DRUG RESISTANCE IN TUBERCULOSIS
INTRODUCTION

Up to 50 million people may be infected with drug-resistant TB.*

Hot zones of MDR-TB such as Russia, Latvia, Estonia, Argentina and the Dominican Republic, where between 7 and 22 percent of TB patients have MDR-TB.*

Cure rates of below 70 percent cause the epidemic—and drug resistance—to rise.*

*TB Advocacy, A Practical Guide 1999, WHO Global Tuberculosis Programme
DRUG RESISTANCE IN TUBERCULOSIS

- Definitions
- Epidemiology of Antitubercular drug resistance
- Reasons for development of drug resistance
- Mechanisms of drug resistance
- Resistance to individual Antitubercular drugs
- Laboratory diagnosis of drug resistance TB
- Treatment
DRUG RESISTANCE*

Defined as a decrease in the sensitivity to a drug of a sufficient degree to be reasonably certain that the strains concerned are different from a sample of wild strains of human type that have never come into contact with the drug.

A strain should be considered resistant if 1% or more of the bacterial population is resistant to a designated concentration of drug.

PRIMARY RESISTANCE

- It is that which has not resulted from the treatment of the patient with the drug concerned.
- It includes resistance in wild strains which have never come into contact with the drug (natural resistance) and the resistance occurring as a result of exposure of the strain to the drug but in another patient.
ACQUIRED RESISTANCE

- It results from exposure of the strain to the drug and the consequent selecting out of resistant mutant bacilli.
INITIAL RESISTANCE

- It is the resistance in a patient who gives a history of never having received chemotherapy in the past.
- It includes primary resistance and resistance to previous treatment concealed by the patient or of which he was unaware.
MULTI DRUG RESISTANT TUBERCULOSIS

- It has been defined as mycobacterium tuberculosis resistant at least to isoniazid and rifampicin with or without resistance to other drugs.
## Prevalence of Drug Resistance

<table>
<thead>
<tr>
<th>Patterns of resistance</th>
<th>New Cases</th>
<th></th>
<th></th>
<th>Previously treated cases</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Strains resistant to 1 drug</td>
<td>6071</td>
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<td>60.9</td>
<td>1476</td>
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<td>Strains resistant to 2 drugs</td>
<td>2486</td>
<td>3.2</td>
<td>24.9</td>
<td>1052</td>
<td>8.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Strains resistant to 3 drugs</td>
<td>877</td>
<td>1.1</td>
<td>8.8</td>
<td>860</td>
<td>6.7</td>
<td>20.4</td>
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<tr>
<td>Strains resistant to 4 drugs</td>
<td>530</td>
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<td>19.6</td>
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<tr>
<td>TOTAL RESISTANCE</td>
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<td>TOTAL STRAINS TESTED</td>
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<td>100.0</td>
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### Monoresistance

<table>
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<th>Drug</th>
<th>New Cases</th>
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<th></th>
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<tbody>
<tr>
<td>- Isoniazid (INH)</td>
<td>2591</td>
<td>3.4</td>
<td>26.0</td>
<td>754</td>
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<td>17.9</td>
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<tr>
<td>- Rifampicin (RMP)</td>
<td>323</td>
<td>0.4</td>
<td>3.2</td>
<td>193</td>
<td>1.5</td>
<td>4.6</td>
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<tr>
<td>- Ethambutol (EMB)</td>
<td>226</td>
<td>0.3</td>
<td>2.3</td>
<td>84</td>
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<td>2.0</td>
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<tr>
<td>- Streptomycin (SM)</td>
<td>2931</td>
<td>3.8</td>
<td>29.4</td>
<td>445</td>
<td>3.4</td>
<td>10.6</td>
</tr>
</tbody>
</table>

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*World Health Organization Geneva 2004 ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD Third Global Report*
## Global Patterns of Drug Resistance

