Primary resistance to anti tuberculosis drugs in Chile

Chile has conducted several initial study of resistance to first line anti tuberculosis drugs as part of the Drug Surveillance Resistance in tuberculosis promoted by the WHO. The last study was carried out in 2011-2012 showing an overall level of TB drug resistance of 8.6% (Table 1) and a prevalence of multidrug resistance of 1.3%.

Since 2014 the monitoring of drug resistance to TB is universally performed to avoid sub-diagnosis and treat each case according to the susceptibility profile.

Table 1: Cumulative prevalence of resistance to first line anti tuberculosis drugs. Chile 2011-2012

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5,1</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1,3</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>5,9</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>0,17</td>
</tr>
</tbody>
</table>

Strategies to fight against MDR-TB

<table>
<thead>
<tr>
<th>STRENGTH</th>
<th>AREAS FOR IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal DST for first- and second-line drugs</td>
<td>Early diagnosis (new diagnostic tools)</td>
</tr>
<tr>
<td>Specific treatment for resistance profile</td>
<td>Improve de adherence to sensitive tuberculosis cases</td>
</tr>
<tr>
<td>Central committee to decide clinical management</td>
<td></td>
</tr>
<tr>
<td>Centralized drug distribution (not in market)</td>
<td></td>
</tr>
<tr>
<td>Universal cover of DOTS</td>
<td></td>
</tr>
<tr>
<td>Clinical guidelines</td>
<td></td>
</tr>
</tbody>
</table>
Background

China is estimated to have nearly a quarter of all global MDR-TB patients. We started programmatic management of drug-resistance in 2006, supported by the Global Fund project. Until the end of the Global Fund projects on June 30, 2014, one third of the cities in 30 of the 31 provinces have been covered.

After the end of the Global Fund project, the Chinese government continues to carry out and scale up PMDT with domestic funds.

The mode of PMDT in China is city level responsibility for diagnosis and treatment, county level responsibility for suspected recommendations and community responsibility for the management of patients. The treatment follows the regimen that WHO recommended. The treatment of patients is covered by medical health insurance, the reimbursement ratio is at least 70%. Poor patients will be aided by the Civil Affairs Department.

Accomplishments

● Issued NTP for the 12th 5-year plan in which the coverage of PMDT at city level reached 50%, the screening rate of MDR-TB high risk groups reached 60%. Actually, we have exceeded the established objectives. Coverage and screening rates were 70% and 74% respectively at the end of 2015.

● Developed some technical documents:
  - Working Guideline for the Programmatic Management of Multi-Drug Resistant Tuberculosis
  - Guideline for MDR-TB Chemotherapy
  - Guideline for Infection Control of Tuberculosis
  - Clinical Pathway of MDR-TB
  - Standardized training series materials for MDR-TB prevention and control (province and prefecture level, county and district level, community and village level)

● Established an internet-based real-time information collection and management system for MDR-TB

● 70% of the cities can carry out the molecular DST with Xpert MTB/RIF and LPAs; nearly a third of the counties can use Xpert MTB/RIF for detection of resistance to rifampicin

● Conducted the National Drug Resistance Surveillance in 2007-2008, the second National Drug Resistance Surveillance is being carried out.
BACKGROUND

Indonesia has implemented Programme Management of Drug Resistant-TB (PMDT) as the national management system for MDR-TB, established from 2006. The aim is to manage MDR-TB and can be seen from the data of estimated burden of TB in Indonesia as shown below:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Level</th>
<th>Total cases of TB per 100,000 Year Day Hour</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Global</td>
<td>15,000,000</td>
<td>1,440</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>1,600,000</td>
<td>163</td>
</tr>
<tr>
<td>Incidence</td>
<td>Global</td>
<td>6,000,000</td>
<td>913</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>1,000,000</td>
<td>214</td>
</tr>
<tr>
<td>Mortality</td>
<td>Global</td>
<td>1,100,000</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>100,000</td>
<td>11</td>
</tr>
</tbody>
</table>

Within the data above, particularly estimated burden of MDR-TB and TB-HIV comes out.

