“Totally Drug-Resistant TB”: a WHO consultation on the diagnostic definition and treatment options

Dates: 21-22 March 2012
WHO/HQ Geneva, Switzerland

Background
Within a year of the first reports of extensively drug-resistant TB (XDR-TB) in 2006, two patients with strains having resistance to all first and second-line anti-TB drugs which were tested were reported from Italy [Migliori et al, 2007]. In 2009, 15 TB patients in Iran were reported to be resistant to all anti-TB drugs tested [Velayati et al, 2009]. New terms like “extremely drug resistant” (“XXDR-TB”), “super XDR-TB” and “totally drug-resistant TB” (“TDR-TB”) were used to define such resistance patterns. In December 2011, clinicians in Mumbai, India described four patients with “TDR-TB” [Udwadia et al, 2012]. A few weeks later, the Times of India reported another eight cases in Mumbai.

The World Health Organization (WHO) decided to convene a Technical Consultation to discuss the current information on XDR-TB cases with additional second-line drug resistance, to study the feasibility and implications of a definition to cover more advanced patterns of resistance than XDR-TB, and to provide specific guidance on treatment options for patients with XDR-TB with or without additional second-line drug resistance.

This report summarises the presentations made at the meeting, the discussions that followed, the main conclusions drawn and action points which were agreed upon (see Annexes for the list of participants and observers and the meeting agenda).

Wednesday, 21 March 2012
The participants were welcomed by Dr Paul Nunn, Coordinator of the MDR-TB Unit at the Stop TB Department of WHO.

All participating experts declared their interests prior to the consultation. Most reported none relevant to the subject of the meeting. Three participants declared potential conflict. Dr Charles Daley declared that he is Consulting/Chair of the Monitoring Committee for clinical trials of Otsuka Pharmaceutical Co Ltd. Dr Francis Varaine declared he is coordinator of the TB working group of Médecins Sans Frontières. Dr Michael Rich stated that he is employed by Partners in Health and undertakes consultation and technical advisory work to countries for WHO. These declarations were not considered to conflict with the full participation of these experts on this consultation.

Dr Zarir Udwadia (Hinduja National Hospital and Medical Research Centre, Mumbai, India) presented the recent medical history of the 12 patients who became the focus of the media attention on the “TDR” event at the beginning of 2012. He described how their diagnosis was delayed or missed, and how they were consequently under-treated, and he extrapolated this experience to the majority of MDR-TB patients managed under low-resource conditions. Both public and private sectors played a role in the creation of very advanced drug-resistance in these patients. Events suggest that laboratory drug-susceptibility testing (DST) capacity and access to rapid diagnostics need to improve, DST be offered earlier to patients, funds secured to treat MDR within the national TB programme, a more effective implementation of public-private mix (PPM), and the enforcement of regulations to
ensure that existing drugs are prescribed responsibly. He concluded by asking how XDR-TB patients who have failed treatment should be managed.

As the official representative of the Indian government could not attend the meeting, Dr Paul Nunn summarized the actions taken by the Indian authorities in response to the event, as well as WHO’s reaction to it. In the week after the media reports in early January, the Stop TB Department refreshed the information on drug-resistant TB on its website, including a “frequently asked questions” piece on XDR-TB. It also called for the present Technical Consultation. In India, WHO provided support to the Central TB Division (CTD). The CTD sent a team to Mumbai and developed a response plan. Biological samples were taken for further laboratory testing, contacts were traced, and free diagnosis and treatment offered. Drugs for XDR-TB patients were made available. Notification of all cases in the public and private laboratories was mandated, training on infection control was done in all hospitals and the availability of DST expanded in some of the city’s major health facilities. A TB officer was put in place in Mumbai and 24 district officers appointed for all municipal wards. The budget for 2012-2013 was increased by more than 6 times. At the national level, a letter was sent to each State from the Union Health Secretary, and the aim is to have all states in India providing full PMDT coverage by the end of 2012 and some 15,000 patients enrolled by then. A national consultation will be held in April to discuss notification, regulation of sales of anti-TB drugs and of prescription, PPM and central procurement of XDR-TB drugs.