### Prevalence of Drug Resistance

<table>
<thead>
<tr>
<th>Patterns of resistance</th>
<th>New Cases</th>
<th></th>
<th></th>
<th>Previously treated cases</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Double Resistance</strong></td>
<td>2486</td>
<td>3.2</td>
<td>24.9</td>
<td>1052</td>
<td>8.2</td>
<td>25.0</td>
</tr>
<tr>
<td>- INH + RMP</td>
<td>382</td>
<td>0.5</td>
<td>3.8</td>
<td>423</td>
<td>3.3</td>
<td>10.0</td>
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<td>- INH + EMB</td>
<td>109</td>
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<td>1.1</td>
<td>34</td>
<td>0.3</td>
<td>0.8</td>
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<td>- INH + SM</td>
<td>1833</td>
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<td>18.4</td>
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<tr>
<td>- RMP + EMB</td>
<td>27</td>
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<td>0.3</td>
<td>18</td>
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<td>- RMP + SM</td>
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<td>- EMB + SM</td>
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<td>0.6</td>
<td>15</td>
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<td>0.4</td>
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<tr>
<td><strong>Triple Resistance</strong></td>
<td>877</td>
<td>1.1</td>
<td>8.8</td>
<td>860</td>
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<td>20.4</td>
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<tr>
<td>- INH + RMP + EMB</td>
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<td>1.0</td>
<td>101</td>
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<td>- INH + RMP + SM</td>
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<td>- INH + EMB + SM</td>
<td>196</td>
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<td>2.0</td>
<td>93</td>
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<td>2.2</td>
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<tr>
<td>- RMP + EMB + SM</td>
<td>12</td>
<td>0.0</td>
<td>0.1</td>
<td>19</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Quadruple Resistance</strong></td>
<td>530</td>
<td>0.7</td>
<td>5.3</td>
<td>828</td>
<td>6.4</td>
<td>19.6</td>
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### Any Resistance

<table>
<thead>
<tr>
<th>Drug Resistance</th>
<th>New Cases</th>
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<tbody>
<tr>
<td>- Isoniazid (INH)</td>
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<td>- Rifampicin (RMP)</td>
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<td>20.2</td>
<td>2299</td>
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<td>- Ethambutol (EMB)</td>
<td>1258</td>
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<td>1192</td>
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<td>28.3</td>
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<tr>
<td>- Streptomycin (SM)</td>
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<td>8.0</td>
<td>62.3</td>
<td>2609</td>
<td>20.2</td>
<td>61.9</td>
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*World Health Organization Geneva 2004 ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD Third Global Report*
GLOBAL PATTERNS OF DRUG RESISTANCE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Range (%) of drug resistance during the period</th>
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<tr>
<td></td>
<td>Initial</td>
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<tr>
<td>Isoniazid</td>
<td>1.5-31.7</td>
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<tr>
<td>Streptomycin</td>
<td>0.3-28.0</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.0-16.8</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0.0-9.9</td>
</tr>
<tr>
<td>MDR (range)</td>
<td>0.0-14.4</td>
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# PATTERNS OF DRUG RESISTANCE IN INDIA

