INTRODUCTION
The standardized drug regimens used by RNTCP are highly effective, with low failure rates of around 2% and 6% amongst Category I and II cases respectively but the issue of the treatment of tuberculosis is not yet resolved. Their previous treatment history and profile may provide clues as to who are most likely to develop MDR-TB. However, clearly not all such patients develop MDR-TB, and their treatment needs further investigation. The aim of this study was to determine risk factors which might predict possibility of development of Multi drug resistance in the sputum positive pulmonary tuberculosis patients who failed on category II treatment under Revised National Tuberculosis Control Programme (RNTCP).

MATERIAL AND METHOD
The study was a prospective case control study conducted from 01st April 2007 to 31st March 2008 at Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi. Patients were enrolled from the DOTS Centres under the domiciliary areas of the Institute. Twenty MDR-TB patients in the case group and forty patients matched by age, sex and subtype of CAT-II were enrolled in the control group. Patient’s demographical, clinical, bacteriological, radiological and haematological profile was recorded as per the protocol.

Result
It was observed that the total number of antitubercular treatment courses more than two, total duration of anti tubercular treatment more than 11 months, presence of cavities, bilateral and far advanced disease on the chest X-ray were statistically significant factors. Factors like high initial sputum grade, treatment interruptions, low education, smoking, alcoholism and low BMI were not associated with development of MDR-TB.

Conclusion
The detailed past history regarding antitubercular treatment courses and radiological findings at the beginning of category II treatment, may provide clues as to who are most likely to develop MDR-TB. However as the number of patients is small, more detailed study is required.

KEY WORDS: MDR-TB, DOTS, Plus, Category II failures, predictors.
overall group of cases and controls was determined. Comparisons of difference of mean were made with independent-
samples T-test. The data was further analyzed using Chi-square
test and Fisher’s exact test. Odds ratio (OR) and 95% CI were
Calculated to measure the association between variables at the
univariate and multivariate level. A value of p<0.05 was
considered statistically significant.

RESULTS AND OBSERVATIONS

Twenty patients in the case group and forty patients matched by
age, sex and subtype of CAT-II in the control group were enrolled.
The case population consisted of 12 (60%) males and 8 (40%)
females. Age and sex distribution given in Table-1.

Table-1: Age & Sex Distribution

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>CASES (n = 20)</th>
<th>CONTROLS (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td>15 – 24</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25 – 34</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>35 – 44</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>45 – 54</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>55 – 64</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

The control group had 24 (60%) males and 16 (40%) females. The
age of the patients in the case group ranged from 19 to 60 years
with a mean (SD) of 30.05 10.36 while that of control group
ranged from 15 to 56 years with a mean (SD) of 28.53 9.74. Eighty
percent cases were in the age group of 15-34 years. The BMI of the
patients in the case group and control group ranged from 10.80 to
27.55 kg/m2 (mean 17.05) and 12.32 to 24.24 kg/m2 (mean
18.09) kg/m2 respectively which was not statistically significant.
Among cases 14 patients were overweight, 5 were normal
weight and only 1 patient was overweight. Among controls 24
patients were overweight, 16 were normal weight and none was
overweight.

Education level was low (below High school) in 70% of cases and
80% of controls. The difference in socio-economic status among
cases and controls was not statistically significant because
maximum no. of cases as well as controls belonged to lower socio-
economic class.

Only one patient (5%) among case group and no patient among
controls had history of contact with MDR-TB patient. Hence, this
factor could not be analyzed.

Smoking habit was seen in 7 (35%) patients in the case group and
13 (62.5%) patients in the control group. Alcoholism was seen in
25% of patients each in case and control group. These differences
in the personal habits between the two groups was not statistically
significant (p>0.05).

No patient was positive for HIV in the case group and only one
patient from the control group turned out to be positive for the
Human Immuno-deficiency virus.

Non adherence to treatment was seen in 8 (40%) patients in the
case group and 18 (45%) patients in the control group. This
difference was not statistically significant (p>0.05).

This univariate and multivariate analysis of the various factors
studied is given in Table-2 and Table-3 respectively.

Table-2: Results of univariate analysis of Different
parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n=20)</th>
<th>Controls (n=40)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of t/t received = /2</td>
<td>9 (45%)</td>
<td>36 (90%)</td>
<td>11.0 (2.42, 54.71)</td>
<td>0.000 *</td>
</tr>
</tbody>
</table>

The remaining six (30%) cases and 27 (67.5%) controls showed no
cavity. On univariate analysis this difference between case and
controls was found to be statistically significant (p<0.05).

X-rays of all patients were reviewed and it was seen that fourteen
(70%) patients among the case group and 13 (62.5%) patients
among control groups showed the presence of cavitating diseases.
The remaining six (30%) cases and 27 (67.5%) controls showed no
cavity. On univariate analysis this difference between case and
controls was found to be statistically significant (p<0.05). The x-
rays which showed the presence of cavity were further classified
on the basis of having single or multiple cavities. In the cases
group, 02 (14.2%) and 12 (85.7%) patients had single and
multiple cavities respectively. In the control group, 06 (46.1%)
patients had a single cavity and 07 (53.8%) patients had multiple

Table-3: Multivariate analysis using Logistic Regression of
Different parameters

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>REFERENCE CATEGORY</th>
<th>ODDS RATIO</th>
<th>95% CONFIDENCE INTERVAL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of ATT courses received</td>
<td>= 2</td>
<td>6.160</td>
<td>1.444, 33.175</td>
<td>0.034</td>
</tr>
<tr>
<td>Total duration of ATT received</td>
<td>Up to 11 Months</td>
<td>1.452</td>
<td>0.310, 6.796</td>
<td>0.636</td>
</tr>
<tr>
<td>Cavity</td>
<td>No</td>
<td>1.633</td>
<td>0.231, 11.536</td>
<td>0.623</td>
</tr>
</tbody>
</table>

*ATT- Anti tubercular treatment

Table-3. Multivariate analysis using Logistic Regression of
Different parameters
cavities. This observation was not statistically significant (p=0.05). Thus, although presence of cavitating disease was associated with development of MDR-TB among category II failures, the number of cavities present did not have an influence on it.

