N. Guo*, F. Marra*,#, J.M. FitzGerald¶, R.K. Elwood#,¶ and C.A. Marra*

*Faculty of Pharmaceutical Sciences, University of British Columbia, #British Columbia Centre for Disease Control, and ¶Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.

Correspondence: C.A. Marra, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, V6T 1Z3 Vancouver, BC, Canada. E-mail: carlo.marra@ubc.ca

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Development of a standardised tool to survey MDR-/XDR-TB case management in Europe

To the Editors:

The emergence of multidrug-resistant tuberculosis (MDR-TB, defined as *in vitro* resistance to isoniazid and rifampicin) [1–5] and extensively drug-resistant TB (XDR-TB, defined as *in vitro* drug resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable drugs: capreomycin, kanamycin or amikacin) represents a major threat to TB control at the global level [1–5].

In 2007, the World Health Organization (WHO) estimated a prevalence of 511,000 MDR-TB cases (with 150,000 deaths) and 50,000 XDR-TB cases (and 30,000 deaths) [1]; 14 out of 19 high-MDR-TB burden territories are located in Former Soviet Union (FSU) countries [1].

XDR-TB is a manmade product, resulting, in essence, from clinical mismanagement of newly diagnosed pan-susceptible TB cases as well as MDR-TB cases [1, 2]. There is evidence that suboptimal TB case management in parts of Europe contributes to the development of resistance to the XDR-TB defining drugs [4–7].

In spite of the growing amount of public awareness about TB drug resistance, the essential variables necessary to fully understand MDR-TB and XDR-TB are unfortunately not systematically collected, analysed and reported in published studies [2, 8]. Although the international community is providing a rapid response to XDR-TB (formulation of an emergency plan [9]; development of an instrument to support implementation and scale-up of national strategies and to assess programmatic needs [10]), no standardised and comprehensive tool is available to survey the key factor responsible for the emergence of MDR-/XDR-TB: inappropriate TB case management.

The aim of this letter is to describe the process undertaken by the Tuberculosis Network European Trialsgroup (TBNET) in collaboration with the European Centre for Disease Prevention and Control (ECDC) to develop a standardised tool to survey MDR-/XDR-TB case management in the European Union/European Economic Area (EU/EEA) countries and the validation process used to finalise the tool.

This instrument was devised to survey original clinical records of susceptible TB and MDR-/XDR-TB cases to ascertain if case management activities were performed according to established guidelines and national regulations [11, 12]. It was not designed to detect pathogenetic mechanisms or risk factors involved in the emergence of drug-resistance in selected TB cases.

The tool identifies the most critical gaps in susceptible TB/MDR-/XDR-TB case management that need to be addressed urgently to prevent adverse outcomes for both individual patient and public health.

Data elements were organised taking into account the following. 1) Structure and content of clinical records in a sample of European countries participating in the ECDC European survey on case management of MDR-TB (five EU countries, representing different TB and MDR-TB incidence: one high TB/high MDR-TB; two low TB/low MDR-TB in Northern and Southern Europe; one high TB/intermediate MDR-TB; and one intermediate TB/low MDR-TB). 2) The recommendations of the TBNET systematic review on XDR-TB management [2]: a) prospective study design, standardised, internationally accepted definitions, quality-controlled laboratory testing for all first- and second-line drugs defining XDR-TB; agreed-upon set of standard variables allowing for comparison of approaches and results across studies; b) the

variables collected should include: measures of disease severity (number of drugs to which isolates are resistant, clinical features), treatment history, number and type of active drugs used in treatment, time to sputum smear and culture conversion, treatment duration, adverse events related to treatment and treatment outcome.

The tool is composed of three parts and one annex: Part 1 summarises the features of the setting surveyed (62 items); Part 2 collects information on individual clinical records surveyed (one line per clinical case, 141 items); Part 3 allows comparison of the key case management decisions taken on each individual case against internationally agreed standards (25 scored questions). Standards are summarised in the Annex for easy reference.

Development of the draft tool included item formulation and two reviews by a core group of experts in specific areas of TB control and one review of the draft tool by a larger international expert group. Two phases of pre-testing occurred, including use by writing committee members, and desk simulations using data from clinical records of previous TBNET studies [4–7]. A preliminary field test was conducted at Sondalo Hospital (Italy) in October 2009 (19 records). The final revision and presentation of the tool took place at an initial workshop (Stockholm, 19 November 2009), where both consultants and clinical counterparts from each clinical site to be surveyed were trained in its use.

During testing, data elements were added, consolidated, revised or deleted based on their utility in evaluating the key elements of MDR/XDR-TB case management. The tool incorporates a scoring system for the final survey data elements. The scoring system was designed to identify areas for strengthening within the MDR-/XDR-TB case management by a self-evaluation. Scores are summed by survey component (medical history, diagnosis, treatment, treatment monitoring, outcome allocation, infection control) only, *i.e.* no overall score is produced, and provide a relative measure of the strengths and gaps between components to help prioritise remedial actions.

Scores were assigned through a Delphi process aimed at defining a specific weight for each data element in terms of importance for MDR/XDR-TB case management based on expert opinion. As no data exist to rank the essential elements of MDR-/XDR-TB case management, 35 expert reviewers were asked to assign a ranking score to each element (from highest to lowest importance on a scale of 1–5). Data element scores were then weighted according to the mean value assigned by the expert panel. Each component in Part 3 is followed by summary scores and a proposed interpretation of score ranges (see table 1).

From the first to the final draft, the total number of columns increased from 187 to 228 (for Part 1 from 55 to 62, for Part 2 from 108 to 141, for Part 3 from 24 to 25). In pre-testing and pilot evaluations, the tool proved useful in collecting the relevant data for evaluation of case management and provided data that can be used to improve clinical practices.

