4. EPIDEMIOLOGY & OPERATIONAL RESEARCH

Completed Studies:

Mortality surveys in Andhra Pradesh and Orissa:

Background:
The mortality data from these surveys will be used as baseline information for evaluating the impact of the RNTCP.

Aims:

- To estimate crude mortality rate in the states of Andhra Pradesh and Orissa
- To estimate the TB mortality rate among the general population aged ≥ 15 years

Sample Size, sampling design and methodology were described in detail in the previous annual report.
The coverages are presented in this report. The analysis is in progress.

Table 4.1: Sample units and coverage in Andhra Pradesh

<table>
<thead>
<tr>
<th>State/Districts</th>
<th>Total</th>
<th>Rural</th>
<th>Urban</th>
<th>Total</th>
<th>Alive</th>
<th>Dead</th>
<th>Moved out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>380</td>
<td>304</td>
<td>76</td>
<td>395886</td>
<td>389743</td>
<td>2344</td>
<td>3799</td>
</tr>
<tr>
<td>Mehabub Nagar</td>
<td>69</td>
<td>62</td>
<td>07</td>
<td>74203</td>
<td>72711</td>
<td>448</td>
<td>1044</td>
</tr>
<tr>
<td>Khammam</td>
<td>51</td>
<td>41</td>
<td>10</td>
<td>52602</td>
<td>51916</td>
<td>276</td>
<td>410</td>
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<tr>
<td>Vizia Nagar</td>
<td>44</td>
<td>36</td>
<td>08</td>
<td>45728</td>
<td>45013</td>
<td>308</td>
<td>407</td>
</tr>
<tr>
<td>Krishna</td>
<td>82</td>
<td>56</td>
<td>26</td>
<td>85263</td>
<td>84186</td>
<td>472</td>
<td>605</td>
</tr>
<tr>
<td>Prakasam</td>
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<td>51</td>
<td>09</td>
<td>61836</td>
<td>60587</td>
<td>353</td>
<td>896</td>
</tr>
<tr>
<td>Chittor</td>
<td>74</td>
<td>58</td>
<td>16</td>
<td>76254</td>
<td>75330</td>
<td>487</td>
<td>437</td>
</tr>
</tbody>
</table>
Table 4.2: Sample units and coverage in Orissa

<table>
<thead>
<tr>
<th>State/Districts</th>
<th>Total</th>
<th>Rural</th>
<th>Urban</th>
<th>Total</th>
<th>Alive</th>
<th>Dead</th>
<th>Moved out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orissa</td>
<td>380</td>
<td>310</td>
<td>70</td>
<td>390362</td>
<td>385160</td>
<td>2011</td>
<td>3191</td>
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<tr>
<td>Bargarh</td>
<td>54</td>
<td>50</td>
<td>04</td>
<td>55169</td>
<td>54463</td>
<td>333</td>
<td>373</td>
</tr>
<tr>
<td>Debagarh</td>
<td>11</td>
<td>10</td>
<td>01</td>
<td>11263</td>
<td>11164</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>Sundargarh</td>
<td>73</td>
<td>48</td>
<td>25</td>
<td>74311</td>
<td>73337</td>
<td>437</td>
<td>537</td>
</tr>
<tr>
<td>Kendrapara</td>
<td>52</td>
<td>49</td>
<td>03</td>
<td>53594</td>
<td>52319</td>
<td>235</td>
<td>1040</td>
</tr>
<tr>
<td>Jagatsinghapur</td>
<td>42</td>
<td>38</td>
<td>04</td>
<td>43007</td>
<td>42447</td>
<td>164</td>
<td>396</td>
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<tr>
<td>Gajapati</td>
<td>21</td>
<td>19</td>
<td>02</td>
<td>21379</td>
<td>20912</td>
<td>152</td>
<td>315</td>
</tr>
<tr>
<td>Rayagada</td>
<td>33</td>
<td>28</td>
<td>05</td>
<td>33708</td>
<td>33316</td>
<td>252</td>
<td>140</td>
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<tr>
<td>Cuttack</td>
<td>94</td>
<td>68</td>
<td>26</td>
<td>97931</td>
<td>97202</td>
<td>372</td>
<td>357</td>
</tr>
</tbody>
</table>

(PI: Dr.C.Kolappan; kola155@trcchennai.in Funding: GFATM-CTD)

Epidemiological impact study: Disease survey

Background:
Directly observed treatment short-course (DOTS) was implemented in Tiruvallur district of Tamil Nadu in May 1999. To assess the epidemiological impact of DOTS strategy, TRC is carrying out a series of sample surveys with 2½ years duration between surveys to estimate the prevalence of disease in this district, covering a population of 5,80,000.