Table 2: Estimated Burden of MDR-TB & TB-HIV in Indonesia 2015

CHALLENGES

1. Slow PMDT expansion and decentralization of services
2. Focus on treatment cascade, burden of having smear-negative pulmonary TB cases is very low
3. Delays in Xpert expansion, Sputum transport a real bottleneck
4. High loss to follow up (initial LFU and during treatment LFU)
5. Limited local level support, including socio-economic
6. Improving counselling practice to support PMDT care
7. Delays in Xpert expansion, Sputum transport a real bottleneck
8. Mortality Global 1,100,000 3,014 156 447
9. Incidence Global 8,000,000 21,918 89 133
10. Expansion the use of Bedaquiline

PLANS & STRATEGIES

1. Expansion of PMDT services to district level
2. Training for support in health facilities and in health community to be in line with PMDT expansion
3. Strengthening local coordination: pre-hospitalization supervision through e-TB Manager Indonesia
4. Development and piloting of community-based PMDT care
5. Providing socio-economic support for all MDR-TB patients
6. Conducting clinical supervision in PMDT hospitals and satellites
7. Regular central reviews on PMDT line
8. Developing joint guidelines for treatment and control of drug-resistant TB
9. Monitoring for implementation of background issues for implementing new drugs and interventions (tuberculosis drug resistance)
10. Exploring the use of new drugs

IMPLEMENTATION

INDONESIA

MINISTRY OF HEALTH
REPUBLIC OF INDONESIA

Provided by:
Dr. Endang Budi Hastuti
National TB Programme (NTP)

Dr. Endang Lukitosari, MPh
Ministry of Health, Republic of Indonesia

APEC CONFERENCE ON PREVENTION, CONTROL AND CARE FOR MDR-TB AND SUPPLY OF 2^ND-LINE ANTI-TB DRUG

Diagram 1: Indonesian Algorithm of TB Diagnosis

Graphic 1 : Case Finding of MDR-TB 2009-April 2016

Graphic 2 : Treatment Outcome of MDR-TB (%) 2009-2015

Status for case finding of MDR-TB from 2009 - 2016 is shown respectively:

Result for case finding of MDR-TB from 2008 - 2016 is shown respectively:

Total number: 13,621
- Suspicious: 7,981
- Confirmed: 5,080
- Under treatment: 4,871

Implementation of PMDT as the management applied for MDR-TB is strengthened with Facilities both diagnostic and treatment & care aspect. Indonesia has 87 Xpert Machines, 16 labs for M.TB Culture, 13 Labs certified for DST, and 13 labs certified for 1st line DST spread over among provinces. Meanwhile support for treatment and care facilities is available as 34 referral hospitals, 1485 family medicine centers, 13 sub-referral hospitals, and 1505 satellites facilities that has carried out the services. 360 units of Xpert Machines are planned to be procured to be allocated in all over the 33 provinces. Meanwhile support for treatment and care facilities is available as 34 referral hospitals, 1485 family medicine centers, 13 sub-referral hospitals, and 1505 satellites facilities that has carried out the services.

Seven years of implementation give raise to the treatment outcome as follows:

- Under treatment: 4,971
- Result for case finding of MDR-TB from 2009 - 2016 is shown respectively:

True for this year: 100,000
- Total number: 13,621
- Suspicious: 7,981
- Confirmed: 5,080
- Under treatment: 4,871
**POLICY ON MANAGEMENT OF DR-TB PROGRAMME**

- Management of DR-TB is organized around five components like the DOTS strategy, namely:
  1. Sustained government commitment
  2. Accurate, timely diagnosis through quality assured culture and drug susceptibility testing
  3. Appropriate treatment utilizing second-line drugs under strict supervision
  4. Uninterrupted supply of quality assured second-line drugs; and
  5. Standardized recording and reporting system.