Dr Dennis Falzon (Stop TB Dept, WHO, Switzerland) presented the reporting and treatment outcomes of XDR-TB. The detection of XDR-TB remains low as a result of under-detection of MDR-TB and low levels of testing with 2nd line DST. Notified cases of MDR-TB remain very low in comparison to the estimated global burden. Coverage of 2nd line DST in 2010 was only 16% among MDR-TB cases globally (as against the Global Plan target of 100% for 2015). This is a result of low laboratory capacity and inadequate recovery of results (loss of data). WHO has collected aggregated outcomes for >600 XDR-TB cases started on treatment in 2008 in 20 countries: overall outcomes were poor with 24% success and 36% deaths. A recent meta-analysis of treatment outcomes of 560 XDR-TB patients in 13 observational studies (Estonia, Germany, Peru, Rep of Korea, Russian Fed, US; 1984-2008) reported better outcomes: 44% success (95%CLs 33%–55%) and 21% deaths (95%CLs 14%–27%) [Jacobson et al, 2010]. Published work on XDR-TB patient outcomes in the last few years have highlighted the feasibility of outpatient management of XDR-TB patients in a low-resource setting, the beneficial effect of later-generation fluoroquinolones and the importance of HAART in reducing death in XDR-TB patients infected with HIV [Mitnick C et al, 2008; Dheda K et al, 2010].

Dr Matteo Zignol (Stop TB Dept, WHO, Switzerland) presented the global epidemiology of XDR-TB. Seventy-eight countries had reported at least one XDR-TB case by March 2012. Surveillance data on XDR-TB are incomplete though there has been some commendable progress, with fifty-seven countries and three territories reporting data from representative surveillance or surveys which gave an overall prevalence of XDR among MDR-TB cases of 9.4% (95%CI 7.4-11.6). However, few of the reporting sites had more than 10 XDR-TB cases detected. Surveillance completeness should be improved and molecular testing expanded.

Dr Charles Daley (Chairman, gGLC) confirmed that the gGLC committee supported the objectives of the current consultation. The committee members recommended that any additional definition for severe patterns of drug-resistant TB should consider clinical outcomes, its use in surveillance, and laboratory capacity to diagnose it. The gGLC recommended 2 criteria for any change of definition to WHO: that patients within any newly defined group would have significantly different outcomes compared to existing definitions and that the drug susceptibility tests to create a new definition be reliable.
Dr Karin Weyer (Stop TB Dept, WHO, Switzerland) fed back from the 2nd line DST Expert Group Meeting, 19-21 March 2012. The outcome of that meeting will be published in a separate document, but the main results were that the meeting recommended that updates should be made to the methods and concentrations for DST of fluoroquinolones, and to the recommendations on the use of DST to guide MDR-TB treatment in TB patients at high risk of MDR detected with a rapid test as rifampicin-resistant. Such patients should be started with an MDR-TB regimen plus isoniazid until the results of isoniazid DST are available. The DST for drugs used to define MDR and XDR-TB are considered accurate and reproducible. All injectables and all fluoroquinolones should routinely be tested in specimens from confirmed MDR-TB patients to screen for XDR-TB. DST for all other Group 4 and 5 drugs remains problematic for technical reasons, such as drug instability in solution, drug binding to proteins in the culture media, and low pH requirements. It will be important that for drugs under development, the knowledge on DST is transferred rapidly from the research sector to diagnostic laboratories. Both Janssen Infectious Diseases BVBA (previously Tibotec) and Otsuka Pharmaceutical Co Ltd committed to develop an accurate DST in preparation for their requests for approval with FDA or EMA.

Dr Peter Cegielski (CDC, USA) presented treatment outcome data for XDR-TB patients included in the DOTS-Plus Pilot Projects Case-Based Study and the Preserving Effective TB Treatment Study (PETTS). The former is a retrospective study of all MDR-TB cases starting treatment in 2000-2004 within the first five GLC-approved DOTS-Plus projects - Estonia, Latvia, Peru (Lima PIH project), Philippines, and Russian Fed (Tomsk Oblast PIH project). The PETTS is a prospective cohort study in 5 GLC-approved countries (the same countries listed above; 11 sites) and 4 non-GLC projects (Rep. of Korea; South Africa; Taiwan, China; Thailand; 15 sites). Patients were enrolled at the start of their MDR-TB treatment between 2005 and 2008. In the DOTS+ pilot project data, the outcomes for the 57 XDR-TB patients were substantially worse than those for non-XDR MDR-TB cases: success was 54% vs. 68%, failures 23% vs. 6% and deaths 17.5% vs. 11.5%. Success appeared to diminish progressively - while failure and death increased - as the number of drugs to which MDR-TB patients were resistant increased from <5 to 9. A similar trend in success & failure was observed among MDR-TB patients in the PETTS. The 77 XDR-TB patients in the PETTS had much worse outcomes when compared to non-XDR MDR-TB cases (27% success, 26% failure, 31% death - 16% defaulted). A preliminary analysis of these XDR-TB patients showed no statistically significant difference in outcomes between those who were resistant to all 3 injectables and those with resistance to only one or two. A more thorough analysis of these patients is expected to be carried out in the coming months, including an examination of the effect of resistance to later-generation fluoroquinolones.

