimates for a National Burden of Disease study. Adult tuberculosis in Andhra Pradesh, during the 1990s.

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Diversity of epidemiological details, variation in data availability and differences in understanding objectives of the burden of disease estimation exercise may contribute to informed guesses of varying quality. To minimize the scope for such variation in the quality of informed estimates by disease experts, there is a need for more detailed guidelines, particularly with some specific worked out reference cases. These reference cases will exemplify the process of arriving at the first estimate. Here we present an illustration of steps leading to descriptive epidemiology estimates for tuberculosis (TB) for Andhra Pradesh. The approach will have to be suitably in view of the natural history of a disease and availability of data.

Problem Definition:

It is common to find a distinction being made between pulmonary and extra-pulmonary TB. Hence, one alternative is to follow this traditional distinction. However, this distinction is more a result of difficulty in detecting a case of extra-pulmonary TB by commonly followed epidemiological survey methods. Hence, most studies have reported incidence, prevalence figures for pulmonary tuberculosis. Perhaps to retain the purity of estimates extra-pulmonary tuberculosis got segregated during the course of time. Pulmonary and extra-pulmonary tuberculosis are two different responses of hosts to the same infection. Hence, it should be possible to arrive at estimates of extra-pulmonary tuberculosis by establishing a relationship between pulmonary and extra-pulmonary tuberculosis.

Tuberculosis among HIV infected cases has not been included in the scope of the current estimates. In USA the incidence of tuberculosis began to increase about ten years after the initial detection of AIDS cases. The reported TB incidence rates from New York city have gone up from 20 cases per 100,000 inhabitants in 1982 to 50 by 1993 (News Week, 1993 May 17). If we assume that HIV and tuberculosis follow a similar relationship in India also, the first cases of AIDS reported in India around 1986 would begin to influence the incidence of tuberculosis around late_nineties or early 21st century. The present study estimates burden of disease for the 1990s. Hence, the AIDS epidemic would not significantly affect our estimate.

This chapter estimates only the adult tuberculosis (TB) burden and does not include primary phase of tuberculosis. There is very rich epidemiological literature on tuberculosis for age groups of 15 and above. The literature for children up to 14 years is of a different nature. Because of this, different methods of adjustment to available epidemiological findings are required to estimate the true epidemiological picture. We decided to exclude primary tuberculosis to keep our illustration simple and task within manageable limits.

Steps leading to estimation of TB incidence & prevalence in AP:

Following are the steps followed to estimate the incidence, duration and case fatality rates of tuberculosis in Andhra Pradesh.

1. Natural history of the disease is described briefly, based on a review of standard text books of medicine (for example, Wolinsky, 1992) and / or books on tuberculosis.
2. Case definition is arrived mainly on the basis of the BCG trial.
3. The pattern and not necessarily the quantum of age, sex specific incidence derived from the BCG trial data is assumed to be valid for Andhra Pradesh.
4. It is then examined whether the prevalence of tuberculosis has changed or remained constant over the last 30 years.
5. Adjustment factor for urban areas is arrived after establishing the rural urban relationship of TB prevalence.
6. Adjustment factor for screening method is arrived after establishing the relationship of true prevalence to different screening methods.
7. Adjustment factor for extrapulmonary tuberculosis was arrived after establishing relationship in prevalence of pulmonary tuberculosis to extrapulmonary tuberculosis.

8. A review of available epidemiological studies of TB prevalence in AP is undertaken. These studies include mainly published, but also old and unpublished studies of recent origin in rural area.

9. Estimates of pulmonary tuberculosis from published studies are adjusted by correcting for deficiency in screening method on the basis of the estimated relationship of the measured prevalence to true prevalence. Further adjustment is done for extrapulmonary tuberculosis.

10. Estimates of pulmonary tuberculosis from unpublished studies are adjusted by correcting for deficiency in screening method on the basis of the estimated relationship of the measured prevalence to true prevalence. Further adjustment is done for extrapulmonary tuberculosis.

11. Adjusted estimates from published and unpublished studies are compared and a golden mean estimate for current prevalence of tuberculosis in rural areas of AP is arrived at.

12. The estimate for urban areas is derived by applying the rural urban relationship.

13. Estimate of age specific remission (or duration) and case fatality rates is arrived at on the basis of available epidemiological evidence in India.

14. The age, sex specific incidence pattern (step 3 above), remission and case fatality rate (step 13 above) are used as inputs to DISMOD. By an Iterative process in DISMOD prevalence arrived in step 11 and 12 for rural and urban areas respectively is yielded. The age, sex specific incidence, duration and case fatality are taken from DISMOD.

Natural History:

Tuberculosis is mostly caused by Mycobacterium tuberculosis, which commonly affects the lungs. Transmission is by repeated cycle of new infections resulting from infected droplets coughed into the air by adults with cavitary pulmonary tuberculosis. Rarely the infection is through the digestive tract due to consumption of contaminated milk containing Mycobacterium bovis from cows suffering from tuberculosis. The bacilli reaching the lungs cause a local non-specific inflammatory response known as primary complex in the lung and in the corresponding lymph nodes. In most instances, both the lesions of the primary complex heal spontaneously leaving dormant bacteria which may get re-activated during the later part of the life. Thus, the clinical disease may occur weeks to years after primary infection. The usual incubation period from infection to primary lesion is between 4-12 weeks. Allergy and immunity against tuberculosis are produced within 6-8 weeks. This results in formation of granuloma around the focus of bacilli. The most important aspect of the natural history of the tuberculosis is that infection may lead to relatively small proportion of cases at a later date. Occasionally, in case of new borne and small children, the infection may progress resulting in serious forms of tuberculosis such as miliary tuberculosis or tuberculous meningitis.