Initial drug resistance among M.tuberculosis isolates in India

<table>
<thead>
<tr>
<th>Location</th>
<th>Period</th>
<th>No. of isolates</th>
<th>Any resistance (%) to</th>
<th>S</th>
<th>H</th>
<th>R</th>
<th>SH</th>
<th>HR</th>
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<tbody>
<tr>
<td>9 Centres–ICMR II</td>
<td>1964-65</td>
<td>1838</td>
<td></td>
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<td>12.5</td>
<td>ND</td>
<td>6.5</td>
<td>ND</td>
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<tr>
<td>GCI-SH, Chennai</td>
<td>1976</td>
<td>254</td>
<td></td>
<td>14.2</td>
<td>15.4</td>
<td>ND</td>
<td>4.7</td>
<td>ND</td>
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<tr>
<td>Bangalore¹⁰</td>
<td>1980's</td>
<td>436</td>
<td></td>
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<td>17.4</td>
<td>3.0</td>
<td>3.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Wardha²¹</td>
<td>1982-89</td>
<td>323</td>
<td></td>
<td>14.9</td>
<td>21.4</td>
<td>8.0</td>
<td>8.0</td>
<td>5.3</td>
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<tr>
<td>Gujarat²²</td>
<td>1983-86</td>
<td>570</td>
<td></td>
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<td>13.8</td>
<td>0.0</td>
<td>4.2</td>
<td>0.0</td>
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<tr>
<td>Bangalore¹⁰</td>
<td>1985-86</td>
<td>588</td>
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<td>17.3</td>
<td>2.9</td>
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<tr>
<td>North Arcot¹³</td>
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<td>2779</td>
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<td>11.6</td>
<td>21.3</td>
<td>1.7</td>
<td>8.0</td>
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<tr>
<td>Pondicherry¹⁵</td>
<td>1985-91</td>
<td>1841</td>
<td></td>
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<tr>
<td>Kolhapur¹⁹</td>
<td>1987-89</td>
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<td>32.9</td>
<td>4.4</td>
<td>4.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Raipur¹²</td>
<td>1988-89</td>
<td>244</td>
<td></td>
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<td>19.3</td>
<td>3.3</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>North Arcot*</td>
<td>1989-90</td>
<td>241</td>
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<td>12.9</td>
<td>2.5</td>
<td>2.5</td>
<td>1.7</td>
<td>1.7</td>
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<tr>
<td>North Arcot*</td>
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<td>747</td>
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<td>11.8</td>
<td>4.4</td>
<td>4.4</td>
<td>4.4</td>
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<tr>
<td>Jaipur²³</td>
<td>1989-91</td>
<td>1009</td>
<td></td>
<td>7.6</td>
<td>10.1</td>
<td>3.0</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>New Delhi²⁵</td>
<td>1990-91</td>
<td>324</td>
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<td>ND</td>
<td>18.5</td>
<td>0.6</td>
<td>ND</td>
<td>0.6</td>
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<td>Military Hosp. Pune²⁶</td>
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<td>1.0</td>
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<td>Tamil Nadu state¹¹</td>
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<td>15.4</td>
<td>4.4</td>
<td>4.4</td>
<td>3.4</td>
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<tr>
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<td>23.4</td>
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<td>8.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Raipur¹²</td>
<td>1999</td>
<td>278</td>
<td></td>
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<td>18.7</td>
<td>2.5</td>
<td>4.0</td>
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<tr>
<td>Wardha**</td>
<td>2000</td>
<td>197</td>
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<td>15.0</td>
<td>0.5</td>
<td>3.0</td>
<td>0.5</td>
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<tr>
<td>Jabalpur**</td>
<td>2002</td>
<td>273</td>
<td></td>
<td>7.0</td>
<td>16.5</td>
<td>1.8</td>
<td>2.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Tuberculosis Research Centre, unpublished data
** Tuberculosis Research Centre, interim findings, unpublished data
S, streptomycin; H, isoniazid; R, rifampicin; ND, not done

