Information Note

WHO call for patient data on the treatment of multidrug- and rifampicin resistant tuberculosis

In order to ensure that the upcoming comprehensive revision of WHO policies on treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) is based on the most recent evidence and scientific analysis, the WHO Global TB Programme is issuing a call for individual patient data on MDR-TB treatment.

Please submit your notice of intent by 01 March 2018.

1. Minimum requirements for individual patient datasets (IPD)

Data that have already been reported to the existing individual patient dataset coordinated by McGill University should not be reported again.

Data from studies that have not yet been reported in peer-reviewed publications but otherwise fulfilling the below criteria will be considered for inclusion:

- Individual datasets of at least 25 patients;
- Patients with rifampicin-resistant TB confirmed using a WHO-recommended phenotypic or molecular test (including MDR-TB, MDR-TB with additional resistance to either a fluoroquinolone or injectable drug, or XDR-TB);
- Cases without confirmed rifampicin-resistant TB are not eligible. Baseline drug susceptibility results for fluoroquinolones, second-line injectable agents and for pyrazinamide would be highly desirable;
- Regimens may be a longer regimen lasting 18 months or more or the standardised shorter regimen.¹
- Patients treated with MDR-TB regimens, with or without newer medicines – bedaquiline and delamanid – are eligible for inclusion;
- Regimens composed solely of first line agents (rifampicin, isoniazid, pyrazinamide, ethambutol, as well as streptomycin) or those with experimental drugs only will not be considered.

¹ The shorter regimen refers to standardized 9-12 month regimens with a typical composition of 4-6KmMfxPtoCfzZHhE/ 5-8MfxCfz2E.
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- Patients started on MDR-TB regimens in 2010 or later and who have completed treatment and in whom an end-of-treatment outcome was assigned. Outcomes need to be as per WHO definitions\(^2\) (outcomes as per 2005 definitions for earlier cohorts are also accepted).\(^3\)
- For the individual patient data (IPD) analyses, records of patients who are still on treatment and whose outcome was not evaluated, CANNOT BE USED;
- Data should be organised in anonymised, individual records (i.e. one row per treatment episode) for the minimum set of variables, preferably coded in a standard way (see Annex 1). Datasets for which data for key variables is missing in 50% or more of records cannot be used.
- Background information on inclusion/exclusion criteria used for the shorter MDR-TB regimen will be important. Although not obligatory, other information which may be helpful includes: i) number of patients with confirmed MDR/RR-TB that were evaluated for treatment; ii) number that were considered ineligible; and iii) number of patients eligible who did or did not start treatment in the site and at the time of the study data provided.

If data relevant for the guidelines update are only available in aggregated format, please note also the following:

2. Minimum requirements for aggregated datasets

Data that have already been provided to WHO for policy development should not be reported again.

Data from studies that have not yet been reported in peer-reviewed publications but otherwise fulfilling the below criteria will be considered for inclusion:

- Individual datasets of at least 25 patients;
- Patients with rifampicin-resistant TB confirmed using a WHO-recommended phenotypic or molecular test (including MDR-TB, MDR-TB with additional resistance to either a fluoroquinolone or injectable drug, or XDR-TB);
- Cases without confirmed rifampicin-resistant TB are not eligible. A summary of baseline drug susceptibility results for fluoroquinolones, second-line injectable agents and for pyrazinamide would be highly desirable;
- Regimens may be a longer regimen lasting 18 months or more or the standardised shorter regimen.\(^1\) Patients treated with MDR-TB regimens, with or without newer medicines – bedaquiline and delamanid – are eligible for inclusion;
- Regimens composed solely of first line agents (rifampicin, isoniazid, pyrazinamide, ethambutol, as well as streptomycin) or those with experimental drugs only will not be considered.