Dr Richard Menzies (McGill University, Canada) presented an analysis based on the Individual Patient Data ("IPD") of MDR-TB cases collected for purposes of the update of the PMDT guidelines in 2011. Of the 8955 MDR-TB cases from 32 sites, 6724 cases had DST results for at least one fluoroquinolone and one 2nd line injectable. 405 XDR-TB cases were identified. In order to inform the discussion on associations between outcomes and drug-resistance patterns, three XDR-TB patient groupings were used based on their DST results. These were cases (i) resistant to all 2nd line injectables (N=82), (ii) resistant to all 2nd line injectables plus any other drug tested (N=32) and (iii) resistant to all drugs tested which included at least one Group 4 drug (N=48). Deaths increased from 18% to 27% to 30% in groups (i), (ii) and (iii) respectively and were higher than in XDR-TB cases without additional resistance (14%). In cases with XDR-TB and no additional resistance, cure was higher (44%) than among those with additional resistance (24-34%) while failure was lower (20% vs. 31-33%). However, after adjustment, no significant differences were observed in the outcomes of these different XDR-TB groups.

Dr Patricia Bartholomay Oliviera (NTP Brazil) presented the situation of MDR-TB and XDR-TB care in Brazil. While DST for first-line drugs is available in all state laboratories in the country, only two test
for 2nd line drugs and only fluoroquinolones and injectables are tested routinely. A total of 105 XDR-TB patients have been detected and placed on treatment since 1994. The results for the 70 who finished treatment (enrolled between 1994 and 2009) revealed a very unfavourable picture: 53% died, 31% failed treatment, 13% were cured and 3% defaulted. Among the XDR-TB patients, it was reported that 16 had additional resistance to ethionamide, 2 to terizidone and 2 to clofazimine.

In the discussions that followed, the participants acknowledged that patients infected with TB strains resistant to a wide range of drugs, beyond the definition of XDR-TB alone, exist and reports of such cases are increasing. Their emergence is a wake-up call for Ministries of Health. The group urged the global TB community to make greater efforts to prevent drug resistance and to scale up the provision of appropriate care to avoid a scenario where TB becomes progressively incurable. Prevention through strong basic TB care and proper management of drug-resistant TB still remain of the utmost importance. The group considered if "totally drug resistant" TB is an appropriate definition and would a revised definition require clinical criteria attached to it. The advocacy potential of a new definition for strains with advanced patterns of drug resistance was discussed. It was mentioned that the term ‘totally’ may create unnecessary fear among health care providers and general community and stigmatization of patients. Such terminology may also have an impact on the biosafety level for specimen transport, and regulatory issues for new drug development and approval. It may also lessen the impact of other important messages about drug-susceptible TB, and distort the public concept of what the experience of the average TB patient in the world really is.

Thursday, 22 March 2012
Dr Charles Daley summarized the conclusions of the first day of the meeting. The group acknowledged that there are forms of drug-resistant tuberculosis with a more advanced pattern than extensively-drug resistant disease which pose a formidable challenge to the clinician. Reports of such cases are increasing. The term “total” drug-resistance is an inadequate term to describe such an entity given that (i) the DST for drugs other than those which define XDR are problematic to interpret, (ii) the meaning of "total" may differ between settings given the differences in capacity for laboratory testing and availability of antibiotics for patient treatment and (iii) new drugs are expected to enter into clinical practice in future and they may still be effective against these XDR strains. It is also important to keep in perspective the impact that a label such as “total” drug resistance will have on the individual patient affected by it as well as the carers of that patient. It is likely that health care workers called to treat such patients may be more concerned for their own safety than when they deal with other TB patients given the lowered chances for a cure should they get infected with such a strain and eventually fall ill with TB. This may happen regardless if the transmissibility potential between drug-resistant and susceptible strains is any different. The overall conclusion is that a new definition for a drug resistance pattern beyond the one that currently exists for XDR-TB is neither feasible nor desirable at this stage.