**Indian J Med Res 120, October 2004, pp 377-386
# PATTERNS OF DRUG RESISTANCE IN INDIA

Acquired drug resistance among M. tuberculosis isolates in India

<table>
<thead>
<tr>
<th>Location</th>
<th>Period</th>
<th>No. of isolates</th>
<th>Any resistance (%) to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Gujarat²²</td>
<td>1980-86</td>
<td>1574</td>
<td>47.7</td>
</tr>
<tr>
<td>Gujarat²²</td>
<td>1983-86</td>
<td>1259</td>
<td>81.1</td>
</tr>
<tr>
<td>Wardha²¹</td>
<td>1982-89</td>
<td>302</td>
<td>47.0</td>
</tr>
<tr>
<td>North Arcot¹⁶</td>
<td>1988-89</td>
<td>560</td>
<td>67.0</td>
</tr>
<tr>
<td>Raichur¹⁷</td>
<td>1988-89</td>
<td>111</td>
<td>52.3</td>
</tr>
<tr>
<td>New Delhi²³</td>
<td>1990-91</td>
<td>81</td>
<td>60.5</td>
</tr>
<tr>
<td>Tamil Nadu (4 districts)²⁷</td>
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<td>162</td>
<td>—</td>
</tr>
<tr>
<td>Tamil Nadu State¹¹</td>
<td>1997</td>
<td>16</td>
<td>(50.0)</td>
</tr>
<tr>
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<td>1999</td>
<td>16</td>
<td>(81.0)</td>
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<td>Raichur¹²</td>
<td>1999</td>
<td>11</td>
<td>(100.0)</td>
</tr>
<tr>
<td>Wardha*</td>
<td>2000</td>
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<td>(78.0)</td>
</tr>
<tr>
<td>Jabalpur*</td>
<td>2002</td>
<td>31</td>
<td>87.1</td>
</tr>
</tbody>
</table>

Brackets indicate that the percentage is based on isolates less than 25
*TRC, unpublished interim findings

**Indian J Med Res 120, October 2004, pp 377-386**
PATTERNS OF DRUG RESISTANCE IN INDIA

Acquired drug resistance among M.tuberculosis isolates in India

- DRS data obtained from 440 patients from the model DOTS area in Tiruvallore district of Tamil Nadu (1999-2003) revealed the incidence of MDR TB to be 11.8 per cent (TRC, unpublished).**

**Indian J Med Res 120, October 2004, pp 377-386**
REASONS FOR THE DEVELOPMENT OF ACQUIRED DRUG RESISTANCE

Clinical

• Treatment with a single drug (monotherapy)
• Inadequate dosage of drugs
• Insufficient duration of treatment
• Treatment with indigenous system of medicines
REASONS FOR THE DEVELOPMENT OF ACQUIRED DRUG RESISTANCE

Administrative

• Insufficient supply of drugs
• Purchase of sub-standard drugs because of government regulations and cost considerations
• Non compliance
REASONS FOR THE DEVELOPMENT OF ACQUIRED DRUG RESISTANCE

Administrative

• Irregular intake
• Premature discontinuation of treatment
• Self medication
MECHANISMS OF DRUG RESISTANCE

Three theories are of relevance to development of drug resistance in M. tuberculosis

1. Interference in uptake or penetration of the drug into the bacterial cell.


3. Destruction of Drugs
MECHANISMS OF DRUG RESISTANCE

• Drug Resistance in Mycobacterium Tuberculosis occurs only by mutations which occur at a constant but very low frequency.
• MDR-TB reflects the stepwise accumulation of individual mutations in several independent genes* and not the block acquisition of multidrug resistance.

RESISTANCE TO ISONIAZID

• *Mechanism of action*: Isoniazid is actively taken by *M. tuberculosis* and is oxidized by the mycobacterial catalase – peroxidase.
RESISTANCE TO ISONIAZID

• In the presence of an intact catalase-peroxidase an active intermediate is generated which inhibits the activity of an enzyme involved in the synthesis of mycolic acid: the enoyl – ACP reductase encoded by inhA gene.
RESISTANCE TO ISONIAZID

Genes Involved:

1. katG (catalase - peroxidase)
2. inhA (enoyl – acyl carrier protein reductase)
3. ahpC (alkyl -hydroperoxide reductase)
RESISTANCE TO ISONIAZID

• Several other genes being investigated as potentially relevant to the action and resistance to isoniazid are:

1. kasA (ketoacid synthase)
2. ceoA (UDP galactopyranose reductase)
3. Mycobacterial NADH and malate dehydrogenases.
RESISTANCE TO ISONIAZID

Mechanism of resistance:

1. Mutations in katG gene results in failure to generate an active intermediate of isoniazid.
2. Mutations of the inhA gene result in upregulation of the inhA gene expression which encodes the enoyl – ACP reductase. Increased amounts of this corresponding enzyme overwhelms the inhibitory action of the drug.
RESISTANCE TO ISONIAZID