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- Patients started on MDR-TB regimens in 2010 or later and who have completed treatment, with an end-of-treatment outcome assigned. Outcomes need to be as per WHO definitions\(^2\) (outcomes as per 2005 definitions for earlier cohorts are also accepted).\(^3\)
- Patients started on MDR-TB regimens with bedaquiline or delamanid in 2010 or later who have:
  - Completed treatment with an end-of-treatment outcome assigned. Outcomes need to be as per WHO definitions\(^2\) (outcomes as per 2005 definitions for earlier cohorts are also accepted);\(^3\) or
  - Completed at least six months of treatment with either or both drugs and for whom culture conversion data are available (Culture conversion need to be as per WHO definitions.\(^2\)
- Background information on inclusion/exclusion criteria used for the shorter MDR-TB regimen will be important. Other information may be helpful - although not obligatory - on the number of patients with confirmed MDR/RR-TB that were evaluated for treatment, number that were considered ineligible, and the number eligible that did or did not start treatment in the site and at the time of the study data provided.
- At the time of submission (by 15 April) the data should be organised in summary tables to address priority questions about the effectiveness and safety of regimens (e.g. Ahuja et al.;\(^4\) Bastos et al.;\(^5\)) Further detail about the data aggregations will be provided to those who express an intent to report.

Correspondence

Please send all electronic correspondence, including enquiries to: **LDR.POLICIES@WHO.INT**


Annex 1: List of minimum data elements for individual patient datasets (IPD)
(Highlighted under green area= essential data. Not highlighted = of interest, but not essential)

i) Baseline data at treatment initiation

<table>
<thead>
<tr>
<th>Domain</th>
<th>Data element</th>
<th>Answer options and other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Geographic area</td>
<td>Country, region, district, city or ward in which the patient is started on treatment; use unique codes for place names.</td>
</tr>
<tr>
<td></td>
<td>Facility name</td>
<td>Unique code of reference of the health centre</td>
</tr>
<tr>
<td></td>
<td>Facility type</td>
<td>Public/private; specialized or general; primary, secondary, tertiary</td>
</tr>
<tr>
<td>Identification and demographic</td>
<td>Unique registration number</td>
<td>The code for the specific MDR-TB treatment episode being registered. The same patient may have &gt;1 code assigned over time for different treatment episodes. Important for data linkages between different data sources, e.g. recovery of DST results from laboratory databases</td>
</tr>
<tr>
<td></td>
<td>Date of birth</td>
<td>If full date (i.e. dd/mm/yyyy) is not known provide the year of birth or age in completed months or years</td>
</tr>
<tr>
<td></td>
<td>Sex at birth</td>
<td>Male, female</td>
</tr>
<tr>
<td></td>
<td>Origin</td>
<td>By country of birth or, if not available, citizenship. Race or ethnicity is used in some countries.</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>Employed, retired, student, unemployed</td>
</tr>
<tr>
<td></td>
<td>Imprisonment</td>
<td>If yes, to identify if current/previous and duration of imprisonment</td>
</tr>
<tr>
<td></td>
<td>Current homelessness</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Baseline clinical assessment</td>
<td>Date of diagnosis</td>
<td>The date (dd/mm/yyyy) when the patient was first diagnosed with the current episode of RR-/MDR-TB (based on clinical manifestations, or radiology plus bacteriology and DST</td>
</tr>
<tr>
<td></td>
<td>Site of disease</td>
<td>Pulmonary, extrapulmonary (exact site)</td>
</tr>
<tr>
<td></td>
<td>Previous TB</td>
<td>Yes, no, unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Yes, date of diagnosis of each episode, number of treatments, drug regimen composition and duration, and DST pattern Assign the standard WHO patient registration group²</td>
</tr>
<tr>
<td></td>
<td>Previous treatment with first line TB medicines</td>
<td>Indicate medicines and durations in standard notation if known (e.g.2RHZE/4RH)</td>
</tr>
<tr>
<td></td>
<td>Previous Treatment with second Line TB medicines</td>
<td>Indicate medicines and durations if known (e.g.6KmLfxEtoCsZ/18LfxEtoCsZ)</td>
</tr>
</tbody>
</table>
### Domain Data element Answer options and other remarks