Case definition:

Pulmonary tuberculosis:

In epidemiological surveys, a case of pulmonary tuberculosis is identified on the basis of smear positivity (either on direct microscopy or culture) and or X-ray abnormality suggestive of tuberculosis. All the cases diagnosed on the basis of X-ray abnormality need not be due to tuberculosis. Moreover, reliability and validity of X-ray readings has been demonstrated to be low by various epidemiologic studies. The population based longitudinal studies undertaken by Tuberculosis Research Centre (BCG trial), and National Tuberculosis Institute (NTI) have included only the bacillary cases for arriving at the incidence of tuberculosis. Administrating a course of nonspecific antibiotic for one week and repeating the X-ray to exclude non specific lesions is one way to improve the positive predictive value of X-ray readings. Another way is to go for improved X-ray technology to give better resolution. On the other hand, most abacillary pulmonary tuberculosis would eventually manifest as bacillary cases. Hence, we have decided to include only the bacillary cases for estimation of incidence and prevalence of pulmonary tuberculosis among the adults in AP. The BCG trial, after undertaking a detailed review, has defined bacillary case of tuberculosis as: a) cases positive on two cultures, or b) cases positive on one culture only and c) cases positive on smear only, excluding those showing 1-3 Acid Fast Bacilli on entire smear .

The BCG trial classified an individual whose sputum is positive on smear and negative on culture as a case of bacillary tuberculosis. The case definitions used by ICMR National Sample Survey (NSS) and NTI did not classify smear positives who are negative on culture as cases of tuberculosis. We have used the BCG trial definition of bacillary cases for the following reasons. There could be two reasons for failure of a smear diagnosed as positive to yield culture. The first one is the time lag between the collection of the sample and setting up the culture. If the time lag is longer, the chances of getting a negative culture will be more even in the presence of bacilli. The second factor is the strength of sodium hydroxide (NaOH) used for preparing the sputum for culture. A stronger NaOH may destroy the live bacilli and hence may not yield a positive culture. There is a difference in defining a case in clinical practice and epidemiological studies. While a clinician can wait and repeat the sputum examination at a later date as his concern is whether to treat the case or not, an epidemiologist has to necessarily decide whether to include such cases in estimating the disease burden. Since the definition of the bacillary case already excludes the sputum samples demonstrating 1-3 bacilli in the entire smear, it is less likely that there is a reading error in smear examination. Hence, it is desirable to include the smear positive and culture negative cases for epidemiological estimates.

Extrapulmonary tuberculosis:

All cases diagnosed on clinical and or X-ray basis as suffering from active extrapulmonary tuberculosis have been included in this group. Common sites incriminated outside of the lungs are; (a) thoracic cavity and chest wall, (b) tuberculous lymphadenitis, (c) genito-urinary tract, (d) skeletal tuberculosis, (e) intestinal tuberculosis, (f) tuberculous meningitis, (h) miliary, i.e. disseminated tuberculosis, etc.

Age sex distribution of incident cases:

In India four studies provide information on incidence of tuberculosis. These include Tuberculosis Prevention Trial undertaken by Tuberculosis Research Centre (TRC, 1990), Chennai (formerly Madras), National Tuberculosis Institute (NTI, 1974) study near Bangalore between 1961-68, Frimodt Muller's (1960) study in Madanapalle between 1950-55 and Pamra's (1973) study in Delhi. Though Madanapalle study was from AP the population covered in each age group is small and nearly four decades have passed since the survey. Pamra's study is also confined to a small urban population of 30,000 which is influenced by urban migration. In the NTI study, the incidence was calculated from the difference noticed between two prevalence surveys and hence missed the new cases occurring between the surveys, which either got cured or died. The TRC study, popularly known as BCG trial, covered a large population and also ensured that new cases appearing between the surveys are not missed. It is also more recent and hence provides a more realistic estimate of incidence. We have used the age and sex distribution of incidence cases reported from the BCG trial.

Table-5.1. BCG Trial - Age, sex specific incidence of tuberculosis, over 2.5 years.

	Males			Females		
Age	Number followed-up	No. of new cases	Incidence / 100,000	Number followed-up	No. of new cases	Incidence / 100,000
1-4	14,439	3	20.7	14,222	2	14.1
5-14	33,188	5	15.1	30,350	10	33
15-24	15,559	60	385.6	13,296	14	105.3
25-34	14,294	105	734.6	16,993	44	258.9
35-44	11,917	169	1,418.1	14,093	58	411.6
45-54	9,509	178	1,871.9	9,994	39	390.2
55-64	5,909	116	1,963.1	5,087	28	550.4
65	2,754	66	2,396.5	1,653	10	605
All	107,619	702	652.3	105,688	205	194

[1] Data obtained from TRC, courtesy, Dr. Manjula Datta

Started in 1968, the BCG trial followed a population of 3,60,000 residing in the Chingleput district, Tamil Nadu every two and half years. All listed persons aged above 10 yrs. were subjected to X ray which was read by two X-ray readers. All the individuals whose X-rays were diagnosed as tuberculosis (both possibly and probably active) were subjected to sputum examination. From each of these individuals, two sputum samples - one supervised spot and another overnight - were collected. The sputum samples thus collected were subjected to smear examination by fluorescence microscopy and culture for a minimum period of 9 weeks. The results of the study were presented in 1980. Longitudinal nature of the study and its rigorous protocol yielded reliable information on incidence. The study provides detailed information on incidence of tuberculosis for both sexes separately at 10 yr. age intervals. We have assumed that the pattern of age and sex distribution of tuberculosis incidence in AP will be similar. The quantum of incidence experienced by the AP population at different ages may or may not be different. Table - 5.1 shows the distribution of incidence cases for two and half years.

Time trends:

It is difficult to get correct data on occurrence of new cases of adult tuberculosis from the same area repeatedly. Hence, repeated estimation of prevalence of tuberculosis infection among children by performing a tuberculin test is commonly used as a proxy to know whether there is any change in the incidence of tuberculosis. Prevalence of tuberculosis infection obtained through repeated tuberculin testing in children, over a period of time, is recognized to be a reliable indicator of tuberculosis incidence and its trend in a community (Styblo, 1980). This is considered to be independent of efficiency of tuberculosis control program. A WHO study group (1981) has recommended that such surveys can be undertaken once in five years.