Aim:
- To study the trends over time for disease and thereby to measure the impact of DOTS strategy in this region

Methods:
All adults aged ≥ 15 years included for the disease survey was screened by two screening methods namely, elicitation of symptoms and X-ray examination. Two sample of sputum specimens were collected from those who were either symptomatics and/or X-ray abnormals suggestive of TB. These specimens were processed for smear and culture and those who became bacteriologically positive were referred for ATT if they satisfied the RNTCP guidelines.
Results:
Two disease surveys were already completed and the second resurvey was completed in June 2006. Coverage in the survey was above 90% for all investigations namely symptoms, X-ray and sputum examination as seen in Table 4.3. Overall, 346 persons were diagnosed to have smear/culture positive TB.

Table 4.3: 2\textsuperscript{nd} Resurvey status

<table>
<thead>
<tr>
<th>Activities</th>
<th>2\textsuperscript{nd} resurvey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible for symptom and X-ray</td>
<td>107676</td>
</tr>
<tr>
<td>Symptom screening</td>
<td>98498 (91%)</td>
</tr>
<tr>
<td>X-rayed</td>
<td>97229 (90%)</td>
</tr>
<tr>
<td>Sputum Eligible</td>
<td>12652</td>
</tr>
<tr>
<td>Sputum collected</td>
<td>11976 (95%)</td>
</tr>
</tbody>
</table>

The data analysis has been taken to estimate the decline in prevalence based on the findings of three surveys.
The 3\textsuperscript{rd} resurvey was started in June 2006. This survey will confirm the decline in TB based on previous three surveys. The coverage in the present survey was above 90% for all investigations as shown in Table 4.4.

Table 4.4: 3\textsuperscript{rd} Resurvey status (till March 2007)

<table>
<thead>
<tr>
<th>Activities</th>
<th>3\textsuperscript{rd} resurvey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible for symptom and X-ray</td>
<td>32404</td>
</tr>
<tr>
<td>Symptom screening</td>
<td>30000 (93%)</td>
</tr>
<tr>
<td>X-rayed</td>
<td>29591 (91%)</td>
</tr>
<tr>
<td>Sputum eligible</td>
<td>4065</td>
</tr>
<tr>
<td>Sputum collected</td>
<td>3956 (97%)</td>
</tr>
</tbody>
</table>

Eighty seven were identified as cases either by smear, culture or both.

(PI: P.G.Gopi; gopipg@trcchennai.in)

Annual risk of tuberculosis infection in Chennai city
Background:
The tuberculin surveys and the computed Annual Risk of Tuberculosis Infection (ARTI) provide the indirect method of assessing the extent of TB infection in the community. The proportion infected was found to be higher in urban compared to rural children in a national sample survey on ARTI conducted during 2000-2003. In the south zone, the proportion infected was 8.8% (ARTI: 1.6%) in urban and 4.7% (ARTI: 0.8%) in rural. The urban population selected for the south zone included children from peri-urban area of Chennai city. Moreover, epidemiological information on TB in the city is very limited.

Aim:
- To conduct a tuberculin survey in Chennai city to provide a precise estimate of prevalence of infection and ARTI

Methods:
The sample size was estimated to be 7000 children aged between 1 to 9 years. A stratified cluster sampling methodology was adopted to select the sample. The number of slum and non-slum streets from each zone was selected based in the ratio of slum to non-slum population in the city (1:3). All children were tested with 1TU of PPD RT23 tuberculin vials and the reaction sizes were read after 72 hours.

