Leprosy one of the major scourges of mankind will be (hopefully) eliminated despite seemingly un-surmountable odds, primarily due to the WHO MDT, political will, donor agencies, NGOs and committed health workers.

Development and implementation of MDT has transformed leprosy into a curable disease.

1985 – 2005: > 15 million persons treated

Registered cases

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>513,793</td>
<td>407,791</td>
<td>295,816</td>
<td>265,661</td>
<td>231,361</td>
</tr>
</tbody>
</table>

The seemingly great success of MDT prompted the World Health Assembly in 1991 to call for elimination of leprosy as a public health problem by the year 2000.
Some landmarks in the treatment of leprosy and the evolution of MDT

- Isolation/Segregation
- Chaulmoogra oil - externally, internally and eternally (Sushruta 600 BC)

1941 - Guy Faget-Promin
1947 - Dapsone (Ambulatory treatment)
1960 - Ridley-Jopling classification
Immunological basis-Mitsuda reaction, T-cells, humoral response, vaccination
1962- Clofazimine – confirmed to be effective in mouse foot pad
1964 - First confirmed dapsone resistance
1965 - Combined therapy to reduce drug resistance (Spickett)
1967 - Rifampicin - most potent bactericidal

1974 - Existence of persisters. Viable *M. leprae* in lepromatous patients treated with dapsone for 10-12 years. Portal of exit and entry of *M. leprae*. Survival of *M. leprae*
- Immunology of Leprosy Programme (IMMLEP), Special Programme for Research and Training in tropical Diseases (TDR)
- Development of drugs, vaccines, diagnostics
1976 - Programme for Research for Chemotherapy of Leprosy (THELEP)
1981 - Study Group for Drug Regimens
Study Group on Chemotherapy of Leprosy

1940 - Promin in Carville
1960 - Mouse foot pad- screening of drugs: dapsone, thiambutosine, ethionamide, thiacetazone, clofazimine
- Clinical observation, bacteriological index
- Efficacy of dapsone, clofazimine and rifampicin was established
1970 - Freerkson- Isoprodian, Malta
1972 - Relapse rather that growth in mouse foot pad as evidence of treatment failure

THELEP (Programme for Research on Chemotherapy of Leprosy, 1976)

- To organise dapsone resistance surveys demonstrating the need for MDT regimens
  - 215 patients, 769 biopsies
  - More than 1/3 primary dapsone resistant bacilli
  - Persisting M. leprae in 9% of all specimens
- Establish the rationale for composition of MDT regimens for PB and MB
- Short term trials - biopsies from patients
- To organise controlled trials
- Screen drugs – animal models
- Mali, Chingelput, London – Persisters, Drug resistance
  MB - India
  PB – Malawi and Indonesia
THELEP/ SWG
Field Trials in Karigiri/Polambakkam, Sungei Buloh & Malta

• No relapses after 2 years of treatment in bacteriologically negative MB patients
  • Rifampicin - 1200mg / month in 2 doses
  • Clofazimine - 1200mg / month in 2 doses
  • Dapsone - 100mg daily
  • Acedapsone - 225mg I/M every 2 months

2200 patients -- no relapses

• Trials conducted in 1973 had shown that intermittent administration of rifampicin was as effective as daily rifampicin – 93 LL patients (India)

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**MDT for MB patients – some successive regimens**

<table>
<thead>
<tr>
<th>References</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Rifampicin: 1200 mg once a month; Dapsone, 50 mg daily</td>
</tr>
<tr>
<td>11a</td>
<td>Rifampicin, 600 mg daily on 2 consecutive days every 4 weeks; Thiacetazone, 1 g weekly intramuscularly</td>
</tr>
<tr>
<td>THELEP Protocol for field trials (1979)**</td>
<td>Rifampicin, 500 mg daily on 2 consecutive days once a month; Clofazimine, 600 mg daily on 2 consecutive days once a month; Acedapsone, 225 mg bimonthly (injections); Dapsone, 100 mg daily</td>
</tr>
<tr>
<td>10</td>
<td>Rifampicin, 600 mg on 2 consecutive days in every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised); Clofazimine, 600 mg daily on 2 consecutive days every 4 weeks (or monthly) (first dose supervised, second dose preferably supervised); Dapsone, 100 mg daily</td>
</tr>
<tr>
<td>22</td>
<td>Rifampicin, 600 mg one monthly, supervised; Clofazimine, 300 mg once monthly, supervised, and 50 mg daily, self-administered; Dapsone, 100 mg daily, self-administered</td>
</tr>
</tbody>
</table>

**Trial started in 1973,**

In: Draft report of the planning meeting for a protocol for field trials of chemotherapy of lepromatous leprosy, Geneva, 15 October 1979.
(1981), THELEP/ SWG/ WHO/ILEP/ Study group on Chemotherapy
of Leprosy
- Dapsone resistance - Secondary and Primary
- Rifampicin anarchy
- Increasing number of patients – general demand for guidance
- Difficulties in implementation of Fifth Report
- To review the information collected since 1976 on drug regimens