#### Baseline clinical assessment (cont)

<table>
<thead>
<tr>
<th>Previous TB treatment outcome</th>
<th>If previously treated the outcome of the latest episode (cured, completed, failed, lost to follow up, unknown)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other medical history</td>
<td>Including diabetes mellitus, malnutrition, renal insufficiency, hepatic insufficiency/ cirrhosis, cardiac dysrhythmias, chronic obstructive pulmonary disease, convulsions, psychiatric conditions, drug use, alcohol use, smoking</td>
</tr>
<tr>
<td>HIV</td>
<td>Known – positive or negative or unknown</td>
</tr>
<tr>
<td>ARV</td>
<td>If HIV positive</td>
</tr>
<tr>
<td>History of allergy or adverse drug reactions</td>
<td>Indicate the medicine and classify the type of reaction according to MedDRA and parameters of severity and seriousness(^6)</td>
</tr>
<tr>
<td>New events</td>
<td>Include all new events or changes in pre-existing conditions that began in the 30 days prior to the baseline interview. Include date of onset, and if applicable, date resolved (dd/mm/yyyy), outcome, severity and seriousness.</td>
</tr>
<tr>
<td>Currently pregnant</td>
<td>Yes, no, uncertain (date of last menstruation may be recorded)</td>
</tr>
<tr>
<td>Breastfeeding infant</td>
<td>Yes, no</td>
</tr>
<tr>
<td>Patient symptoms</td>
<td>Fever, weight loss, cough, haemoptysis, dyspnoea, others (specify)</td>
</tr>
<tr>
<td>Patient height</td>
<td>In centimetres</td>
</tr>
<tr>
<td>Patient body weight</td>
<td>In kilogrammes and expressed as body mass index</td>
</tr>
<tr>
<td>Abnormalities noted at examination</td>
<td>By functional system: head, ears, nose, and throat; vision; thyroid; lymphatic system nodes; cardiac; pulmonary; abdominal (including pancreas); skin; musculoskeletal; urogenital; neurological; extremities; other (specify)</td>
</tr>
<tr>
<td>Functional status</td>
<td>Not ambulatory; ambulatory; able to work</td>
</tr>
</tbody>
</table>

#### Baseline bacteriology and drug susceptibility testing (DST) results

| Date sample collected                  | Standard notation (dd/mm/yyyy) for the date when the specimen confirming MDR/RR-TB was collected (each test) |
| Date result issued                     | Standard notation (dd/mm/yyyy) for the date when the result of the test confirming MDR/RR-TB was reported (each test) |
| Microscopy                             | Use standard notation [see page 11 of reference at footnote 2]                                              |
| Xpert MTB/RIF test                     | Use standard notation [see page 12 of reference at footnote 2]                                              |

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\(^6\) MedDRA. Available from: http://www.meddra.org/
### Domain: Baseline bacteriology and drug susceptibility testing (DST) results (cont)

<table>
<thead>
<tr>
<th>Data element</th>
<th>Answer options and other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPA or sequencing</td>
<td>Report mutation(s) tested for and detected in free text</td>
</tr>
<tr>
<td>Culture</td>
<td>Use standard notation [see page 12 of reference at footnote 2]</td>
</tr>
<tr>
<td>Phenotypic DST</td>
<td>To each first line and second line TB medicines tested. Use standard notation [see page 12 of reference at footnote 2] DST method used (solid/liquid media)</td>
</tr>
</tbody>
</table>

