8th Regional TB Symposium - Tashkent, Uzbekistan

New Frontiers: Innovation and Access

Challenges and opportunities in case finding
Ambulatory DR TB programme with new TB drugs
Mumbai, India

Stobdan Kalon
MSF
February 28th - March 1st 2019
Site: Mumbai, India
MSF Interventions in Mumbai


MSF Privare Clinic
(2006- Till the date)

M/East Ward & Shatabdi collaboration with National TB Programme
(2016- till the date)

Sewri TB Hospital
(2013- till the date)

KEM Hospital - ART centre
Patients enrolled on new TB drugs in MSF Private Clinic

<table>
<thead>
<tr>
<th>Year wise Inclusion</th>
<th>BDQ</th>
<th>DLM</th>
<th>BDQ+DLM</th>
<th>BDQ+DLM (Strengthen the regimen)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2015</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2016</td>
<td>1</td>
<td>21</td>
<td>11</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>2017</td>
<td>3</td>
<td>15</td>
<td>37</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Q1'2018</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Q2'2018</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>42</td>
<td>56</td>
<td>19</td>
<td>132</td>
</tr>
</tbody>
</table>

Highest number of patients on combination of Bedaquiline and Delamanid
## Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>BDQ</th>
<th>DLM+IMP</th>
<th>BDQ+DLM</th>
<th>Bcero</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total treated</strong></td>
<td></td>
<td>2</td>
<td>19</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td><strong>Cured</strong></td>
<td></td>
<td>2</td>
<td>12</td>
<td>17</td>
<td>38    (60.31%)</td>
</tr>
<tr>
<td><strong>Lost to follow up</strong></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5     (7.93%)</td>
</tr>
<tr>
<td><strong>Failed</strong></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5     (7.93%)</td>
</tr>
<tr>
<td><strong>Mortalities</strong></td>
<td></td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>13    (20.63%)</td>
</tr>
<tr>
<td><strong>On treatment</strong></td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2     (3.17%)</td>
</tr>
</tbody>
</table>
India has the highest TB and MDR-TB globally
Nearly 2.8 million people fell ill with TB in India in 2016
84,000 MDR/rifampicin-resistant TB cases (WHO)
Treatment success rate was 46% and 28% in MDR/RR-TB and XDR-TB cases (WHO)
Mumbai: Most populous metropolitan of India. 62% of the population lives in urban slums.
Mumbai houses 12% of the population of Maharashtra state, but accounts for 22% of notified cases of Tuberculosis (TB). (Mistry et al)
Mumbai has higher levels of MDR-TB, than in other states (24%–30% of new cases and 11%–67% of treated case) (Mistry et al)
DR-TB care in MSF-MoH DR-TB OPD in Public Hospital, Mumbai

Since June 2016, MSF collaborates with RNTCP Mumbai for implementing a DR TB programme in M/East Ward of Mumbai.

- A separate DR-TB OPD providing GeneXpert upfront for all presumptive TB patients and baseline DSTs for individualised treatment regimens
- Follow up during treatment for patients in the community at home and primary health care facilities
- In 2018, patients initiated on treatment:
  - MDR-TB – 461,
  - XDR-TB – 82
  - Short Course regimen- 89
  - Bedaquiline- 87
- All initiated on treatment from day 1 on ambulatory care
Active Cohort

- MDR, 939
- PreXDR, 312
- XDR, 141
- MonoH, 49
- PDR, 7
Case Finding Strategy

1. **GeneXpert** for all presumptive TB patients in routine TB programme

2. **Referral from 16 PHCs/ private care providers**

3. **Active Case Finding (ACF):** were carried out in M-East Ward for one year: 2016 Oct-2017 Oct. stopped as not very high yield and to avoid duplication with local actors implementing ACF

4. **Contact tracing:** with support of Community Health Workers.

Jan 2017-Dec 2018:

1986 contacts were traced by the team, of whom 170 were children (aged 5 years and below)

=> 38 were identified with presumptive TB
Challenges:
- Inspite of upfront Xpert and 13 drugs DST – TAT delays remain a challenge
- DR TB diagnosis for Pediatric DRTB
- High proportion of rural-urban migrants, not easy to keep track of
- Very densely populated and compromised living conditions, high transmission rates?

Opportunities:
- RNTCP acknowledging the challenges of diagnosis and treatment delays approved NGS for phased implementation and generate evidence for routine implementation of NGS aided DRTB diagnosis.
  - Proposal being finalised, to be implemented in 2019 in collaboration with RNTCP and JJ Hospital TB Lab
- Paed DR TB : Xpert on stool samples to be implemented soon
Next Generation Sequencing (NGS)/ Targeted Sequencing

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Superintendent, Cama & Albless Hospital, Mumbai
Grant Medical College & Sir J J Group of Hospitals, Mumbai
Global Perspective - Next Generation Sequencing - Part of the Solution