**Classification** of patients into 2 categories. : PB: upto 2 BI, MB>2

Two **Drug Regimens**

<table>
<thead>
<tr>
<th>PB</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months,</td>
<td>24 months / upto smear negativity</td>
</tr>
</tbody>
</table>

- Drugs: *Rifampicin, Dapsone, Clofazmine*
  *Ethionamide, Prothionamide* to be considered

- Research needs
- Operational aspects - case detection, lab. facilities, drug delivery, records and follow up
- Health education

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**Endorsed by WHO Executive Board, May 1982**

**Implementation**: started on pilot basis

<table>
<thead>
<tr>
<th>Year</th>
<th>Coverage</th>
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<tbody>
<tr>
<td>1982-85</td>
<td>1%</td>
</tr>
<tr>
<td>1991</td>
<td>42% “</td>
</tr>
<tr>
<td>1992</td>
<td>50% “</td>
</tr>
<tr>
<td>1997</td>
<td>100% “</td>
</tr>
</tbody>
</table>

- 1987/88 PB- only smear negative cases
- 1991 World Health Assembly
  Elimination of Leprosy by 2000 as a Public Health problem
- 1992 Calendar blister packs
1993/1994
- Fixed duration therapy (FDT) for MB-24 doses
- Post MDT annual surveillance could be discontinued

1998
- Skin Slit Smear done away with
- PB (single lesion) - ROM
- PB (2-5 lesions) - same as before
- MB (more than 5 lesions) - reduced to 12 doses
- Leprosy Elimination Campaigns (LECs)
- Special Action Projects for Elimination of Leprosy (SAPEL)
- 1991- BLP 190 patients -12 months of MB MDT
- 1992- WHO started trials on 12 months of MB MDT

1997: *7th WHO Expert Committee on Leprosy*
'possible to shorten duration of MDT (MB) to 12 months’
- Among newly detected MB cases
  - only 13% SSS +ve (>3)
- RMP kills >99.999% of viable organisms with 3 monthly doses
- DDS + CLF kill > 99.999% of viable *M. leprae* in 3 months
- RFM resistant mutants likely to be eliminated by 3-6 months with DDS+CLF
- Annual relapse rate 0.2% with standard MDT
• **Multicentric double blind trial (15 centres 1992)**
  
  *THEMYC 1997 Report*

  1. 24 mo. WHO MDT
  2. 12 mo. WHO MDT
  3. 12 mo. WHO MDT + OFLO 400 mg daily x 4 wks
  4. Regimen 3 + RFM 600mg daily x4wks

  - similar results in all regimens

• **Results of MB defaulted cases**

  A. 41 pts, retrieved after 1-6 yrs, average Tt. taken 7 months
  - Clinical improvement – all patients, SSS - 29 negative, 5 no change

  B. 139 pts, retrieved after 7.5 yrs, Tt. taken \( \leq \) 12 months
  - Comparable to 24 months treated group

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1999  
Prevalence 4.5/10,000  
Number of newly detected cases-static or even increased

2000  
• Action Plan for Elimination of Leprosy  
• Global Alliance for Elimination of Leprosy  
• WHO Technical Advisory Group on Elimination of Leprosy (TAG)

**THE FINAL PUSH**

• Definition of ‘Elimination’ should be retained  
• Need to improve Reporting System  
• Raise Awareness and Political commitment  
• Establish Task Force in Endemic Countries  
• IEC activities to encourage self reporting
Studies on:

- A-MDT
- Integration
- Relapses
- Impact of IEC & SAPEL
- Leprosy in Urban areas
- Use of Prednipacks
- MDT regimens of shortened duration
- Drug resistance
- Leprosy classification systems
- U-MDT to all (follow up for 7 years)

WHO MDT- the reasons for success/achievements

Was accepted in the absence of convincing field trials and data on adverse drug effects because -

- Core of Leprosy Elimination Strategy – > 25 years, >15 million cases treated, Only 4 countries have to achieve elimination
- Standardization of drug regimens
- Classification of patients into two main categories
- Fixed duration of treatment
- Prevention of development of drug resistance
- Renders patients non-infectious rather quickly
- Very few relapses - MB 0.77%, PB 0.66 -1.07%
- Robust – averages/redundancies built in to prevent treatment failure and overcome operational problems
Relapses:

1980s

MB - 2241 (had prolonged mono-therapy with dapsone)
22% skin smear positive
0.26 / 100 person years

PB 0.65 / 100 person years after 4 years - Malawi
0.12 / 100 person years after 5 years - Indonesia

1990s

Pilot survey by questionnaire - 17 countries

| 100,000 MB | 600,000 person years of observation | Below the acceptable limits of 1 per 100 person years |
| 150,000 PB | |

28 Programmes

| 20,000 MB | 0.77% | 9 years after stopping MDT |
| 25,000 PB | 1.07% | |

ROM & other single dose regimens

- Single skin lesion (SSL)- Single dose
- RCT (1483 patients) - single lesion- India
- ROM vs WHO MDT PB (follow up -18 months)
  - Improvement 51.8% vs 57.3%
  - Complete cure 46.9% vs 54.7%
  - 6 treatment failures in each group
  