The simulation using Sondalo Hospital (Italy) data identified two "major" deviations from internationally agreed standards

TABLE 1	Proposed interpretation of score ranges for each element of the case management survey tool		
		Question weight	Score
Component 1: Medical history			
Investigation previous TB diagnosis		4.4 ± 0.6	18
Investigation previous DST		4.5 ± 0.7	18
Investigation previous treatment		4.6 ± 0.6	18
Investigation contacts		3.3 ± 1.1	13
Section score (maximum 67); possible interpretation			
>53; no major gaps			
53–35; some critical gaps needing action			
<35; major gaps			
Component 2: Diagnosis			
Diagnostic algorithm		4.1 ± 1	16
Microbiology		4.9 ± 0.4	20
Other examinations		3.5 ± 0.9	14
Final decision		4.6 ± 0.9	18
Section score (maximum 68); possible interpretation			
>53; no major gaps			
53–38; some critical gaps needing action			
<38; major gaps			
Component 3: Treatment			
TB regimen choice (four active drugs ensured)		4.9 ± 0.4	19
Dosage		4.9 ± 0.4	20
Duration		4.9 ± 0.3	20
Management adverse events TB treatment		4.5 ± 0.8	18
HIV regimen choice		3.7 ± 1	15
Management adverse events HIV treatment		3.5 ± 1.1	14
Section score (maximum 105); possible interpretation			
>91; no major gaps			
91–76; some critical gaps requiring action			
<76; major gaps			
Component 4: Treatment monitoring			
Necessary examinations performed		4.5 ± 0.7	18
Section score (maximum 18); possible interpretation			
18; no major gaps			
0; major gaps			
Component 5: Outcome			
Correct outcome assigned		4.7 ± 0.5	19
Section score (maximum 19); possible interpretation			
19; no major gaps			
0; major gaps			
Component 6: Infection control		3.7 ± 1.2	15
Administrative measures adequate		4.1 ± 1.1	16
Environmental measures adequate		3.6 ± 0.9	15
Infection control committee		4 ± 1	16
Surveillance system for drug-resistance in the setting		4.5 ± 1	18
Staff personal protective measures adequate		3.9 ± 1.3	16
Cough etiquette		4.2 ± 1.2	17
Availability of respirators		4.4 ± 0.9	17
Training of the staff on infection control		4.4 ± 0.9	17
Section score (maximum: 129); possible interpretation			
>114; no major gaps			
114–99; some critical gaps requiring action			
<99; major gaps			

Data are presented as score or mean±SD. TB: tuberculosis; DST: drug susceptibility testing; Question mean weight: value assigned by expert opinion to the given question in a scale from 1 to 5; Score: actual value of each question composing case management survey tool, at the end of each section of the tool a guide for the possible interpretation of the score achieved by managing each individual case is given. The Section score is designed to guide interpretation of the score sum obtained for every item/question included in Part 3 of the tool. In case of a positive assessment (the activity was managed according to the established guidelines) the maximum score will be given. Zero is assigned in case of a negative assessment.

in the area of infection control (no negative pressure ventilation available, no respirator fit testing done) and the impossibility to perform all second-line drug susceptibility testing (DST) at the Reference Centre (capreomycin), as well as three ''major'' deviations related to drug choice and two ''critical'' deviations related to the diagnostic algorithm in hospitals managing MDR-TB cases before referring them to a Reference Centre (see definitions in table 1).

Analysis of risk factors associated to drug resistance in individual patients is not allowed by the present tool, so that health indicators like odds ratios or relative risks will not be calculated.

As mentioned above, the tool was designed to ascertain if case management activities were performed according to established guidelines. If, for example, the clinician has investigated the patient's previous treatment history or previous DST, he has followed the guidelines even if the information obtained is not complete (as often happens in real life).

As this tool was planned to perform a meticulous survey of the original clinical records of 40 TB/MDR-TB cases (as recommended by international guidelines [13]) in one national reference centre in five different EU member states, the time needed to complete the exercise was relevant: it ranged from 4 to 5 days for a team of two to three trained auditors supported by trained local clinicians.

In conclusion, a standardised tool to survey susceptible TB and MDR-/XDR-TB case management will support global efforts to prevent and contain MDR-/XDR-TB by identifying pitfalls that could benefit from programmatic intervention. The present tool proved able to differentiate two pitfalls in case management occurring in national reference centres and five in general hospitals before cases were referred.

The next steps of the study include surveying the participating European countries and development of a comprehensive report to inform on further actions needed to prevent occurrence of MDR-/XDR-TB in the European Union from a public health perspective.

G. Sotgiu*, R. Centis#, L. D'Ambrosio#, S. De Lorenzo¶, M. D'Arcy Richardson+, C. Lange§, D. Manissero_f_ and G.B. Migliori#, for the TBNET MDR-TB project**
*Hygiene and Preventive Medicine Institute, University of Sassari, Sassari, #WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, ¶E. Morelli Hospital, Sondalo, Italy. +HIV/TB Global Program, PATH, Seattle, Washington, USA. §Division of Clinical Infectious Diseases, Medical Clinic, Research Centre Borstel, Borstel, Germany. _f_Scientific Advice Unit, European Centre for Disease Prevention and Control, Tomtebodavägen, Stockholm, Sweden. **A full list of the TBNET MDR-TB project members and their affiliations can be found in the Acknowledgements section.

Correspondence: G.B. Migliori, WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute/TBNET Secretariat (TuBerculosis Network European Trialsgroup)/Stop TB Italy, via Roncaccio 16, 21049, Tradate, Italy. E-mail: giovannibattista.migliori@fsm.it

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