Source: FIND
<table>
<thead>
<tr>
<th>Targeted Next Gen Sequencing</th>
<th>Whole Genome Sequencing</th>
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</thead>
<tbody>
<tr>
<td><strong>Strengths</strong></td>
<td><strong>Strengths</strong></td>
</tr>
<tr>
<td>• Sequence DNA direct from</td>
<td>• Full genome sequenced</td>
</tr>
<tr>
<td>sputum</td>
<td>• Comprehensive solution</td>
</tr>
<tr>
<td>• Up to 200 gene targets</td>
<td></td>
</tr>
<tr>
<td>• Faster</td>
<td><strong>Weaknesses</strong></td>
</tr>
<tr>
<td>• Simpler</td>
<td>• Slow</td>
</tr>
<tr>
<td>• Less expensive than WGS</td>
<td>• Can’t yet get Mtb WGS</td>
</tr>
<tr>
<td></td>
<td>direct from sputum</td>
</tr>
<tr>
<td></td>
<td>consistently or cost-</td>
</tr>
<tr>
<td></td>
<td>effectively</td>
</tr>
<tr>
<td><strong>Weaknesses</strong></td>
<td>• Expensive</td>
</tr>
<tr>
<td>• Need some pre-knowledge</td>
<td>• Complicated bioinformatics</td>
</tr>
<tr>
<td>of targets</td>
<td></td>
</tr>
<tr>
<td>• Less information than WGS</td>
<td></td>
</tr>
</tbody>
</table>

*Source: FIND*
Global process and timelines for NGS implementation

DNA Extraction (H2H Validation)

DR TB Assays (H2H Validation)

Plot NGS Implementation (4 ref labs in India)

ReSeq WHO Installed

ReSeq WHO Validated

WHO endorsement? (IVD)

Clinical Studies of end-to-end solutions (~4 platforms)

> 12,000 Global Surveillance Strains in ReSeqWHO

Implementation

Source: FIND
Sequencing in India

• 4 reference labs received Illumina platforms and 1 lab has received Pyrrosequencing - to perform WGS for surveillance purposes

• JJ Lab (one of the 4 labs) – plans to collaborate with MSF for implementation of NGS on Illumina platform as a phased implementation for patients from programme site supported by MSF – M East Ward
As low as 100µL clinical sample
- 0.1-100 pg DNA limit of detection (10-100 genomes)
- Recommended for Reference labs.
- Kit runs 48 samples, cost 20-30 €/sample
- Includes software for analysis.

Source: FIND
NGS Deeplex MycTB (Genoscreen kit)

### Direct Sputum Application

**Species ID**

Mycobacterial species (hsp65, rrs, rplC, rrl)

**Drug** | **Gene target**
---|---
Rifampicin | rpoB
Isoniazid | inhA, fabG1, katG, ahpC
Ethionamide | ethA, inhA
Pyrazinamide | pncA
Ethambutol | embB
Streptomycin | rpsL, rrs, gidB
Amikacin | rrs
Kanamycin | rrs, eis
Capreomycin | rrs, tlyA
Fluoroquinolone | gyrA, gyrB
Linezolid | rrl, rplC
Bedaquiline | Rv0678
Clofazimine | Rv0678

**A single 24-plex amplicon mix to identify species, genotype, and drug resistance in 18 gene targets for 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs.**
Current diagnostic algorithm in India

Presumptive TB

Key Vulnerable populations
- Paediatric age group
- People living with HIV
- EPTB
- Smear negative/NA with X-ray suggestive of TB

All Diagnosed TB Patients

CBNAAT

RR TB

For discordance on LPA for RR TB – Repeat CBNAAT at LPA lab

RS TB

SL LPA

FQ abd SLI sensitive

FQ nd/SLI resistance

H Resistance

H sensitive

- Non responders to treatment
- DR TB contacts
- Previously treated TB
- TB-HIV con-infection
- New TB patients

FQ abd SLI sensitive

*Offer molecular testing for H mono/poly resistance to TB patients prioritised by risk as per the available lab capacity
** LC DST (Mfx 2.0, Km, Cm, Lzd) will be simultaneously done. Culture isolates would be preserved for future DST to Cfx & BDQ when available & WHO endorsed
$ States to advance in phased manner as per PMDT Scale up plan for universal DST based on Lab capacity and policy on use of diagnostics
New diagnostic algorithm with NGS

### Presumptive TB/DR-TB
- **Gene Xpert**
- **MTB RIF Resistance**

#### LPA – Second Line
- **Sensitive**
- **Resistance**
  - **Culture DST**
    - 13 drugs (Rif, INH, PZA, Etb, Am, Km, Cm, FQ, Eth, Lzd, Cfx, Bdq)

#### MTB load
- **Low MTB load**
- **Moderate/High MTB Load**
  - **Culture**
  - **Targeted NGS**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mutation</th>
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<tbody>
<tr>
<td>Pyrazinamide</td>
<td>pncA</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>embB</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>rpoB</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>ahpC, fabG1, katG, inhA</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>eis</td>
</tr>
<tr>
<td>Amikacin</td>
<td>rss</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>tlyA</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>gyrA, gyrB</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>gidB, rpsl</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>ethA, inhA, fabG1</td>
</tr>
<tr>
<td>Bedaquiline, Clofazamine</td>
<td>Rv0678, atoE</td>
</tr>
<tr>
<td>Linezolid</td>
<td>rrl, rplc</td>
</tr>
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