Dr Dennis Falzon addressed the ways in which the data from observational studies on MDR-TB could inform policies better in future. The formulation of recommendations according to GRADE requires that the quality of evidence is classified as high, moderate, low or very low. High quality evidence can only be derived from randomized controlled trials, and there are none that have investigated the treatment for MDR-TB, although results of one (TBSTREAM) may be available around 2016. Recommendations are graded as either “conditional” or “strong”, with implications on how they are applied. In assessing the studies in preparation for the 2011 update of the PMDT guidelines, the quality of evidence often slipped from low to very low because of limitations in the study design, inconsistency (heterogeneity), indirectness, imprecision (low number of events) and other bias. Better design of observational studies could limit bias, improve the reliability of data (eg. deaths, DST), increase the completeness of reporting (eg. bacteriological endpoints, key dates to calculate diagnostic and treatment delays), collect additional data of use for policy making (eg. cost, reason
for change in regimen, type of patient support) and standardise further the data (eg. proxies of disease severity).

In the discussion following the presentation, it was mentioned that the lack of sufficient data on DST to the later-generation fluoroquinolones (including in the IPD study) should prompt WHO to look for more exploitable data in other patient series. The importance of more complete testing and of recording of data on results of DST to all types of fluoroquinolones and injectable agents was stressed. An MIC-based approach for TB drugs has limited application in guiding treatment. With respect to what observational studies of treatment for drug-resistant TB should do better to ensure the best possible evidence, the point was raised whether it will be expected that all programmes adhere to the recommended standards for data and parameters or whether these recommendations should only be limited to certain “Centres of Excellence”. In MDR-TB projects using electronic medical records, such as Karachi, Tajikistan and Nepal, this was feasible and these data are being collected routinely. Some centres may be better placed to provide certain data (eg. on cost, special investigations) than others in a more research-oriented framework. Programmes will need guidance to pilot and make the necessary changes to their data recording systems to adhere to the revised requirements and they will need funding to bring their systems up to date.

Dr Charles Daley addressed current guidelines on treatment of XDR-TB cases. Since the 2011 update of the PMDT guidelines did not address recommendations for XDR-TB treatment, the only WHO guidance on how a treatment regimen is to be composed for such patients is the one contained in the 2008 Emergency Update (as summarised in pages 69-70) [WHO 2008; WHO 2011]. These recommendations were not developed using GRADE.

In discussion, it was suggested that the additional analysis that Dr Dick Menzies performed on XDR-TB patients who had been excluded from the IPD study could be used by WHO to derive recommendations using the GRADE approach. The work was already written up as a manuscript. However very few patients in this dataset were treated with later-generation fluoroquinolones and the effectiveness of Group 5 drugs remains uncertain. In addition, there are no agreed procedures for DST on Group 5 drugs. In conclusion, no substantial knowledge-base existed to derive a separate evidence-based recommendation for XDR-TB beyond the advice in the 2008 guidelines.

Dr Kaspars Lunte (Global Drug Facility/Stop TB Partnership (GDF), Geneva, Switzerland) provided information on the availability and cost of Group 5 drugs. Two Group 5 drugs were currently available through GDF – amoxicillin/clavulanate and clarithromycin. With respect to the others:

- The only quality-assured (QA) source of linezolid is still patented by Pfizer (up to 2014 in US and 2016 in Europe). Generic forms are not sufficiently quality-assured. A reply is awaited from Pfizer-US regarding access and prices. Prices from different distributors currently range from USD80-97/tablet.

- Clofazimine is mainly produced by Novartis which donates the active ingredient for use in treating leprosy. No other QA product sources exists. A letter has been sent to CEO Novartis by WHO/STP to make the drug available for MDR-TB patients. It is available for GDF procurement needs through the Victoria Pharmacy in Zurich. One producer in Belgium is preparing a dossier for the Expert Review Panel.

- Thioacetazone: Bayer has stopped production. A reply from Pfizer-India is awaited. The other known producer in the world is Renata in Bangladesh.

- Imipenem/Cilastatin has many producers (Merck, Fresenius, Daiichi Sankyo, etc) and GDF is awaiting replies from Ranbaxy, Lupin, and Cipla.

The discussion that followed was centred on trying to identify priority Group 5 drugs which were not yet available to GDF. It was remarked that the choice of drugs to use in low-resource settings depended very much on what was available. It was felt that clofazimine and linezolid were the most important. The standard adult doses are 100mg and 600mg daily respectively. The Global Alliance for TB Drug Development (Dr Mendel) supported the interest in clofazimine given the reportedly encouraging results in the mouse model. It was felt that appeals to Novartis Foundation to make clofazimine available could be stepped up.