Eighteen (90%) patients among the cases group and 24 (60%) patients among control groups showed the presence of bilateral diseases. The remaining two (10%) cases and 16 (40%) controls showed unilateral disease. On univariate analysis this difference was found to be statistically significant (p<0.05) indicating that bilateral disease on chest X-ray was a risk factor for development of MDR-TB among category II failures. Among the 20 patients in the case group, 17 (85%) had advanced disease and only three patients (15%) had less advanced disease. Among the 40 patients in the control group, 12 (30%) had far advanced disease and 28 (70%) had less advanced disease. On univariate analysis this difference in the extent of disease was highly significant (p=0.000). Hence, far advanced disease on chest X-ray is associated with a high risk for development of MDR-TB among category II failures. During multivariate analysis unilateral Vs. bilateral disease was excluded as unilateral Vs. bilateral and disease severity both indicate almost same thing and may nullify the result. On multivariate analysis far advanced disease was found to be statistically significant (p<0.05).

Eight (40%) and 25 (62.5%) patients from the case group and control group respectively, had initial sputum grading of 1+ and 2+. Twelve (60%) patients from the case group and 15 (37.5%) patients from the control group had initial sputum grading of 3+. Even though the difference is indicative but initial sputum grading was not statistically significant (p=0.05) factor.

Out of 20 patients of case group, 11 (55%) were Relapse, six (30%) were Treatment After Default and three (15%) patients were CAT-I failure. In 40 patients of control group, 22 (55%) were Relapse. 12 (30%) were Treatment After Default and 6 (15%) patients were CAT-I failure. The difference in type of patients among cases and controls was not studied as they were matched at intake.

DISCUSSION

In previous studies younger age has been found to be associated with emergence of multi-drug resistance.5,6,7,8,9,10,11 In the present study, both cases and controls were in the younger age group which is in accordance with the epidemiological findings that, tuberculosis usually affects people in the age group of 15-45.12 However, because the control group was matched for age with the case group hence this issue could not be studied as risk factor for MDR-TB. Further, sixty percent patients were male and forty percent were female amongst, cases which is in accordance with the epidemiological gender trends in most settings.13 Because the control group was matched for sex with the case group, hence this issue could not be studied as risk factor in our study.

In present study education level was low in 70% (35% illiterate+35% primary and middle) of cases and 80% (45% illiterate+35% primary and middle) of controls. The difference was not statistically significant. This finding was similar to that of A. Moniruzzaman et al16 who could not find low education level as a significant risk factor for antitubercular drug resistance. In other studies Faustini A et al7 and Elizabeth Clara et al14 also could not find low education level as a significant risk factor for multi-drug resistance in previously treated cases. In contrast Tanrikulu AC et al15 found a patient on category II treatment, especially in context of duration of anti tubercular treatment received for more than two times.

In a study conducted by M. A. Espinal et al, having received TB drugs for an overall period of time totalling 6 –11 months or > 12 months was associated with MDR-TB. Similarly in our study total duration of antitubercular treatment received for more than eleven months was found to be a significant risk factor for development of multi-drug resistance among CAT-II Failures.

In our study total no. of anti tubercular treatment courses received more than two times was significantly associated with development of multidrug resistance among CAT-II Failures. This observation was similar to that made by Elizabeth Clara et al14 who found that, the risk of development of acquired multidrug resistance was 4.58 times higher in patients, who had received antitubercular treatment for over two times. In our study the risk of development of acquired multidrug resistance was 6.16 times higher in patients, who had received antitubercular treatment courses for more than two times.

No significant difference in the treatment adherence between the cases and controls was observed in the study. This is in contrast to reports by by Elizabeth Clara et al14 and Oguz Karabay et al16 who showed that development of acquired MDR-TB was significantly associated with irregular treatment.

Our study also showed that cavitating disease on chest X-ray was observed to be significantly associated with development of multidrug resistance among CAT-II Failures. Similarly, in various studies conducted by S. K. Sharma et al17, Reuben M. Granich et al19, Elizabeth Clara et al14, Oguz Karabay et al16 and Aquif F. Vieira et al18, cavitating disease on the chest x-ray was significantly associated with development of multidrug resistance among previously treated cases. Further, bilateral and far advanced disease on chest X-ray was observed to be significantly associated with development of multidrug resistance among CAT-II failures which is in accordance with the observations made by Elizabeth Clara et al14. The risk of development of multidrug resistance was increased 13.24 times if patient had far advanced disease on chest X-ray.

No significant association could be seen between initial bacillary load and multi-drug resistance in CAT-II Failures. This finding was similar to the study conducted by Suheyla Surucuoglu et al19 in which sputum smear positivity was unrelated to the development of resistance.

The limitation of our study is small sample size. large scale multicentre studies with a bigger sample size are required in order to validate these results.

Conclusion

Present study concludes that the past history regarding antitubercular treatment, should be taken carefully, when starting a patient on category II treatment, especially in context of duration and number of treatments. The X-ray chest of all patients should be advised at the beginning of category II treatment and patients with far advanced disease could be considered as high risk for development of multidrug resistance among CAT-II Failures. This was similar to the studies done by Manasayan, 32, Netaji Subhash Marg, New Delhi-6.

REFERENCES