- Prevention is the key to effective control of DR-TB.
  - NDR-TB arises as a result of improper management of TB patients.
  - Most cases of XDR-TB arise as a result of poor MDR-TB management.
  - To strengthen case holding of patient with TB. DOT supervisors to ensure patient completed TB treatment and cured.
  - On-going adherence, counseling and psychosocial support is provided to patients and reinforced throughout treatment.
  - Close contacts of patients diagnosed with DR-TB must be screened.
  - DR-TB registers should be kept at hospitals and states level (30%) and updated regularly.

**FOCUS AREAS**

- UP-GRADING LABORATORY FACILITIES
  - DR-TB is a laboratory diagnosis and therefore quality assured laboratory services are importance.
  - Laboratories doing DST must have internal quality assurance measures in place and participate in external proficiency testing programme.
  - Appropriate infection control measures is important to prevent transmission of DR-TB.

- TB/HIV COLLABORATIVE ACTIVITY
  - All patients with TB and DR-TB will be offered HIV counseling and testing.
  - Those who are co-infected should be started on co-trimoxazole and antiretroviral treatment (ART).
  - All co-infected MDR/XDR-TB/HIV patients should receive antiretroviral therapy (ART) depending of their CD4 count.

- NATIONAL GUIDELINES/SURVEILLANCE DR-TB SYSTEM
  - Development of Clinical Practices Guideline for DR-TB in Malaysia; will be national guidance in management of DR-TB.
  - Development of DR Tuberculosis Information System; will consist of national surveillance for DR-TB cases in Malaysia.

**ISSUE & CHALLENGES**

- Detection of TB and DR-TB cases in Malaysia
  - WHO estimated that about 3% of new TB patients in the world would have MDR TB strains.
  - Surveillance programme for DR-TB: Programmatic Management of Drug-Resistant Tuberculosis (PMDT) was initiated and will be implemented in the country.
  - Nearly 1/3rd (30%) of MDR-TB cases were non Malaysian: Issue with case holding, contact tracing, drug supply and treatment.

- The burden of MDR-TB poses a formidable challenge to the prospect of controlling TB.
- More resources need to be committed in future for TB prevention and control.
- Coverage of DST for TB patients still low and thus a minority of drug-resistant TB patients may not detected and notified.
- Reporting of surveillance and monitoring data DR TB need to improve.
- More budget for research of MDR-TB cases should be allocated.
AND SUPPLY OF 2nd-LINE ANTI-TB DRUG

PHILIPPINES

Provided by
Ms. Lucky Cindy Ricafrente  Administrative Officer 1, Administrative Service, Department of Health, Philippines
Mr. Jeff Carl Estioco  Senior Health Program Officer, National Capital Regional Office, Philippines

National TB programme
• Updated National Strategic Plan (2010-2016) Philippines Plan of Action to Control Tuberculosis
• Total needed budget for 6 years is PhP 29 B (US 420 M) with a gap of PhP 8 B (US 129 M)
• With 5 strategies adopted from the global and regional strategies
  • With existing GF grant (2014-2016), with approved 3 year extension (2017)
  • In the process of finalizing the 2017-2022 National Strategic Plan (NSP)
    – Joint Program Review (March 2016)
    – Drafting of NSP (Q3, 2016)

Strategies for PMDT
• Establishment of PMDT diagnostic facilities: culture centers (24), DST centers (5), and Xpert sites (159); microscopy centers (2,585)
• Scale-up of PMDT treatment facilities: Treatment Centers (20), Satellite TCI (103)
• Integration of PMDT policies and procedures with the basic DOTS at local public health facilities (IDDOTs- 284)
• Public-Private Partnership
• Provision of enablers to MDR-TB patients
• Active casefiding among high risk and vulnerable groups

Ongoing Researches
9-Month Treatment Regimen (400mg M/HRPO/C/E; Z/E/MB/C/E)
  – Piloted in 30 PMDT treatment facilities in July 2015
  – As of June 2016: 154 MDR-TB patients enrolled
  – Implementation review will be done in August 2016

Bedaquiline Operational Research
  – Started May 2016
  – Implemented in the 9-MTR study sites also