Dr Christian Lienhardt (Stop TB Dept, WHO, Switzerland) gave a presentation on the compassionate use (CU) of potentially lifesaving treatment with investigational new drugs (INDs) to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. Provisions were needed for such patients to get controlled access to medications that have demonstrated efficacy but which are still in the pre-approval period, i.e. the regulatory process is not complete. This is particularly apposite for TB patients as their drug resistance progressively broadens and treatment options shrink. “Expanded access” (EA) was also discussed, whereby manufacturers make INDs available to treat patients having a serious condition and who cannot participate in a controlled clinical trial. This would be accompanied with intensive data collection on safety and resistance, as well as long-term outcomes (“salvage studies”). For compassionate use to be possible, the appropriate regulatory framework must be in place given that the use of INDs is usually only allowed for a clinical trial. Some National Regulatory Authorities have developed mechanisms to facilitate access to new drugs before market approval based on a set of principles: that the patient provides consent after being informed of risks and benefits; an Ethical Review Board approval is obtained; a health practitioner initiates the request and provides regular reports on outcomes; patient monitoring and pharmacovigilance are adequate; and the manufacturer provides the product and relevant information on the drug to the Regulatory Authority. The drug is never administered as a mono-therapy but needs to be given with others of proven efficacy to prevent emergence of resistance to the experimental drug. It should be free of charge to the patient. CU is not a substitute to properly conducted trials. The implementation of CU and EA face a number of challenges. Firstly, the diversity and complexity of regulatory requirements. There is therefore a need to expand and harmonize these regulations. Secondly, the emergence of resistance to the new drug is a very real risk given that the patient may harbour resistance to most of the other accompanying drugs. It is therefore important to ensure that at least 2 effective drugs accompany the IND in the regimen. WHO can facilitate access to new drugs by issuing appropriate treatment recommendations. Thirdly, compatibility of INDs with other drugs likely to be co-administered to patients (including antiretroviral drugs) may not be fully understood. In order to ensure good monitoring, access should probably be restricted to specialized centres that can ensure a high standard of care and treatment adherence.

Dr Carl Mendel (Global Alliance for TB Drug Development, US) presented a proposal for collaborative work on a “salvage study” for compassionate use employing a number of new chemical entities (NCEs) without pre-existing resistance (TMC207, OPC67683, PA824, PNU100480, SQ109 and possibly Clofazimine). The proposal will be to start a global study of combinations of NCEs in patients with XDR-TB +/- additional resistance at selected centres. The administration of drugs will be similar to that for compassionate use, but data collection will be more intensive and follow up will be long-term. Incremental cost to programmes will be marginal compared with traditional compassionate use. Potential collaborators in this study will be Janssen Infectious Diseases BVBA (previously Tibotec), Otsuka Pharmaceutical Co Ltd., The Global Alliance, Pfizer, and Sequella. Combinations of promising NCEs would be made available pre-approval for those patients with no alternative options. This would be done under supervised conditions, in selected sites, so that long-term outcomes can be observed closely and outcomes can be rapidly incorporated. This would provide detailed information on novel combination use before these agents reach market. Once
collaborators have committed, a mouse relapse model of combination(s) will be built to predict the duration of treatment. The advantages will be that it will encourage the development of “centres of excellence” in low-resource settings; a wider use of DST; pharmaceutical companies work together; and provide a bridge between implementation and R&D. No clear plans were in place to fund the collaborative study. The question to WHO was whether it could facilitate this approach.

In the discussions that followed, it was noted that, beyond compassionate use, countries were still far from providing universal access to treatment with the standard second-line drugs to MDR-TB patients. WHO had a responsibility to promote further expansion of MDR-TB treatment programmes. It also has a role to play in facilitating the development of INDs. The Critical Path to Treatment Regimens (CPTR) initiative, to which WHO participates, is intended to accelerate the development of regimens composed of new drugs. WHO promotes compassionate use of INDs. Apart from the STB Department, WHO’s Department for Essential Medicines and Pharmaceutical Policies was also engaged on the regulatory issues.

The establishment of “regional centres” which can provide care for patients from different countries was thought to be worth considering in parts of Africa and elsewhere although a similar endeavour in the past has not been successful. In the Western Pacific region it was felt that patients should be treated in their own countries. Criteria may be needed to establish “centres of excellence”. Would there only be one per country?