Mechanism of resistance:

3. Search for additional genes lead to the identification of the ahpC gene which encodes the alkyl hydroperoxide-reductase.
RESISTANCE TO ISONIAZID

- Mutations in ahpC may not have a major causal role in resistance in isoniazid and rather serves to identify major lesions in katG *

RESISTANCE TO ISONIAZID

- Frequency of mutation:
  1. katG: 42 – 58 %
  2. inhA: Mutations in the inhA region appear to be responsible for resistance in approximately 21 - 34% of clinical isolates and generally associated with low level isoniazid resistance. (MIC < 1mg/ml).

RESISTANCE TO ISONIAZID

3. ahpC : 10-15%

4. Unknown mechanisms may account for less than 10% of clinical resistance.
   • Mutation rate** : $10^{-8}$
   • Wild type resistance : 1 in $10^6$

** Rate of mutation per cell division at the genes responsible for drug resistance.
RESISTANCE TO RIFAMPICIN

- *Mechanism of action*: Rifampicin is a broad spectrum anti-microbial agent which acts by interfering with the synthesis of mRNA by binding to the RNA polymerase.

- *Gene involved*: rpoB (beta subunit of RNA Polymerase)
RESISTANCE TO RIFAMPICIN

- Mechanism of resistance: Mutations in rpoB prevents interaction with rifampicin.
- Mutation rate*: $10^{-10}$
- Wild type resistance: 1 in $10^8$
- Frequency of mutations associated with the resistance: 96% – 98%.

*Rate of mutation per cell division at the genes responsible for drug resistance.
RESISTANCE TO PYRAZINAMIDE

• *Mechanism of action*: Susceptible strains of *M. tuberculosis* produce enzyme pyrazinamidase which converts pyrazinamide to pyrazinoic acid the putatively active moiety.
RESISTANCE TO PYRAZINAMIDE

• It is thought that the action of pyrazinoic acid is the combined effect of a specific activity and the ability to lower the pH below the limits of tolerance of the target organism. However the exact mechanism of action of the drug has not been firmly established.
RESISTANCE TO PYRAZINAMIDE

• Genes Involved: pncA (pyrazinamidase-nicotinamidase)

• Mechanism of resistance: Loss of pyrazinamidase activity results in decreased conversion of pyrazinamide to pyrazinoic acid, the active moiety.
RESISTANCE TO PYRAZINAMIDE

• Mutation rate* : $10^{-3}$

• Frequency of mutations associated with the resistance : 72 – 97%

• Wild type resistance : 1 in $10^6$

* Rate of mutation per cell division at the genes responsible for drug resistance.
RESISTANCE TO ETHAMBUTOL

- **Mechanism of action**: Ethambutol specifically inhibits biosynthesis of the mycobacterial cell wall
- **Genes involved**: embCAB (arabinosyltransferase)
RESISTANCE TO ETHAMBUTOL

• *Mechanism of resistance*: Resistance to ethambutol is associated with changes in the *embCAB* gene, which encodes arabinosyltransferase, involved in the synthesis of the unique mycobacterial cell wall components arabinogalactan and lipoarabinomannan.
Resistance results from an accumulation of genetic events determining overexpression of the Emb proteins and structural mutation in EmbB.
RESISTANCE TO ETHAMBUTOL

- Mutation rate\(^*\) : \(10^{-7}\)
- Frequency of mutations associated with the resistance : 47 – 65%  
- Wild type resistance : 1 in 10\(^5\)

\(*Rate of mutation per cell division at the genes responsible for drug resistance.*\)
RESISTANCE TO STREPTOMYCIN

• *Mechanism of action*: Inhibition of protein synthesis

• *Genes involved*: 1. rpsL (ribosomal protein S-12)
  2. rrs (16 S rRNA)
RESISTANCE TO STREPTOMYCN