Challenges and Lessons Learned on MDR-TB Implementation
Challenges
• Low TSR due to high lost to follow-up and deaths
• Sustainability since fully funded by GF
• Gap in detection and treatment of cases

Lessons learned
• Services should be closer to the patients
• Advocacy is important to expand PMDT services down to the communities
• Diagnostic and treatment services should be harmonized
• All levels of health care should be involved

PMDT Expansion

<table>
<thead>
<tr>
<th>Year</th>
<th>Regional Expansion (37 Regions)</th>
<th>New Tx Facility (TCBTE)</th>
<th>New Xpert Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2007</td>
<td>NCR</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Regions 7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Regions 1, 4, 5, 10, 11</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>2011</td>
<td>CAR, 6, 9, 12, CAVAGA</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>2012</td>
<td>Regions 48</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>2013</td>
<td>Regions 2, 3, 8</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>2014</td>
<td>ARIBAM</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2015</td>
<td>All regions with access to PMDT services</td>
<td>66</td>
<td>53</td>
</tr>
</tbody>
</table>
Multi-drug Resistant Pulmonary Tuberculosis in Singapore, 2002-2015

Introduction
The Singapore Tuberculosis Elimination Programme (STEP) was launched in 1997. The main aim of STEP is to eliminate TB in Singapore by: 1) detecting, diagnosing and treating all infectious TB cases; 2) identifying and treating infected tuberculosis contacts; 3) preventing the emergence of multi-drug-resistant tuberculosis.

Number of MDR-PTB cases (new & previously treated) Local-born (Singapore/Malaysia) versus Foreign-born, 2002-2015

Distribution of MDR-PTB in foreign-born by visa pass status, 2002-2015

Drug susceptibility results of MDR-PTB by country of birth, 2002-2015

Strategies
Early detection of drug-resistant TB and treatment with appropriate regimens is important in reducing transmission in the community. Use of GeneXpert test in patients with high risk of drug resistance aids in early detection of MDR-TB.

Provided by
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1 TB Control Unit, Tan Tock Seng Hospital, Singapore; Ministry of Health, Singapore
MDR-TB Management in Thailand

Background
Of all new global TB cases, 58% occurred in South-East Asia and Western Pacific Regions. Thailand as a country in South-east Asia has a very long history of TB problem. In 2014, Thailand was estimated to have TB prevalence at about 236/100,000 populations. Approximated number of new cases were at about 120,000 cases (171/100,000 populations). For several years, Thailand has been classified as a country in the list of countries having high burden of TB cases. In 2015, Thailand was also classified to be country that has high burden of MDR-TB and TB- HIV co-infection. Therefore, Thailand has been a country in a list of 14th high burden country-lists in TB. The drug-resistance surveillance (DRS) is a crucial source of information monitored the trend of the situation. Latest round of surveillance in 2012 revealed that MDR-TB were 2.03% in new TB cases. This figure increased from 0.93 % and 1.65 % observed in the year 2001 and 2006, respectively.

One of challenges in MDR-TB management was low coverage of case finding. The clear algorithm of diagnosis and treatment was in need. The Thailand NTP started working with experts from various universities to develop the guideline and supported the programmatic management.

Accomplishment
Thailand has had a National committee of DR-TB specialists who developed the national MDR-TB guidelines and has been responsible for approval on drug regimen to treat XDR-, pre-XDR-, and difficult-to-treat MDR-TB patients.

The DR-TB guidelines provide the clear algorithm (shown in the figure) that is successfully implemented. This resulted in early diagnosis and the coverage of MDR-TB diagnosis gradually increases. Previously the National Health Security Office found approximately 400 MDR-TB cases on treatment each year, then in 2015 the number of cases increasing to 700 cases.

The DR-TB expert committee has another task on analyzing the history of patients and proactively searching for the appropriate drugs before the treatment start. Adherence to the treatment is continuously monitored.

Algorithm of MDR-TB diagnosis and treatment, Thailand