  Indian J Lepr 1997; 69

- ROM Vs ROM + Convit vaccine, India
  - Clinical outcome of test group better
  
  Int J Lepr 2000

- RCT (622 patients) –Single dose vs WHO MDT PB, Zaire,
  Rifampicin (40mg/Kg)+Clofazimine (1200mg)
  Rifampicin (40mg/kg)+Clofazimine (100mg) + Dapsone (100mg)
  +Ethionamide (500mg)

Relapse rates 20.4/1000 person years in the test groups
ROM single dose vs. WHO MDT PB (2-3 lesions)

1. 236 smear negative, 2-3 skin lesions, no nerve trunk involvement
   At 18 months FU (Marked improvement- >90% ↓ clinical score)
   
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ROM</td>
<td>WHO MDT PB</td>
</tr>
<tr>
<td>46.2%</td>
<td>53.4%</td>
</tr>
</tbody>
</table>

   - But, significant difference in favour of WHO MDT PB in patients
     with 3 lesions/ > one body part affected
   - Reversal reactions & adverse drug reactions were minimal in
     both groups

   Indian J Lepr 2001;73:131-43

2. 51 PB patients – FU 2 years
   Clinical/ histopathological improvement similar in both groups

   The operational convenience and drug compliance with ROM
   could make it an acceptable regimen when the disease is
   localized to 2 or 3 skin lesions

   Indian J Lepr 2005

• Long term follow up – ROM
  310 SSL PB cases treated in Bangladesh (1998-2000)
  – 87% retrieved – average FU 6.3 years
    Of these – 76% complete clearance of lesion
      - 10 cases (3.6%) evidence of relapse (PB)
      - None had NFI

   Consideration should be given to possibility of relapse
   in patients received ROM for single lesion leprosy

Lepr Rev 2007;78:160
Monthly ROM for PB & MB leprosy

**WHO trial in Myanmar & Guinea**

- **Once a month ROM** 3 to 6 months - PB
  12 to 24 months - MB
- Final results expected by end 2007

**24 months ROM vs WHO MB MDT in MB leprosy**

- 21 patients randomly allocated to the 2 groups
- ROM as safe & effective as MDT conferring similar bacteriological and histological improvements without increased rates of lepra reactions
- Follow up of 8 years showed similar long term efficacy and safety

Newer Regimens

<table>
<thead>
<tr>
<th>U-MDT</th>
<th>MB MDT</th>
<th>For all x 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROM</td>
<td>PB</td>
<td>Monthly x 3-6 months</td>
</tr>
<tr>
<td></td>
<td>MB</td>
<td>Monthly x 12-24 months</td>
</tr>
</tbody>
</table>

- PMM (Rifapentine 600mg + Moxifloxacin 400mg + Mino100mg)
- MDT for 1 year + Ofloxacin 400mg daily for first 4 weeks
- Ofloxacin 400mg + Rifampicin 600mg daily- 4 weeks (PB)
- Rifampicin + Minocycline + Sparfloxacin + Clarithromycin daily X12 weeks
Deficiencies / Difficulties

• Frequently changing – schedules, definitions
  microbiological rationale?

• Nerve involvement not considered in classification (WHO)
• Slow response in some patients
  MB - 29% lesions still active after 3 years, Thailand
  PB
  6 months resolution - 8%,
  regression – 44%
  increased activity – 16% India

• 1 year visible but not active – 59.6%, Malawi
  visible and active – 2.3%

• Clinically active after treatment - 22%, Thailand

Deficiencies / Difficulties contd...

• Slow fall of BI – especially in those with BI ≥ 3+

• Doing away with slit skin smear and even clinical response

• No effect/worsening of disability status
  - 2.5 -3.3% new /worsening of disability- PB, Malawi
  – 4% at recruitment, 7% at follow up, Thailand

  – Worsening of nerve function impairment
    MB: 8% -13%, PB:4 -7%, Thailand
Side effects of drugs - Variable percentages

- GIT side effects
- Pigmentation with clofazimine
- Rifampicin – daily dose – 8.5%
  monthly- hepatitis (0.8%), allergic reaction (0.2%)

Relapses
- MB- 20.4/1000 person years, India
- PB- 6.5/1000 person years, Malawi
  1.8% Thailand, 2.5% Malawi

Vaccines for Immunotherapy/ prophylaxis

Definitions
- Adequacy & Regularity of Treatment
- Maximum period over which the drugs could be given

Surveillance - epidemiological and operational indicators


- Eradication may take more time
- The operational guidelines are being widely implemented to sustain the gains achieved under elimination of leprosy as a public health problem

- Challenges remain in areas of:
  - Capacity building
  - Maintenance of expertise
  - Referral networks and their integration into GHS
  - Community awareness
  - Emergence of rifampicin resistant strains

(Weekly Epidemiological Record, June, 2007)
• Hence, a number of new more effective and less toxic drugs & regimens are going to be available and are likely to be useful in the future

• However, the development of more powerful regimens doesn’t necessarily result in better disease control

• The key factor is to apply the effective regimens properly under routine field conditions

Thank You