Recently the TRC has undertaken a study which followed up two panchayat unions covered in the BCG trial and repeated tuberculin testing among the children aged 1-9 yrs. Tuberculin testing was done twice at intervals of 10 and 15 yrs. (Mayurnath, 1991). The results of the study have clearly shown that the risk of tuberculosis infection remained unchanged over a period of 15 yrs. Risk of new infection experienced by a child aged 1-9 yrs. in 1984 was same as that experienced by his counterpart 15 years earlier. Studies carried out in Karnataka (NTI) and in other parts of the country have also suggested that the tuberculosis incidence remained more or less constant. Gothi et al (1979) have reported that the prevalence of tuberculosis infection remained constant over a twelve year period (1961-73). No decline in prevalence of infection was noticed among the children aged 0-9 yrs over a period of five years (1974-79) in a study undertaken by Chakraborthy et al (1982) in Bangalore district of Karnataka state. In another study undertaken by Goyal et al (1978) at Delhi, no appreciable change in tuberculosis situation was noticed over a period of 15 yrs (1962-77). In the state of Andhra Pradesh, no such longitudinal studies were undertaken to assess the tuberculosis situation. However, considering the similarities in population characteristics, socioeconomic situation and geographical proximity of AP to Tamil Nadu and Karnataka, we have assumed that the tuberculosis situation in AP also remained constant.

Adjustment factor for urban areas:

Most of the available population based data on tuberculosis is confined to rural areas only. Hence, we felt it desirable to apply an adjustment factor for the data reported from the rural areas to estimate the incidence of tuberculosis in urban areas. Of the available studies, only the ICMR National Sample Survey covered both urban and rural areas of Andhra Pradesh adopting the same protocol. Though this study did not show any difference between the urban and rural areas at National level, in the state of AP higher prevalence was reported in the towns. Out of the two zones covered in AP, we have relied more on Madanapalle data, as the team which undertook the survey was involved in tuberculosis control activities for long and the chances of missing a bacillary case were less. This was particularly evident when the yield of bacillary cases was compared between the two zones.

Table-5.2. Adjustment factor for urban area based on Madanapalle data of ICMR NSS

Area	Males	Females	Both
Towns	1,628	599	1,144
Villages	1,191	491	857
Adjustment factor	1.37	1.22	1.33

Since the prevalence of bacillary cases in towns is 1.33 times that of villages, we have assumed that this would be the adjustment factor for estimating the incidence rates in urban areas from the data reported from the rural areas (Table-5.2).

Screening procedure and case yield:

The yield of the tuberculosis cases in population based surveys is determined by the type of screening method adopted. Table-5.3 shows the yield of cases achieved by different screening methods. Conventionally two screening methods are used to detect a case of tuberculosis in the surveys. These screening methods are summarised herewith.

1. Initial screening of all eligible persons is done with X-ray. All those with X-rays read as abnormal are subjected to sputum and/or culture examination. This approach will miss the sputum positive cases which do not exhibit any radiological abnormalities.

2. The second approach, which is currently being followed in the national programme, identifies the symptomatics first. The symptomatics are then subjected to sputum examination followed by an X-ray. Since all the cases suffering from tuberculosis need not be symptomatic, this approach will miss the asymptomatic cases.

3. A third screening method was followed in the Bhadrachalam study. The symptomatics identified by door to door survey were first subjected to X-ray. Only the symptomatics having abnormal X-rays were subjected to on the spot sputum microscopy. This screening method will miss the cases among asymptomatics and also symptomatic X-ray normals.

Table-5.3. Yield of cases by method of screening, from TRC study in North Arcot

Method of screening	X ray result	Examined for sputum	No. of sputum positives S+C+	S+C-	S-C+	All
Symptom survey followed by	Normal	3,828	6	20	35	61
X-ray and smear examination	Abnormal	684	44	3	27	74
X-ray followed by sputum exam.	Abnormal	1,495	18	8	44	70
Total		6,007	68	31	106	205

[1] Data obtained from TRC, courtesy, Dr. Manjula Datta. Total study population = 25,688

If we can estimate a relationship of the cases to different screening methods, it will be possible to derive the true estimate of prevalence from almost all studies. The TRC study (1990) in North Arcot district in Tamil Nadu provides useful data to estimate this relationship. The results of this study help to estimate the missing cases. About 25,688 individuals were included in the study out of whom sputum samples were collected from 6007 on the basis of symptomatic status or X-ray abnormality (Table-5.3). The 205 sputum positive cases detected in North Arcot study gives a prevalence of 800 per 100,000. If only X rays are used for screening, 144 cases would have been identified which gives a prevalence of 560/100,000. Similarly if screening is confined only for symptomatics, it would yield 135 cases which gives a prevalence of 526/100,000. Thus, either methods of screening would miss about a third of the existing tuberculosis cases. About a half of the smear positive cases did not show any bacilli on direct microscopy and were detected on the basis of positive culture. About 15% of the smear positive cases, though positive on direct microscopy, did not yield any positive culture. Based on these relationships, we have arrived at adjustment factors to correct for cases missed by each of the screening method. This approach helps in arriving at a more accurate estimate of tuberculosis prevalence. Table-5.4 shows the adjustment factor arrived at for different types of screening procedures.

Table-5.4. Adjustment factor for type of screening procedure, based on North Arcot study data

Screening method	No. of + ve cases	Adjustment factor[1]
1 Survey of symptomatics followed by smear examination	73	2.808
2 Survey of symptomatics followed by smear examination and culture	112	1.830
3 Screen by X-ray followed by smear examination	73	2.808
4 Screen by X-ray followed by smear examination and culture	133	1.541
5 Survey of symptomatics followed by X-ray and smear examination	47	4.362
6 Survey of symptomatics followed by X-ray, smear & culture	71	2.887
7 Total smear and culture positive cases i.e. true TB cases	205	

[1] Adjustment factor = True TB cases / cases detected by respective survey method.