Janssen Infectious Diseases BVBA stated that in principle they agree to support the collaborative study proposed by the TB Alliance but it anticipate problems as not all drugs are in the same stage of development. Janssen Infectious Diseases BVBA had already recruited about 50 patients (in Georgia, South Africa and elsewhere) on a compassionate use programme using a combination with 3 other drugs to which the strain was susceptible. It was an ethical challenge on how to deal with patients who have broad patterns of resistance and expressed difficulties in procuring Group 5 drugs. Otsuka Pharmaceutical Co Ltd. had started discussions with Médecins Sans Frontières and other groups about establishing a CU programme. Up to now, no patients have been started on treatment. MSF stated that national regulatory requirements were an important hurdle to get CU implemented. CU needs to be considered on a case-by-case basis and a national committee decides on the candidate patients. It may also provide an opportunity to study the effect of new regimens.

There was a discussion about the public perception of CU as a “last resort” and an end-of-life type of treatment. The question was posed as to why CU should be discussed in a meeting dedicated to the theme of very broad patterns of drug resistance when patients with such conditions may not be those to benefit most from the INDs. Some participants felt that it is difficult to dissociate CU from terminal care as applied in oncology. Pharmaceutical companies need to prepare themselves on how to handle an understandable surge in individual requests in future for drugs for CU and expanded access.

**Conclusions**

1. Reports of TB patients with severe patterns of drug resistance, worse than XDR-TB alone, are increasing and present clinicians with a formidable challenge. However, a new definition of resistance beyond XDR-TB is not recommended, given technical difficulties with DST of many anti-TB medicines, the lack of standardised DST methods for several anti-TB drugs (including new investigational drugs) and insufficient evidence to link such DST results to treatment outcomes of patients.
2. DST for drugs used to define MDR and XDR-TB are accurate and reproducible. The methods and critical concentrations for determining resistance are standardised. All injectables and all fluoroquinolones should be tested routinely in specimens from confirmed MDR-TB patients to
screen for XDR-TB. DST for all other drugs remains problematic for technical reasons. For some drugs, particularly Group 5 and new investigational drugs, no methods currently exist. The development of DST for clofazimine, linezolid and imipenem/cilastatin would be welcome. Molecular DST offers promise: however, only a few mutations conferring resistance have been described for most second-line drugs and testing is technically demanding and expensive. As a result, molecular DST for 2nd line drugs cannot yet replace phenotypic methods.

3. WHO will promote initiatives for early collaboration among pharmaceutical companies producing investigational new TB drugs to use these drugs in novel combination regimens and to facilitate their introduction into clinical settings. This will also help protect the effectiveness of fluoroquinolones.

4. The compassionate use of new TB drugs, in patients with advanced forms of drug-resistant TB, and for whom other treatment options are limited, will require collaboration between national TB control programmes, Ministries of Health and pharmaceutical companies to ensure that the necessary regulatory frameworks are in place to facilitate access while preventing the development of resistance to the new drugs as a result of misuse.

5. There is a pressing need for properly conducted studies, in different epidemiological settings, linking DST results to patient management and clinical outcomes. WHO will take the lead in providing guidance on the evidence which national TB control programmes and other implementing partners need to collect on patients being treated for drug-resistant TB and ensure that these data provide a more robust knowledge base to inform future policy decisions. It would also strive to get more and better data reported from programmes treating MDR-TB patients.

Action Points
- WHO/HQ will draft a note for the media at the end of the meeting and a report of the meeting will be circulated to all participants within a couple of weeks.
- Further information from CDC concerning the associations between outcomes and resistance to later-generation fluoroquinolones and/or all injectable agents among XDR-TB patients in the PETTS database will be reviewed when available. If there are any important findings, the results should be published and a further consultation may be in order.
- WHO will set up a Working Group made up of Mohamed Abdel Aziz, Peter Cegielski, Charles Daley, Dennis Falzon, Aamir Khan, Christian Lienhardt, Dick Menzies, Michael Rich, and Kitty van Wezenbeek to develop and publish guidance on what observational studies of treatment for drug-resistant TB should do better to ensure the best possible evidence.
- WHO will continue to try to accelerate the process that has already started to improve the availability and affordability of clofazimine and linezolid, even ahead of the patent expiry of the latter drug.
- WHO will continue to support the CPTR and any other such initiatives to strengthen the collaboration between drug developers to come up with effective combination of drugs in the shortest possible time.
- If pharmaceutical companies wish to organise the distribution of NCEs for compassionate use they should work closely with the WHO regional offices concerned as the Regions are well placed to help.
References
1) Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. Euro Surveill. 2007 May;12(5):E070517.1
Annex-1: List of participants and observers

**Amy BLOOM** (unable to attend)
Senior Technical Advisor
US Agency for International Development (USAID)
BGH/OHIV/TLRD
5.10.45, 5th Floor, RRB
1300 Pennsylvania Ave
20523-5900 - Washington, DC
UNITED STATES OF AMERICA