- **Mechanism of resistance**: M. tuberculosis becomes resistant by mutating the target of streptomycin in the ribosomes.
- The principle site of mutation is the rpsL gene, encoding the ribosomal protein S12.
- The loops of 16S rRNA that interact with the S12 protein constitute a secondary mutation site.
RESISTANCE TO STREPTOMYCIN

- Mutation rate*: $10^{-8}$
- Frequency of mutations associated with the resistance:
  1. rpsL : 52 – 59%
  2. rrs : 8 – 21%
- Wild type resistance : 1 in $10^7$

*Rate of mutation per cell division at the genes responsible for drug resistance.
RESISTANCE TO FLUOROQUINOLONES

- **Mechanism of action**: Inhibition of DNA gyrase.
- **Genes Involved**: 
  1. gyrA (DNA gyrase subunit A) 
  2. gyrB (DNA gyrase subunit B) 
  3. IfrA gene
Mechanism of resistance: The molecular basis of resistance to fluoroquinolones is a complex multistep process.
RESISTANCE TO FLUOROQUINOLONES

- Research has shown the presence of resistance mutations in the DNA gyrase (composed of subunits GyrA and GyrB), the topoisomerase IV and the cell membrane proteins that regulate the intracellular concentration of the drug by mediating drug permeability and efflux.
RESISTANCE TO FLUOROQUINOLONES

- Step wise accumulation of mutations in several of these genes is necessary to achieve high levels of resistance.
RESISTANCE TO FLUOROQUINOLONES

• The recent characterization of a mycobacterial efflux pump, the ifrA gene (which confers lower level quinolone resistance) and of gyrB mutations contribute to more complete understanding of the mechanisms of resistance to fluoroquinolones in mycobacteria.
RESISTANCE TO FLUOROQUINOLONES

- Mutation rate: ?
- Frequency of mutations associated with resistance: 75-94%
- Wild type resistance: ?
LABORATORY DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

A) Conventional methods

1. Absolute concentration method:
   - Inoculation of control media and drug containing media.
   - Media containing several sequential two fold dilutions of each drug are used.
   - Resistance is indicated by the lowest concentration of drug which will inhibit growth.
LABORATORY DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

A) Conventional methods

2. Resistance ratio method:
   - A variant of absolute concentration method.
   - Resistance ratio – minimal concentration inhibiting growth of test strain divided by minimal concentration inhibiting growth of standard susceptible strain.
   - Resistance ratio: $\leq 2$ – susceptible
     $\geq 8$ -- resistance
A) Conventional methods

3. Proportion method:
   - The ratio of the number of colonies growing on the drug containing medium to that on the drug free medium indicates proportion of the drug resistant bacilli.
   - Below a certain proportion (critical proportion)- susceptible and above resistant.
   - Critical proportion- 1% for INH, PAS and Rifampicin and is 10% for other drugs.
B) Rapid methods:

1. *Radiometric method (BACTEC)*:
   - 7H12 medium containing $^{14}$C-palmitic acid is inoculated and evolution of $^{14}$CO$_2$ is measured over a period.
   - Results in about 18 days.
   - Costly.
LABORATORY DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

B) Rapid methods:

2. **Luciferase reporter mycobacteriophage test (LRM test)**:

- Introduction of luciferase gene into mycobacteria through specific reporter phage system.
- Exposure of luminous mycobacteria to antimycobacterial agents would block light production in sensitive bacilli.
- Very sensitive, specific & rapid. Gives result in 48-72 hours, need to develop standard method.
B) Rapid methods:

3. *Mycobacteria growth indicator tube*:

- Oxygen sensitive fluorescent compound contained in a silicone plug at the bottom of tube with mycobacterial growth medium.