Establishing relationship between pulmonary and extrapulmonary tuberculosis:

Very little population based data is available on the prevalence of extrapulmonary tuberculosis. The intensified case detection camp held in Bhadrachalam (AP) in 1982 shows that out of the total pulmonary (bacillary) and extrapulmonary cases detected, 15% were constituted by persons suffering from extrapulmonary tuberculosis. An analysis of all tuberculosis patients attending different departments at Gandhi Hospital, Hyderabad indicated that 16% of the total cases were extrapulmonary (Eswariah, 1994). This, however, may not reflect the community situation. The pulmonary tuberculosis patients are more likely to receive domiciliary treatment and only more complicated cases tend to come to hospitals. On the contrary, higher proportion of extrapulmonary tuberculosis patients will attend hospitals. We arbitrarily assume that one out of three cases of pulmonary tuberculosis will attend a hospital. In case of extrapulmonary tuberculosis, we can assume that either all the affected or at least half of the affected will attend a hospital. We have taken average of these two and applied this relationship to arrive at the adjustment factor for extrapulmonary tuberculosis (Table-5.5).

Table- 5.5. Adjustment factor for Extra pulmonary tuberculosis

Setting	Pulmonary cases	Extrapulm. cases	Total cases
Experience at Gandhi Hospital, Hyderabad	84	16	100
A hypothetical community, which contributes 1/3 rd pulmonary cases and half of extrapulmonary cases to the hospital.	252	32	284
A hypothetical community, which contributes 1/3 rd pulmonary cases and two thirds of extrapulmonary cases to the hospital.	252	16	268
Community average	252	24	276
Adjustment factor for extrapulmonary tuberculosis (276/252)			1.095

Note that the database to estimate the extrapulmonary adjustment factor is the weakest. Our estimate of the adjustment factor is mostly conjectural. It will be desirable to focus research efforts to understand the true incidence and prevalence of extrapulmonary tuberculosis. This extrapulmonary adjustment factor will increasingly be of greater significance in view of the AIDS epidemic. For example, it has been observed in the United States that the number of extrapulmonary cases remained the same, while the pulmonary cases declined (Wolinsky, 1992). In England, extrapulmonary tuberculosis is mainly reported in recent immigrants from the Asian subcontinent. This would imply that the incidence of extrapulmonary TB may even be higher than what we have estimated.

Review of Studies on TB prevalence in AP:

Out of the published studies, the National Sample Survey undertaken by ICMR in 1955-58 is a large scale survey and has followed a well standardised protocol. Recently two population based surveys were undertaken in the districts of Khammam and Medak by the TB control programme officers. The emphasis of the Khammam study was on tribal population, while the Medak study covered the rural population. Both studies have not been published. We have obtained data on these studies from the program authorities. We, however, restricted the data from these studies only to population above 15 yrs. The reasons for this is that the pulmonary tuberculosis is less common below 15 yrs. and such analysis helps to make the data comparable with other studies.

ICMR National Sample Survey (1955-58):

The first major attempt to assess the magnitude of tuberculosis in the community was undertaken by ICMR in 1955-58. The survey covered a population of 116,539,000 aged above five years. Two zones (Hyderabad & Madanapalle) out of the total six zones covered in the study included parts of AP. Each zone was further stratified into city, towns and villages. Entire population residing at the selected sampling unit was listed. All those above the age of five years constituted the eligible and were subjected to a miniature radiogram. Each X-ray film was read by two independent readers. A sample of the abnormals was sent to a central reader for consistency check. Bacteriological examination (on spot specimen) was carried out in all cases which were considered abnormal by one or both readers. The material collected for bacteriological examination consisted of sputum (two slides) for direct smear examination and sputum (2 tubes) for culture. If sputum was not available, laryngeal swabs (2 tubes) were collected for culture. The group that undertook the survey in Madanapalle zone was involved in tuberculosis control activities for a long time. Hence, the bacillary case yield was noticed to be higher compared to Hyderabad zone. The reported prevalence of bacillary cases in Madanapalle zone was 1144/100,000 and 850/100,000 in towns and villages respectively.

Tuberculosis prevalence survey in Rural Medak district 1992:

To assess the prevalence of tuberculosis in the rural community, a survey was undertaken in Medak district during the year 1992. The study also aimed to understand the epidemiological pattern of the disease and assess the extent of utilisation of health services available for TB control. The study was undertaken in thirty three randomly selected villages in the district. A door to door survey was undertaken covering all the residents aged above five years in the selected villages to identify chest symptomatics. NTI protocol which is standardised for health workers bias, was used for symptomatic survey. The proportion of symptomatics above the age of 15 yrs. reported in the study is comparable to that of North Arcot and Raichur studies undertaken by TRC. On the spot sputum was collected and a single sputum examination done to detect Acid Fast Bacillus (AFB) by Ziehl Neelsen's stain. No culture or concentration techniques have been used. During the second phase, chest symptomatics identified were subjected to Mass Miniature Radiography (MMR). The MMR was read by a single reader trained at the National Tuberculosis Institute (NTI).

Table-5.6. Data from the Medak survey, 1992

Description	Number	Percentl
Total population enumerated	48,223	
Population above 15 yrs.	30,863	100
Chest symptomatics listed	1,196	3.9
Symptomatics subjected to sputum examination	847	70.82
Prevalence of smear positives	50	0.2
Symptomatics subjected to MMR	712	59.53
MMRs technically adequate	631	
MMR Positives	129	0.4
Extra pulmonary tuberculosis	2	0

A total of 48,223 individuals were listed from the 31 villages covered (Table-5.6). The total population above 15 yrs was 30,863. Out of the population above 15 yrs., 1196 symptomatics were identified. Out of the chest symptomatics identified, 847 (70.82%) could be subjected for sputum examination and successful MMRs could be taken for 662 (55%). A total of 50 smear positive cases were detected. This gives a prevalence rate of 162/100,000 for sputum positive cases. The prevalence rates were higher among males (male female ratio = 7:3).