Results:
Of the 7354 children tested, reaction was read in 7098 (96.5%) children. The mode at the right hand side is fairly located at 17mm. Using the mode at 17mm, the prevalence of infection among unvaccinated, vaccinated children and children irrespective of BCG scar was estimated to be 10.5, 9.2 and 9.5% respectively. The difference in the proportions of children infected among unvaccinated and vaccinated was not statistically significant. The computed ARTI was 2.0, 1.7 and 1.8% respectively. The infection among children in slum (11.1%) was significantly higher than that among children in non-slum (8.9%) (p<0.01).

Conclusion:
The risk of infection was significantly higher among children in slum area compared to non-slum area. This information can be used as baseline information for monitoring the epidemiological trends in future.

(PI: P.G.Gopi; gopipg@trcchennai.in)

Prevalence of tuberculosis in different economic strata: a community survey from south India

Background:
Series of community surveys on prevalence of pulmonary TB were undertaken in a rural community in south India. A prospective socio-economic survey was added to one of the surveys.

Aim:
- To measure the prevalence of TB in different economic strata

Methods:
Head of the house-holds included in the TB prevalence survey were interviewed to collect socio-economic data and assets owned by the family using a semi-structured questionnaire. Based on the data collected, standard of living index (SLI) was constructed. Cases of TB were identified by sputum smear examination among those with chest symptoms and/or abnormal shadows on X-rays. SLI was correlated with prevalence of TB.

Results:
The survey covered 32,780 households. The SLI was low, medium and high in 22%, 36% and 42% of the study population, respectively. The corresponding prevalence of TB was 343, 169 and 92 per 100,000, a statistically significant trend (p<0.001). Among the TB patients identified, 57% were from low SLI; prevalence of TB was higher amongst the landless, those who were living below poverty line and living in katcha houses.

Conclusion:
More than half of the TB patients in the prevalence survey were from low SLI, confirming that TB disproportionately affects the poor.

(PI – Dr. Rajeswari Ramachandran; rajeswarir@trcchennai.in. Funding WHO-USAID)

Ongoing studies:
Increased yield of smear positive pulmonary TB patients by screening patients with $\geq 2$ weeks cough, compared to $\geq 3$ weeks and adequacy of 2 sputum for diagnosis of sputum positive patients

**Background:**

RNTCP recommends diagnosis of pulmonary TB by examining three sputum smears for AFB from chest symptomatics (CSs) with cough of $\geq 3$ weeks. A multi-centric study was undertaken by TRC to compare the yield of smear positive cases among CSs with cough of $\geq 2$ weeks and $\geq 3$ weeks. There was a 46% increase in the yield of sputum positive cases if duration of cough was reduced to 2 weeks. Various other studies have shown that $\geq 95\%$ of pulmonary TB cases can be diagnosed by doing two smears examination. To validate the above findings the study was repeated in different settings in five geographical areas in the country.

**Aims:**

- To assess the yield of sputum positive cases among CSs with cough of $\geq 2$ weeks compared to cough of $\geq 3$ weeks
- To compare the efficacy of two smear examination instead of three smears, among CSs

**Methods:**

This was a cross sectional multicentric study carried out in five states conveniently selected in the country namely; Andhra Pradesh, Maharashtra, Orissa, West Bengal and Rajasthan where there was 100% coverage for RNTCP. From each of these states, three districts each were selected; with low, medium and high target achievements for case detection rates as per the RNTCP performance report, India, fourth quarter, 2004. A convenient sample of 90 primary and secondary level health facilities with high out-patient attendance were selected from these districts in order to obtain about 10,000 samples from each state.

All the health workers and medical officers were briefed about the purpose and trained in the procedures of the study. Supervisory visits were made to ensure good quality sputum smear microscopy and good coverage of all eligible patients. The patients were asked for their complaints first and for those who did
not give history of cough on his own, it was elicited by a direct question using a simple structured questionnaire. Three sputum specimens were collected from the eligible patients and smear microscopy was done as per the programme recommendation.