- Dissolved oxygen in the medium quenches fluorescence.
LABORATORY DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

B) Rapid methods:

3. *Mycobacteria growth indicator tube*:
   - Mycobacterial growth utilises oxygen and the compound fluoresces detected by UV transilluminator.
   - Results in 8-14 days.
   - High cost.
B) Rapid methods:

4. *Rapid genotype based novel techniques:*
   - Analysis of mutations conferring drug resistance by disruption mycobacterial cell wall by boiling or mechanically.
   - Amplification of genomic region conferring resistance by PCR.
   - Post amplification analysis of mutations – automated DNA sequencing, single strand conformation polymorphism (SSCP).
LAboratory Diagnosis of Drug Resistant Tuberculosis

B) Rapid methods:

5. Restriction fragment length polymorphism (RFLP) analysis: - categorize & compare isolates of bacilli with drug sensitive/multiple drug resistant strains.
TREATMENT*

Principles of chemotherapy of drug resistant Tuberculosis

1. Drugs are to be given in adequate doses & for adequate duration.

2. Drugs selected for the treatment should have not been used in past or used regularly for shorter duration.

3. Use of first line drugs to be preferred because they are effective & less toxic.

*TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES World Health Organization – Geneva 2003
4. Cross resistant drugs should be avoided as they are not effective & increase toxicity.

*Drugs with one way cross resistance*

a) Viomycin & Capreomycin
b) Viomycin & Kanamycin
c) Kanamycin & Streptomycin
d) Thiocetazone & PAS
TREATMENT*

Drugs with complete cross resistance:-

a) Ethionamide & prothionamide

b) Thioamides (Ethionamide & prothionamide) & Thioacetazone

c) Kanamycin & Amikacin

d) Fluoroquinolones (ofloxacin, ciprofloxacin & sparfloxacin).

e) Cycloserine & Terizidone.

*TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES World Health Organization – Geneva 2003
5. Addition of single drug in failing regimen is contra-indicated.

6. Considering the toxicity of reserve drugs, doses should be increased in time with optimal tolerance of the patient to achieve best results.

*TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES World Health Organization – Geneva 2003*
7. Intermittent therapy is normally not effective & should not be given in MDR –TB

8. Retreatment should always be given preferably in hospital under strict supervision for close observation of adverse drug reactions commonly associated with the reserve drugs.

*TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES World Health Organization – Geneva 2003
9. Regimen should include at least 4 drugs, including an injectable agent & a fluoroquinolones in the initial phase & at least 3 of the most active & best tolerated drugs in the continuation phase.

10. Initial phase of at least 6 months should be followed by a continuation phase of 12-18 months.
11. Treatment should be directly observed.

12. If results of susceptibility test is available –

treatment should be based on it.
13. Pyrazinamide & Ethambutol can be included in the regimen because of lower probability of resistance.

14. The treatment with these weaker regimens should be continued for at least 18 months after sputum conversion to prevent relapse.
TREATMENT

15. Monitor bacteriological results (smear and culture) monthly from the second month until the sixth month, and then quarterly until the end of treatment.**

16. An early surgical interference can be planned if disease is limited & patient’s general condition permits.**

**GUIDELINES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS World Health Organization 1997**
## Reserve Antitubercular Drugs

<table>
<thead>
<tr>
<th>Reserve Drug (Abbreviation)</th>
<th>Mode of Action</th>
<th>Recommended Daily Dosage(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amikacin (Am)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 15, Minimum (mg): 750, Maximum (mg): 1000</td>
</tr>
<tr>
<td>capreomycin (Cm)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 15, Minimum (mg): 750, Maximum (mg): 1000</td>
</tr>
<tr>
<td>ciprofloxacin (Cx)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 10-20, Minimum (mg): 1000, Maximum (mg): 1500</td>
</tr>
<tr>
<td>cycloserine (Cs)</td>
<td>bacteriostatic</td>
<td>Average (mg/kg): 10-20, Minimum (mg): 500, Maximum (mg): 750</td>
</tr>
<tr>
<td>ethionamide (Et)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 10-20, Minimum (mg): 500, Maximum (mg): 750</td>
</tr>
<tr>
<td>kanamycin (Km)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 15, Minimum (mg): 750, Maximum (mg): 1000</td>
</tr>
<tr>
<td>ofloxacin (O)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 7.5-15, Minimum (mg): 600, Maximum (mg): 800</td>
</tr>
<tr>
<td>(p)-aminosalicylic acid (PAS)</td>
<td>bacteriostatic</td>
<td>Average (mg/kg): 150, Minimum (mg): 8, Maximum (mg): 12</td>
</tr>
<tr>
<td>protonamide (Pt)</td>
<td>bactericidal</td>
<td>Average (mg/kg): 10-20, Minimum (mg): 500, Maximum (mg): 750</td>
</tr>
</tbody>
</table>