### Results of other investigations at baseline

<table>
<thead>
<tr>
<th>Data element</th>
<th>Answer options and other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date sample collected</td>
<td>Standard notation (dd/mm/yyyy) for each test</td>
</tr>
<tr>
<td>HIV test</td>
<td>Positive, negative, indeterminate</td>
</tr>
<tr>
<td>CD4 count</td>
<td>In cells/mm$^3$ (=cells/µL or cells/microliter)</td>
</tr>
<tr>
<td>Glucose</td>
<td>In mmol/L or as mg/dL</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Levels of potassium, magnesium, calcium</td>
</tr>
<tr>
<td>Renal function</td>
<td>Urea, creatinine, creatinine clearance</td>
</tr>
<tr>
<td>Liver function</td>
<td>ALT (SGPT), AST (SGOT), bilirubin, albumin</td>
</tr>
<tr>
<td>Blood indices</td>
<td>Haemoglobin, haematocrit, leukocytes, platelets</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>Rate; rhythm; trace; QTc interval</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Cavitary; extent of parenchymal disease; uni- or bilateral (useful in grading extent and severity of disease)</td>
</tr>
<tr>
<td>Other</td>
<td>Specify (e.g. thyroid stimulating hormone)</td>
</tr>
</tbody>
</table>

### Treatment given

<table>
<thead>
<tr>
<th>Data element</th>
<th>Answer options and other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of registration for second-line treatment</td>
<td>Standard notation (dd/mm/yyyy) for date when the record was entered in the Second-line TB treatment register</td>
</tr>
<tr>
<td>Date second-line treatment started</td>
<td>Standard notation (dd/mm/yyyy) for each TB medicine taken at any time in the previous 30 days</td>
</tr>
<tr>
<td>Date second-line treatment stopped</td>
<td>Standard notation (dd/mm/yyyy) for each TB medicine taken at any time in the previous 30 days</td>
</tr>
<tr>
<td>TB medicine</td>
<td>For each TB medicine give: name, dosage, frequency, route If date started and stopped is not available give duration in days or months</td>
</tr>
<tr>
<td>Shorter regimen use</td>
<td>Yes / No. Refers to standardized shorter regimens lasting 9-12 months and based on the 2016 recommended regimen $^\text{Error! Bookmark not defined.}$</td>
</tr>
<tr>
<td>For shorter regimens: Switch from shorter regimen to a longer individualized regimen</td>
<td>Provide: indication for change from shorter to longer regimen (e.g. no conversion / treatment failure / acquired drug resistance / clinical deterioration not meeting criteria for bacteriologic failure / adverse reactions); date of change.</td>
</tr>
<tr>
<td>Duration – Initial phase and total</td>
<td>Specify planned and actual duration of each phase of treatment</td>
</tr>
</tbody>
</table>
ii) Data collected at MDR-TB patient review

<table>
<thead>
<tr>
<th>Domain</th>
<th>Data element</th>
<th>Answer options and other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Date of final outcome</td>
<td>Standard notation (dd/mm/yyyy) for date first outcome met</td>
</tr>
<tr>
<td></td>
<td>Adverse events – during treatment</td>
<td>Indicate if any AE occurred during treatment – that caused any TB medicine to be permanently stopped – identify medicine stopped and type of AE</td>
</tr>
<tr>
<td></td>
<td>Final treatment outcome</td>
<td>Cured, treatment completed, treatment failed, died, lost to follow up, not evaluated (as defined in page 7 of reference at footnote 2; for older datasets outcome coding as per the 2005 recommendations is also accepted. ICD code for cause of death is recommended.</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>Indicate if relapse is monitored, and if so for how long, and if occurred. Provide date of specimen collection for each post-treatment culture performed to assess for relapse (provide date irrespective of result). Indicate if reinfection excluded (by genotyping)</td>
</tr>
<tr>
<td></td>
<td>Culture conversion</td>
<td>Indicate if this was measured, and if so the time of culture conversion (in months) and if conversion occurred by 6 months (if shorter regimen is used, then also report whether culture conversion occurred by 2 months)</td>
</tr>
<tr>
<td>Resource use</td>
<td>Hospitalization</td>
<td>Number of days hospitalized</td>
</tr>
<tr>
<td></td>
<td>Surgery – (lung resection only)</td>
<td>If surgery – type of surgery, and what removed. Dates of surgery /s (variable highly desirable but not essential)</td>
</tr>
</tbody>
</table>