Intensified TB case finding in Bhadrachalam, 1982:

An intensified case finding activity was undertaken in Bhadrachalam division of Khammam district in 1982, by the TB control programme of AP. Initial enumeration of population was done to list the population aged above five years. A door to door survey was undertaken by the paramedics to identify the chest symptomatics among the listed population. The symptomatics listed were subjected to MMR. The X-rays were read by one reader trained at NTI. Only the individuals diagnosed to be having abnormal X-rays were subjected to sputum examination which included direct microscopy of on the spot sputum sample.

Table-5.7. Data from the Bhadrachalam study, 1982.

Description	Number	Percent
Total population	146,449	
Population above 15 yrs.	92,263	100
Chest symptomatics listed	5,189	5.6
No. of symptomatics subjected to MMR	5,183	99.9
MMR i.e. X-ray positives	1,465	1.6
Symptomatics subjected to on the spot sputum exam	1,267	24.42
Sputum positives	473	0.5
Extra pulmonary tuberculosis	84	0.1

Table-5.7 summarises the data collected from this survey. Out of the total 1,46,449 population surveyed, 92,263 individuals above the age of fifteen years were listed. The screening for symptomatics yielded 5,189 symptomatics. Out of the symptomatics listed 5,183 were subjected to MMR. Among the individuals subjected to MMR, 1465 were diagnosed as X-ray positive for TB. Out of the 1465 X-ray positive individuals, sputum examination was done for 1267 and 473 persons were detected to be smear positives. The study gives a prevalence rate of 513/100,000. Out of the detected cases, the male female ratio was around 2:1. The prevalence of tuberculosis among tribal and non-tribal population was similar.

Adjusting estimates from published and unpublished data:

It is difficult to achieve 100% coverage in population based surveys and tuberculosis surveys are no exception in this regard. This can happen in two ways i.e., failure to cover the total population in identifying the eligible and failure to subject all the eligible for screening test. Since the reported coverage of these surveys is around 90%, we have assumed that the prevalence of tuberculosis among missed cases is not different from the cases covered. Accordingly, we have applied appropriate adjustment factor for coverage.

Table-5.8. Adjusted TB prevalence estimate from ICMR National Sample Survey

Study population	13,645
Population coverage (c)	0.88
Total bacillary cases identified (b)	117
Adjustment factors for	
Under coverage (1/c) = x	1.136
Screening method(Table-4, Serial no.4) = y	1.541
Extra-pulmonary TB = z	1.095
Total adjustment factor (a) = x * y * z	1.917
Prevalent cases after all adjustments (a * b)	224
Prevalence after all adjustments / 100,000 pop	1642

Table-5.9. Adjusted TB prevalence estimates from Medak and Bhadrachalam Studies

	Medak	Bhadrachalam
Study population (n)	30,863	92,263
Population coverage (c)	0.71	0.86
Total sputum + ve cases detected (b)	50	473
Adjustment factors for		
Under coverage (1/c) = x	1.408	1.163
Screening method = y	2.808	4.362
Extrapulmonary TB = z	1.095	1.095
Total adjustment factor (a) = x * y * z	4.329	5.555
Prevalent cases after all adjustments (a * b = p)	216	2627
Prevalence after all adjustments / 100,000 pop = (p/ n) * 100,000	700	2847

Estimate of current prevalence of tuberculosis in rural AP:

Out of the three studies, Medak study is most recent. The ICMR sample survey was conducted nearly four decades back, when there was no National programme for tuberculosis control and anti tuberculosis drugs were not freely available. This makes it inconsistent with the burden of disease methodology which estimates the burden at the current operational efficiency of the intervention programme (Table - 5.8). The Bhadrachalam study was undertaken in a tribal area. As the tribal population constitutes about 6% of the total population of the State, the results of this study cannot be applied for the entire State. The population residing in tribal areas are included in the rural population in census data. The rural population constitutes about 73% of the total State's population. Out of the rural population, 8.65% is constituted by Scheduled tribes. We have arrived at the mean prevalence of tuberculosis for rural population by applying prevalence rates of Medak study to the non tribal rural population (91.35%) and prevalence rates of Bhadrachalam study to the tribal population (8.65%) (Table - 5.9) . Estimated prevalence of TB in rural AP= (700 X 0.9135) + (2847 X 0.0865)=886/100,000 adults. This estimate is close to the results of recent survey undertaken by the Tuberculosis Research Institute (TRI, 1989) at Raichur district in Karnataka (1090/100,000 population).

Estimate of tuberculosis prevalence in urban AP:

We have applied the adjustment factor for urban areas derived earlier to the prevalence rates estimated in the rural areas. This gave a prevalence rate of 1178/100,000 population residing in urban areas.

Estimation of age specific remission and case fatality rates:

Remission rates:

The burden of disease methodology requires remission rate or duration. However, the TB epidemiologists usually express remission in terms of conversion rates. The conversion rate is defined as proportion of bacillary cases becoming abacillary among the surviving TB patients. On the other hand, remission rate is defined as the proportion of bacillary cases becoming abacillary out of the total TB cases. Thus, there is a difference between the denominators. The former excludes the cases dying while the latter includes them. Hence, it is possible to derive remission rate from the conversion rate using the following formula.

$$r = C(1 - m)$$

Where

r = Remission rate

c = Conversion rate

$$m = \text{Mortality among TB cases} = \frac{\text{No of TB Cases Dying}}{\text{Total TB Cases}}$$

i.e. the case fatality proportion

Both conversion rates and mortality rates are influenced by severity of disease at the time of diagnosis, regularity in receiving treatment, age and sex of the patient. No study on TB remission rates is available. Few studies provide information on conversion and mortality rates among TB cases. This makes it possible to derive remission rates and in turn duration of TB. We have reviewed two such studies.