**Peter CEGIELSKI**
Team Leader, MDR TB
International Programs and Research Branch, Division of Tuberculosis Elimination Centers for Disease Control & Prevention (CDC)
Mailstop E-10
1600 Clifton Road, NE
30333 - Atlanta, Georgia
UNITED STATES OF AMERICA

**Jeremiah CHAKAYA**
Chief Research Officer,
Centre for Respiratory Diseases Research
Kenya Medical Research Institute
47855
00100 - Nairobi
KENYA

**Chen-Yuan CHIANG**
Director
Department of Lung Health and NCDs
International Union Against Tuberculosis and Lung disease
68, bd Saint-Michel
75006 Paris
FRANCE

**Daniela Maria CIRILLO**
Head, Emerging Bacterial Pathogens Unit
San Raffaele del Monte Tabor Foundation
San Raffaele Scientific Institute
A4 Dibit 2, Via Olgettina 60
20132 - Milano
ITALY

**Charles DALEY**
Division of Mycobacterial and Respiratory Infections
National Jewish Medical and Research Center
1400 Jackson Street
Denver, CO 80206
UNITED STATES OF AMERICA

**Gunta DRAVNIECE**
PMDT Technical officer
PMU KNCV Tuberculosis Foundation
Parkstraat 17, 2514 JD The Hague
THE NETHERLANDS

**Hamidah HUSSAIN**
Research Associate
McGill University,
Montreal Chest Institute
3650 St. Urbain St.
Montreal, PQ,
CANADA

**Surinder K. JINDAL** (unable to attend)
Professor and Head
Department of Pulmonary Medicine
WHO Collaborating Centre for Research and Capacity Building in Chronic Respiratory Diseases,
Postgraduate Institute of Medical Education and Research
Chandigarh
INDIA

**Aamir KHAN**
Chair MDR-TB Working Group
Director
MDR-TB Control Program
The Indus Hospital
Korangi Crossing
75190 – Karachi
PAKISTAN
Erica LESSEM  
Acting Director, TB/HIV Project  
Treatment Action Group  
261 Fifth Avenue, Suite 2110  
New York, NY 10016  
UNITED STATES OF AMERICA

Richard MENZIES  
Director, Respiratory Division, MUHC and  
McGill University,  
Montreal Chest Institute  
3650 St. Urbain St.  
Montreal, PQ,  
CANADA

Patricia Bartholomay OLIVEIRA  
Secretariat of Health Surveillance, Ministry of Health  
Ministro da Saúde,  
BRAZIL

Gaby PFYFFER (unable to attend)  
Department of Medical Microbiology  
Kantonsspital  
CH-6000 Lucerne 16  
SWITZERLAND

Michael RICH  
Instructor & Associate Clinician  
Division of Global Health Equity  
Harvard Medical School  
641 Huntington Ave., 4th Floor  
Boston, MA 02115  
UNITED STATES OF AMERICA

John RIDDERHOF  
Senior Advisor for Planning  
Laboratory Science, Policy and Practice Program Office  
Office of Surveillance, Epidemiology, and Laboratory Services  
Centers for Disease Control and Prevention  
1600 Clifton Rd. Atlanta, GA 30333  
UNITED STATES OF AMERICA

Salman SIDDIQI  
Consultant Mycobacteriologist  
15 Glencoe Manor Court  
Sparks, MD 21152  
UNITED STATES OF AMERICA

Thomas M. SHINNICK  
Associate Director for Global Laboratory Activities  
Centres for Disease Control and Prevention  
1600 Clifton Road  
MS-G35, NE  
30333 Atlanta, GA  
UNITED STATES OF AMERICA

Paul THORN  
Director  
TB Survival Project  
4 Golf Drive  
BN1 7H7 - Brighton  
UNITED KINGDOM

Zarir F UDWADIA  
Hinduja National Hospital and Medical Research Centre,  
Veer Savarkar Marg. Mahim,  
Mumbai 400 016  
INDIA

Francis VARAINE  
International Medical Co-ordinator  
Médecins sans Frontières - France  
8, rue St Sabin  
75544 - Paris Cedex 11  
FRANCE

Observers:  
Myriam HAXAIRE  
Compound Development Team Leader  
Janssen Infectious Diseases BVBA (previously Tibotec)  
Turnhoutseweg 30  
2340 Beerse  
BELGIUM
Davide MANISSERO  
Director Public Health Programmes  
Otsuka Pharmaceutical  
3 Rue du Marche  
1204 Geneva  
SWITZERLAND