During the study period, 96,787 out patients were registered in the selected centers of 5 states. Among them 69,209 (72%) were new adult (aged >15 years) out patients. The study has been completed and data analysis is in progress.

(PI – Dr. Aleyamma Thomas; aleyammat@trcchennai.in; Funding: WHO-USAID)

**Reasons for hospitalization of TB patients**

**Background:**

DOTS strategy with decentralization of diagnosis and treatment of TB has been implemented under RNTCP in India since 1998. Uninterrupted supply of good quality drugs and quality assured sputum smear microscopy has been made available at the peripheral health institutes. Treatment is provided at a place convenient to the patient, by a provider, acceptable to the patient and accountable to health system. Still many TB patients are treated as in-patients in a TB hospital. The reasons for hospitalization of these patients, even after decentralization of management of TB have not been documented.

**Aim:**

- To find out the various reasons for hospitalization of TB patients

**Methods:**

Four hundred and fifty patients admitted in three TB hospitals of Tamil Nadu. (Government Hospital of Thoracic Medicine, Tambaram, Government, Tiruvotteeswarar Hospital, Otteri, Chennai, Government Thoracic Hospital, Austinpatti Thoppur, Madurai -150 patients from each hospital) were interviewed. The study period was from February 2006 to November 2006. The information was collected by using a semi-structured interview schedule. The clinical characteristics and medical details at the time of admission were collected from patients’ case records by a Medical Officer. The socio economic characteristics were collected by a Medical Social Worker by using a questionnaire.

A total of 489 patients admitted in 3 hospitals were assessed. Of these, 95 were excluded from the analysis as they did not have active TB requiring treatment.
Hence 394 patients who were on treatment for TB are included for the analysis. The intake to the study is over. The data analysis is in progress.

(PI – Dr. Pauline Joseph; josephp@trcchennai.in; Funding: WHO-USAID)

**Drug susceptibility profile of *M. tuberculosis* isolates from patients who remain smear positive at fourth month or later during treatment with category-II regimen**

**Background:**

All new TB patients are treated with either Category-I or Category-III regimen in the RNTCP in India. Category II (2EHRZS₃/ 1EHRZ₃/ 5HRE₃) regimen is the re-treatment regimen of RNTCP. Patients who fail to Category II regimen have to be referred to a speciality centre for culture and DST and for further management. The drug susceptibility profile (DSP) of bacilli from these patients has not been documented by any study. Information about this will be of help for evolving standardized regimens for these patients under programme conditions.

**Aim:**

- To assess the drug susceptibility profile of *M. tuberculosis* isolates from patients who remain smear positive at fourth month or later during treatment with Category II regimen

**Methods:**

Patients for this study are being recruited from Tiruvallur District (all 6 TB units) and Chennai Corporation area. Two sputum specimens are being collected for drug sensitive test from patients on Category-II regimen, who remain smear positive at fourth month or later. It is planned to include 250 patients to the study. The study started in May 2006. So far, 120 patients have been enrolled to the study. The study is in progress.

(PI – Dr. Pauline Joseph; josephp@trcchennai.in; Funding: WHO-USAID)

**Utility of two antibiotic algorithms and repeat sputum smear microscopy to improve the efficiency of diagnosis in smear negative TB**

**Background:**

The diagnosis of smear negative pulmonary TB cases is vital as these cases are likely to break down to smear positive cases if left untreated. A break down rate
of about 28% in six months and 40% in two years has been reported. Importantly, nearly half of smear-negative cases who required treatment developed active disease with in first three months.

**Aims:**

**Primary objectives:**
- To assess the utility of two antibiotic algorithms to improve the efficiency of diagnosis in smear negative TB
- To study the role of repeat sputum microscopy for symptomatics with persistent symptoms after a course of antibiotics

**Secondary objectives:**
- To study the proportion of TB patients among this group (confirmed by culture) and their correlation with chest x-ray finding
- To obtain the information on the etiological profile of respiratory infections and their sensitivity pattern and appropriateness of antibiotic algorithm

**Methods:**

Patients with cough of 3 weeks or more and 3 smears negative by sputum microscopy are being recruited to the study. It is proposed to admit 700 patients to each antibiotic arm.