Table-5.10. Outcome of TB cases diagnosed in NTI survey

Type of cases	Between surveys	% Cured	% Dead	% remained bacillary
Incidence	I & II	52.3	14.3	33.4
cases1	II & III	28.2	38.5	33.3
Prevalence	I & II	27.8	30.2	42.1
cases	II & III	23.6	21.1	56.4
	III & IV	17.1	14.3	68.6

[1] Data available for three rounds only

The first study is the longitudinal study undertaken by NTI (1974) in rural south India between 1961-68. This study provided information on outcome of both incidence and prevalence cases (Table-5.10). The outcome of the incidence cases described the fate of new cases detected between two surveys. A separate cohort analysis was undertaken for the prevalence cases detected at the first survey which were followed up for a period of five years.

Table-5.11. Outcome of the TB cases attending PHIs by age and sex[1]

Age	Males								Females							
group	Remission		Bacillary		Dead		Total cases		Remission		Bacillary		Dead		Total cases	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<15	5	71.4	2	28.6	0	0	7	100	6	50	3	25	3	25	12	100
15-24	115	57.8	51	25.6	33	16.6	199	100	75	56	33	24.6	26	19.4	134	100
25-44	418	51.4	188	23.1	208	25.5	814	100	178	53	80	23.8	78	23.2	336	100
45-64	365	44.1	164	19.8	299	36.1	828	100	61	49.2	27	21.8	36	29	124	100
65 +	39	39.8	17	17.3	42	42.9	98	100	2	40	1	20	2	40	5	100
Total	942	48.4	422	21.7	582	29.9	1,946	100	322	52.7	144	23.6	145	23.7	611	100

Source:TRC study at North Arcot

The second study, undertaken by Manjula Datta (1991), described the outcome of smear positive cases registered by the District Tuberculosis Centre (DTC) between 1986-1988 in North Arcot district, Tamil Nadu. The study provides conversion rates among those who attended Primary Health Institutions (PHIs1) (Table-5.11) and those who did not attend (Table-5.12). The NTI studies reveal that only a third of the total TB cases attend PHIs. Hence, to arrive at the conversion rates among all TB cases among the population, we need to estimate conversion rates among those who did not attend PHI also. The North Arcot study design did not provide for this estimate. However, it will be safe to assume that conversion rate is largely dependent on compliance to treatment. The North Arcot study provides us with conversion rates for cases at different stages of compliance. A study by Uplekar (1993) in Bombay gives an idea about the degree of compliance to anti TB treatment in the private sector. He reported a compliance of less than 50% for cases attending the private clinics located in low income urban areas. We have assumed that compliance of those who did not attend PHIs would be similar to what is observed in private sector. The North Arcot study gives a conversion rate of 58% among cases with compliance less than 50%.

[1] Includes Primary Health Centres, Dispensaries, and Clinics

Table-5.12. Outcome of the TB cases not attending PHIs by age and sex[1]

Age	Males								Females							
group	Remission		Bacillary		Dead		Total cases		Remission		Bacillary		Dead		Total cases	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<15	1	50	1	50	0	0	2	100	2	40	1	20	2	20	5	100
15-24	27	39.2	19	27.5	23	33.3	69	100	20	37.7	14	26.4	19	35.8	53	100
25-44	117	32.5	84	23.3	159	44.2	360	100	42	33.1	30	23.6	55	43.3	127	100
45-64	104	28.9	76	21.1	228	63.3	408	100	15	30	11	22	24	48	50	100
65 +	8	20.5	6	15.4	25	64.1	39	100	0	0	0	0	2	100	2	100
Total	257	29.3	186	21.2	435	49.5	878	100	79	33.3	56	23.6	102	43.1	237	100

Source:TRC study at North Arcot

This study provides us with the most recent estimates of conversion rates, while the NTI study was undertaken about three decades ago when National Tuberculosis Control Programme was in its initial stages. The North Arcot study was undertaken with the National Tuberculosis Control Programme in place, and hence is consistent with the burden of disease methodology approach of est - ıating epidemiological parameters with current levels of intervention. Hence, we have used the North Arcot study results to estimate the remission rates separately for males and females (Table - 5.13).

Table-5.13. Computation of remission rates in males and females

	Males		Females	
	Attending PHIs	Not attending PHIs	Attending PHIs	Not attending PHIs
Conversion rate (c)	0.6900	0.5800	0.6900	0.5800
Mortality among TB cases (m)	0.2990	0.4940	0.2370	0.4300
Within strata remission rate r = c (1-m)	0.4837	0.2930	0.5260	0.3310
Weighted remission rate (0.33 attending and 0.67 not attending)	(0.4837 X 0.33) + (0.293 X 0.67) = 35.6%		(0.526 X 0.33) + (0.331 X 0.67) = 39.5%	

Case fatality rates:

All deaths among the tuberculosis patients may not be due to tuberculosis. Tuberculosis may increase the risk of dying due to other conditions also.

Thus mortality among TB cases represents the combined impact of general morality risk and excess mortality risk due to other diseases associated with tuberculosis and the TB case fatality rate. It is difficult to distinguish between these conditions. Some crude indicators used by TB experts to classify the death as due to tuberculosis include presence of bacilli in the sputum during a period of 6 months preceding the death, death after a massive bout of haemoptysis, death among those with massive destruction of lung due to tuberculosis, progressive tuberculosis etc. None of the population based studies could provide this data. A five year longitudinal study undertaken by the National Tuberculosis Institute (NTI, 1974) in rural south India provides useful information on mortality among TB patients (Table - 5.14). One hundred and twenty six TB cases identified during the first survey were followed up for a period of five years. Three resurveys were undertaken during this five year period. The first two follow-up surveys were carried out after an interval of one and half years, while the last resurvey was carried out after an interval of two years. A total of 62 deaths were reported during the study period. These deaths, however, were not uniformly distributed during the study period. About a third of the deaths (61.3%) took place during the first one and half years. We have attempted to estimate the TB case fatality using this data. First we have estimated the person years lived by surviving and dead. Then we have calculated the total deaths for 100 person years. The reported general mortality rate was deducted from this to estimate the mortality due to TB. We have assumed that 75% of these deaths are due to TB.