\(^a\) Thrice-weekly regimens are not recommended.
Acceptable “third line” regimens if there is resistance to isoniazid but susceptibility to rifampicin**

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Minimum duration in months</td>
</tr>
<tr>
<td>Isoniazid (streptomycin, thioacetazole)</td>
<td>1 rifampicin 2 aminoglycoside (^c) 3 pyrazinamide 4 ethambutol</td>
<td>2-3 2-3 2-3 2-3</td>
</tr>
<tr>
<td>Isoniazid and ethambutol (streptomycin)</td>
<td>1 rifampicin 2 aminoglycoside (^c) 3 pyrazinamide 4 ethionamide (^d)</td>
<td>3 3 3 3</td>
</tr>
</tbody>
</table>

\(^c\) streptomycin, if still active; if resistance to streptomycin, use kanamycin or capreomycin

\(^d\) if ethionamide is not available or poorly tolerated (even at a dose of 500 mg/day), use ofloxacin.
## Suggested Treatment Regimens

<table>
<thead>
<tr>
<th>Susceptibility Testing to Essential Drugs</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not available</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Km&lt;sup&gt;b&lt;/sup&gt; + Et + Q&lt;sup&gt;c&lt;/sup&gt; + Z +/- E</td>
<td>At least 6 months</td>
</tr>
<tr>
<td><strong>Available:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance to H + R</td>
<td>S&lt;sup&gt;d&lt;/sup&gt; + Et + Q&lt;sup&gt;c&lt;/sup&gt; + Z +/- E</td>
<td>At least 6 months</td>
</tr>
<tr>
<td>Resistance to all essential drugs</td>
<td>1 injectable +1 fluoroquinolone + 2 of these 3 oral drugs: PAS, Et, Cs</td>
<td>At least 6 months</td>
</tr>
<tr>
<td>Susceptibility testing to reserve drugs available</td>
<td>Tailor regimen according to susceptibility pattern&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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<sup>a</sup> Use of a standardized regimen could be feasible in resource-limited countries with a high burden of TB and a strong and efficient NTP.

<sup>b</sup> Am or Cm could also be used. However, since there is cross-resistance between Km and Am, if either drug was used previously or if resistance to them is suspected, Cm is the preferred choice.

<sup>c</sup> Fluoroquinolone (ciprofloxacin or ofloxacin).

<sup>d</sup> If resistance to S is confirmed, replace this drug with Km, Am or Cm.

<sup>e</sup> Individualized regimen is probably more feasible in designated centres of excellence.

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The Place of Surgery

Surgery should be considered for a patient with bacilli resistant, or probably resistant, to all except two or three relatively weak drugs.

Guidelines for the Management of Drug-Resistant Tuberculosis

World Health Organization 1997
THE PLACE OF SURGERY**

If the patient has a large localised cavity with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered.

**GUIDELINES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS World Health Organization 1997**
**THE PLACE OF SURGERY**

To avoid serious, and potentially fatal tuberculosis complications of surgery, operate when the bacillary population is likely to be at its lowest.

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**GUIDELINES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS**

*World Health Organization* 1997
TREATMENT

THE PLACE OF SURGERY**

If only a very weak regimen is available, experience has shown that the most favourable time is after two months’ treatment.

After surgery, the same regimen should be continued for at least 18 months.

**GUIDELINES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS World Health Organization 1997
All the best..