Carl MENDEL  
Senior Vice President, Research and Development  
Global Alliance for TB Drug Development  
40 Wall Street  
10005 - New York, NY, NY  
UNITED STATES OF AMERICA

WHO Headquarters  
Mario RAVIGLIONE, Director, STB

STB/MDR Unit  
Paul NUNN, Coordinator  
Susanne CARAI  
Dennis FALZON  
Tauhid ISLAM  
Ernesto JARAMILLO  
Fraser WARES

STB/TBL Unit  
Karin WEYER, Coordinator  
Chris GILPIN  
Jean de Dieu IRAGENA  
Fuad MIRZAYEV  
Wayne VAN GEMERT

STB/PSI Unit  
Christian LIENHARDT, STB/PSI

STB/TME Unit  
Matteo ZIGNOL, STB/TME

Stop TB Partnership  
Lucica DITIU, Executive Secretary  
Suvanand SAHU  
Kaspars LUNTE, STP/GDF

WHO AFRO  
Wilfred NKHOMA (unable to attend)

WHO EURO  
Kristin KREMER

WHO EMRO  
Mohamed Abdel AZIZ

WHO SEARO  
Rajesh BHATIA

WHO WPRO  
Catharina (Kitty) VAN WEEZENBEEK
Annex-2: Agenda

“Totally Drug-Resistant TB”: a WHO consultation on diagnostic definition and treatment options
Date: 21-22 March, 2012
WHO/HQ Geneva, Switzerland - D4 6025 “HTM-65” (D Bldg, 4th Floor)

DAY -1: Wednesday, 21 March 2012
Chairs: C Daley and P Nunn
Rapporteur: T Islam

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1: Does the correlation between DST to Group 4 and Group 5 drugs and clinical outcomes warrant a specific definition?</th>
</tr>
</thead>
</table>
| 14.00-14.20 | Welcome of participants  
Declaration of Interests  
Meeting Objectives                                               | P Nunn  
F Wares  
F Wares |

Session 1:

Does the correlation between DST to Group 4 and Group 5 drugs and clinical outcomes warrant a specific definition?

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1: Does the correlation between DST to Group 4 and Group 5 drugs and clinical outcomes warrant a specific definition?</th>
</tr>
</thead>
</table>
| 14.20-15.30 | “Totally Drug-Resistant TB” event in India  
“Totally Drug-Resistant” Tuberculosis: global response  
XDR-TB: definition, reporting and treatment outcomes  
Global epidemiology of XDR-TB  
Feedback from gGLC meeting, 28-29 February 2012 | Z F Udwadia  
P Nunn  
D Falzon  
M Zignol  
C Daley |
| 15.30-16.00 | Coffee break                                                     | |
| 16.00-18.00 | Feedback from SLD-DST Expert Group Meetings, 19-21, March 2012:  
• Assessment of reliability and reproducibility of DST  
• Assessment of the prognostic value of in vitro DST  
• R resistance as proxy for MDR  
• LPA for second-line drugs  
Comparing outcomes of patients with different resistance patterns:  
US CDC PETTS study  
Individual MDR-TB Patient Data from 32 sites  
Patient cohorts- Brazil  
Discussion  
- Can “Totally Drug Resistant TB” be defined?  
- If not, what else do we need to be able to define it in future | K Weyer  
P Cegielski  
D Menzies  
P B Oliveira |
### Session 2:
**What are the implications of resistance beyond XDR on the composition and duration of treatment regimens?**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Discussion Topics</th>
<th>Speakers</th>
</tr>
</thead>
</table>
| 09.00 – 10.30 | Summary of Day 1 discussions  
What is needed to better inform future policies?  
Current guidelines on treatment of XDR-TB cases  
Discussion:  
- What are the treatment options?  
- Are existing data sufficient to derive useful additional recommendations on treatment?  
- How should data be collected and presented in future to help the development of policy? | C Daley  
D Falzon  
C Daley |
| 10.30 – 11.00 | Coffee break                                                                 |                                                                                     |          |
| 11.00 – 13.00 | Availability and cost of second-line anti-TB drugs, including Group 5 drugs  
Compassionate use: challenges and opportunities  
Compassionate/expanded use for multiple novel regimens  
Discussion:  
- What steps should be taken to improve access to Group 5 drugs and investigational new drugs (INDs)? | K Lunte  
C Lienhardt  
C Mendel |
|          | Final conclusions and next steps                                                |                                                                                     | C Daley and P Nunn |