Table-5.14. Mortality data among TB patients from NTI study

Period between	Duration between surveys (Yrs.)	No. surviving	No. dead	Cumulative deaths
Ist & II surveys	1.5	88	38	38
IInd & IIIrd surveys	1.5	75	13	51
IIIrd & IVth surveys	2	64	11	62

Total person years lived by those surviving at the end of 5 yrs.= 64X5 = 320 yrs.

To estimate the Person years lived by dead we have used the following formula:

(Total dead-cumulative deaths during the period) X interval between the surveys + Persons dead during the period X (0.5 X interval between surveys)

Person years lived by the dead:

Between Ist and IInd surveys= (62-38) X 1.5 + (38 X 0.75) = 64.5

Between IInd and IIIrd surveys = (62-52) X1.5 + (13 X 0.75) = 26.25

Between IIIrd and IVth surveys = 0 + (11X1) = 11

TOTAL PERSON YEARS LIVED BY THE DEAD= 101.75

Total Person Years lived by surviving and dead = 320 + 101.75= 421.75

Total deaths reported= 62

Mortality rate = 62/421.75 X 100= 14.7 %

General Mortality rate during the study period= 1.1 %

Excess mortality among TB patients = 14.7-1.1= 13.6 %

Mortality directly attributed to TB= Excess mortality among TB cases X 0.75=13.6 X 0.75=10.2%

Deriving age & sex specific incidence of Tuberculosis in rural and urban AP using DISMOD:

DISMOD was used to check the consistency of the epidemiological estimates. The DISMOD requires instantaneous case fatality and remission rates as inputs. By adjusting the incidence rates through an iterative process, the prevalence estimates provided from epidemiological studies can be cross checked. The number of deaths estimated using the model can also help in checking the consistency of mortality estimates made using the Survey of cause of death (Rural AP) and Medical Certification of death data (Urban).

To calculate instantaneous rates, longitudinal studies which provide follow-up information are needed. We have reviewed two such studies. The BCG trial by the TRC provides information only on age and sex specific incidence. The NTI study provides information on outcome of the cases (cured, remained bacillary, as well as died). However, the number of cases followed up is very small in NTI study. We have used the NTI data to calculate the instantaneous rates.

As mentioned earlier, the mortality among TB cases combines both general mortality and excess mortality due to TB. To separate these two fractions, we have applied the reported general mortality rates of the resident study population on the 126 followed-up patients and calculated the expected number of deaths due to general mortality. By subtracting these deaths from the total reported deaths, we have arrived at an estimate of excess mortality among TB cases. We have calculated instantaneous incidence rates using the reported remission, case fatality and incidence rates as follows.

Let:

i: instantaneous incidence rate (assumed) r: instantaneous remission rate

u: general mortality rate

m: Instantaneous case fatality rate

Sn= Susceptible for a given day

Sn-1 = Susceptible of previous day

Cn= Cases for a given day

Cn-1= Cases of previous day

The susceptibles and cases were calculated using the following formula:

$S_n = (S_{n-1}) - (S_{n-1})^*(i+u) + C_{n-1}^* r$

$C_n = (C_{n-1}) + (S_{n-1})^* i - C_{n-1}^*(r+m)$

By starting with a hypothetical population, estimates of susceptibles and cases were made for a period of 5 years. We have then adjusted the instantaneous incidence rate through an iterative process to match the reported incidence between Ist and IInd surveys.

To achieve this, we have calculated the ratio of cases to the total of susceptibles and cases on 548th day (one and half years) and divided it by a factor of 1.5. This gave us the reported age specific incidence rate and we have adjusted the instantaneous incidence rates to achieve the reported annual incidence.

Table-5.15. Age and sex specific instantaneous rates used as inputs for DISMOD

Age Group	Male				Female			
	Inst. Incidence	Remission	Case Fatality	Annual Incidence	Inst. Incidence	Remission	Case Fatality	Annual Incidence
1-4	0.00018	0.34	0.05	13.8	0.00015	0.34	0.05	11.25
5-14	0.00056	0.34	0.05	42	0.00070	0.34	0.05	53
15-34	0.00180	0.13	0.15	147	0.00200	0.13	0.15	165
35-54	0.00251	0.13	0.15	206	0.00134	0.13	0.15	111
55 +	0.00840	0.06	0.15	746	0.00158	0.06	0.15	140

Out of the 126 cases for which follow-up data is available form NTI study, females constituted 32. As the follow-up data is available only for broad age groups (5-14, 15-54, 55 and above) we could estimate the remission and case fatality for these age groups only. Since the numbers are very small, we have made combined estimates for both sexes. However, we have attempted to make separate estimates for instantaneous incidence rates for other age and sex groups by using the reported general mortality rates for that age and sex groups and by matching the incidence at one and half years to the reported incidence of that age and sex group. The NTI study does not provide data on children less than 5 years. Only BCG trail provides data on incidence of tuberculosis in 1-4 years. We have assumed that the instantaneous remission and case fatality in this age group does not differ from that of 5-14 years and arrived at an estimate of instantaneous incidence by matching the incidence at one and half years with incidence reported for that age group in BCG trial. Table-5.15 shows the final inputs and Table-5.16 shows the corresponding output from DISMOD.