**Antibiotic regimen**

Patients are being randomly allocated to one of the following antibiotic regimens:

1) **Co-trimoxazole** (sulphamethaxozole-160 mg) twice daily for 10 days
2) **Doxycycline** 100mg twice a day on first day then once a day for 4 days followed by Amoxicillin 500mg three times a day for 5 days)

Recruitment of patients to the study is in progress.

(PI – Dr. D. Baskaran; baskar.d@trcchennai.in.)

**Evaluation of a diagnostic algorithm for HIV positive TB suspects who are initially smear negative**

**Background:**

Since the advent of HIV there has been a disproportionate increase in the reported rates of smear negative TB. There is a delay in diagnosing this condition leading to higher mortality rates. The WHO has recommended certain
revisions in the existing guidelines to the diagnosis of smear negative TB in HIV patients. This differs from the RNTCP guidelines that are currently being practiced in India. We have tried to amalgamate the two (WHO & RNTCP guidelines) and develop a new algorithm to diagnose smear negative TB in HIV positive patients.

Aims:

- To develop & evaluate a diagnostic algorithm for HIV positive persons suspected to have TB, but who are smear negative for AFB during the initial screening for TB
- To determine the utility of initial chest x-ray (CXR) & sputum culture, in the RNTCP diagnostic algorithm in identifying TB cases among the initial smear negative HIV positive chest symptomatic

Patient enrollment to this study started in February 2007 and 46 patients have been enrolled in to the study up to March 2007.

(PI: Dr.Padmapriyadarsini, padmapriyadarsinic@trcchennai.in.; Funding: WHO-USAID Collaboration with NARI, Pune)

Survey of the prevalence of anti-tuberculosis drug resistance in Gujarat state

Background:
Drug resistance surveillance (DRS) in the state of Gujarat is being conducted to obtain baseline information on the level of drug resistance for four primary anti-TB drugs after implementation of RNTCP in the state.

Aims:

- To determine the prevalence of drug resistance in ‘new’ smear positive pulmonary TB patients
- To determine the prevalence of drug resistance in ‘previously treated’ smear positive pulmonary TB patients
- To establish the foundation for routine surveillance of drug resistance in order to observe trends in drug resistance

Methods:
The study was a population based study and conducted during the period August 2005 - May 2006. This period included patient intake, data analysis, submission of technical and financial reports, report on the performance of culture laboratory
at State TB Training and Demonstration Centre (STDC) (Ahmedabad), and the External Quality Assurance (EQA) of smear microscopy, culture and DST of STDC and Intermediate Reference Laboratory (IRL).

Culture and Susceptibility testing was done as per the National DRS protocol developed by the Central TB division. Briefly, the specimens received in 1% cetyl pyridinium chloride (CPC) - 2% sodium chloride (NaCl) was centrifuged, washed and inoculated on to Lowenstein Jensen (LJ) media and incubated at 37°C for eight weeks. Reading of growth was recorded every week. Identification was done by growth on 500 μg/ml of para-nitro benzoic acid (PNB) and niacin test. Economic variant of Indirect Proportion method was followed for susceptibility testing for four primary drugs H, R, Streptomycin (Sm) and E as per the DRS protocol.

Results:
The prevalence of MDR among new cases was 2.4% and 17% among previously treated cases. The resistance pattern among new and re-treated cases is given in table 4.5.

Table 4.5: Resistance pattern among new and re-treated cases

<table>
<thead>
<tr>
<th></th>
<th>New Case</th>
<th>Re-treated Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with DST results</td>
<td>1571</td>
<td>1045</td>
</tr>
<tr>
<td>Total Susceptible</td>
<td>1236</td>
<td>562</td>
</tr>
<tr>
<td>Total Any resistance</td>
<td>335</td>
<td>483</td>
</tr>
<tr>
<td>HR resistance</td>
<td>37</td>
<td>180</td>
</tr>
</tbody>
</table>

The intake into the study is completed and data analysis is in progress.

(PI: Dr. Ranjani Ramachandran; ranjanir@trcchennai.in; Funding: CTD)