Table-5.16. Tuberculosis - output from DISMOD for rural AP

Age group	Males				Females			
	Prevalence	Annual Incidence	Cause sp. mortality	TB Deaths / Year	Prevalence	Annual Incidence	Cause sp. mortality	TB Deaths / Year
0-4	18	14	0.008	25	15	12	0.007	20
5-14	116	56	0.058	327	141	70	0.070	382
15-44	636	201	0.931	10,671	600	178	0.880	9,700
45-59	1,257	424	1.820	5,633	518	141	0.758	2,342
60 +	3,728	810	5.430	8,443	747	157	1.089	1,840
Crude	721	213		25,099	429	128		14,284

The outputs obtained from DISMOD were compared with the results of other studies and cause of death estimates.

Table-5.17. Comparison of incidence rates from DISMOD with TRC and NTI study results

Age group	Males			Females		
	DISMOD	TRC	NTI	DISMOD	TRC	NTI
0-4	14.3	13.8		11.7	11.3	
5-14	55.9	20.5	42	69.9	19.8	53
15-34	179	317.6	147	198.8	133.3	165
35-54	248.8	843.8	206	133.1	254.1	111
55 +	813.8	1,265.2	742	157	433.2	140
Crude	213	366.1	176	128	131	110

The crude incidence rates generated from DISMOD were in between the reported TRC and NTI estimates (Table-5.17). On the basis of its observed relationship between Annual Rate of Tuberculosis Infection (ARTI) and smear positive tuberculosis from several epidemiological studies, Styblo (1980) had estimated that for ARTI of one, there will be 49 new smear positive cases of TB in 100,000 population every year. Using this approach and extrapolating the observed relationship of smear negative and extra pulmonary TB to the smear positive TB, the GBD team estimated that 110 new cases of tuberculosis would occur for every 100,000 population. Considering the reported ARTI of 1.74 from TRC studies in South India, we can arrive at an annual crude incidence of 187.5. The DISMOD gave a crude incidence of 213 for males and 128 for females which is comparable with the GBD estimates.

When we compared the age and sex specific incidence estimated from DISMOD with TRC and NTI rates, they were mostly in between. However, higher age specific incidence was observed among the age groups of 5-14 years (both males and females) and 15-34 years (females). This may be due to the fact that the number of cases that could be followed up in this age group was very small (8). In case of females in 15-34 years, we have used the combined estimate of both sexes, as we could not get the segregated data for remission and case fatality which could have resulted in an overestimate.

Table-5.18. Comparison of prevalence estimates from DISMOD with TRC and NTI study results

Age	Males			Females		
group	DISMOD	TRC	NTI	DISMOD	TRC	NTI
0-4	18			15		
5-14	116	82	134	141	69	54
15-34	636	989	500	600	329	248
35-54	1,257	2,830	833	518	777	355
55 +	3,728	3,763	1,862	747	850	386
Crude	721	1,688	589	429	471	217

Table-5.18 compares the prevalence estimates from DISMOD with the TRC and NTI reports. The crude age specific prevalence rates from DISMOD (males = 721, females = 429 per 100,000) were also between the NTI and TRC estimates and much lower than the rural estimates of National Sample Survey (1955-58) prevalence, reported from Madanapalle in Andhra Pradesh (males = 2323, females = 1158 per 100,000). These estimates were, however, marginally lower than our estimate of 886 / 100,000 (both sexes). In the age groups of 5-14 and 15-34 years among females, the estimates of age specific prevalence were higher for which, the explanation given earlier holds good.

Table-5.19. Estimated annual incidence and prevalence in urban and rural AP with DISMOD

Age	Male				Female			
	AnnualIncidence		Annual Prevalence		Annual Incidence		Annual Prevalence	
Group	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban
0-4	14.3	18.6	18.2	23.77	11.7	15.3	15	19.6
5-14	55.9	72.7	116.1	151	69.9	90.8	140.9	183.8
15-44	201.1	261.3	635.8	827.9	177.9	230.3	600.1	779.4
45-59	423.6	546.2	1,256.6	162.5	140.7	182.7	518.6	674.3
60 +	809.8	1,040.3	3,728.1	485.2	157	203.6	747.2	971.1
Crude	213.2	254.1	720.8	836.1	128.2	167.5	429.2	556.2

Based on the observed relationship between the prevalence in urban and rural areas in the National Sample Survey (1955-58), we have applied an adjustment factor of 1.3 on the instantaneous incidence rates (assuming that remission and case fatality would be similar to rural areas) and we have estimated the incidence, prevalence and mortality due to tuberculosis in urban AP using the DISMOD (Table-5.19).

Table-5.20. Comparison of cause specific deaths due to tuberculosis estimated from DISMOD and Mortality data from SCD & MCCD

Age	Male				Female			
	Rural		Urban		Rural		Urban	
Group	DISMOD	SCD	DISMOD	MCCD	DISMOD	SCD	DISMOD	MCCD
0-4	25	509	12	479	20	218	9	257
5-14	327	185	159	136	382	316	183	72
15-44	10,671	6,268	5,511	2,370	9,700	4,199	4,906	837
45-59	5,633	14,296	2,378	2,211	2,342	10,590	943	651
60 +	8,433	9,784	2,681	1,867	1,840	5,296	649	1,119
Total	25,089	31,042	10,741	7,063	14,284	20,619	6,690	2,936

Based on SCD data, we have estimated that 31,042 deaths among males and 20,619 deaths among females occur in rural AP for the year 1991 (Table-5.20). The DISMOD estimates gave a figure of 25,089 among males and 14,284 among females. We feel that the SCD data tended to overestimate the deaths as nearly 25-30% of deaths above 45 years were attributed to TB. When age specific deaths were compared, maximum number of deaths were noticed in the age group of 15-44 years in epidemiological model, while estimates based on SCD data gave maximum number of deaths in 45-59 years. Considering our understanding of the natural history of tuberculosis, we felt that the distribution of the epidemiological estimates is more plausible.

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