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Supporting clinical management of the difficult-to-treat TB cases: the ERS-WHO TB Consilium



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ABSTRACT

Multi-drug and extensively drug-resistant tuberculosis (MDR/XDR-TB) are considered a serious threat for TB control and elimination. The outcome of these patients is still largely unsatisfactory as of today, with treatment success rates being consistently below 50% at global level.

The World Health Organization (WHO) recommends that management of MDR-TB cases is supported by a specialized team, including complementary medical professionals able to cover several perspectives (clinical, both for adults and children; surgical; radiological; public health; psychological; nursing, among others). Implementation of such a body (known as Consilium in most of the former Soviet Union countries) is often a pre-requisite to apply for international TB control funding and concessionally priced medicines to treat M/XDR-TB cases.

The primary objective of the ERS/WHO TB Consilium is to provide clinical consultation for drug-resistant TB and other difficult-to-treat TB cases, including co-infection with HIV and paediatric cases. Through technical guidance to clinicians managing complex TB cases, the main contribution and outcome of the initiative will be a public health response aimed at achieving correct treatment of affected patients and preventing further development of drug resistance. The Consilium's secondary objective is to ensure monitoring and evaluation of clinical practices on the ground (diagnosis, treatment and prevention).

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The emergence and spread of multidrug-resistant tuberculosis (MDR-TB), defined as TB caused by *Mycobacterium tuberculosis* strains resistant to isoniazid and rifampicin (the two most important anti-TB drugs currently in use), and extensively drug

resistant tuberculosis (XDR-TB), defined as MDR-TB caused by strains resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug in addition to isoniazid and rifampicin, has attracted interest at different levels^{1–5}. In recent years, the alarming rates of M/XDR-TB in Eastern Europe and other settings of the world resulted in strong expressions of concern by national and international health authorities, partners and scientific societies.

At media level, the key words MDR-TB and XDR-TB have caught spikes of citations and consistent interest since the time the term XDR-TB appeared for the first time, as a simple Google search can testify (Figure 1).

From the public health point of view, M/XDR-TB is considered a serious threat for TB control and elimination. Therefore, the

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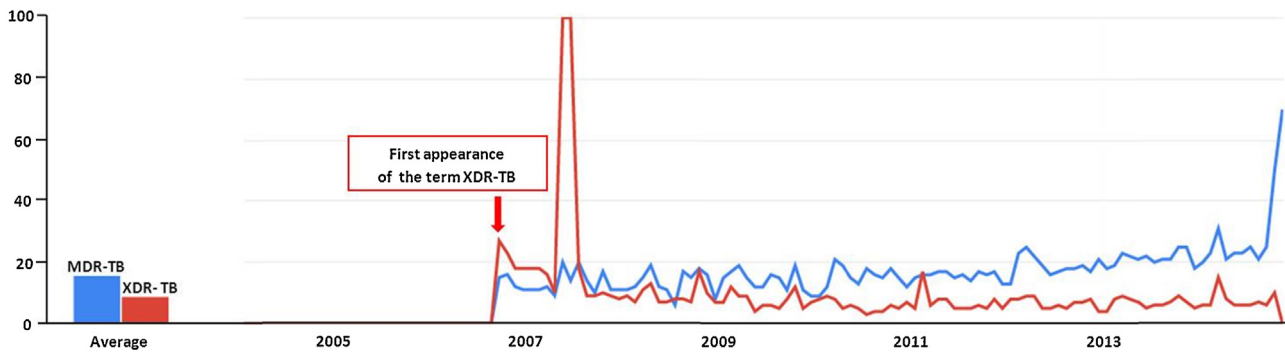


Figure 1. MDR-TB and XDR-TB web searches at media level (as of September 2014)

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: Extensively drug-resistant tuberculosis

The numbers on the graph indicate the number of web searches performed with a specific time limit to the total number of searches done on Google over time. They do not convey absolute values of search volume, as data are normalized and presented on a scale from 0 to 100. Each point on the graph is divided by the highest point and multiplied by 100. If the data are not sufficient, 0 is displayed. When comparing two or more elements, some bars are displayed next to the graph. The height of the bar represents the average of all the points on the graph for that search term.

The arrow shows the year (2006) when the term XDR-TB was used for the first time. In March 2006, following the epidemic in South Africa, the term appeared, and in October 2006 the World Health Organization developed the consensus-based definition. The first peak in the figure was registered in September 2006 (web search: MDR-TB:0; XDR-TB: 31), while the highest point was in June 2007 (web search: MDR-TB:18; XDR-TB: 100).

international community and national governments prioritize monitoring and evaluating prevalence and incidence rates as well as special and temporal trends of drug resistant TB at both global and regional level^{2,3}.

Globally, in 2013, there were an estimated 480,000 (range: 350,000-610,000) new cases of MDR-TB. Among notified TB patients in 2013 there were an estimated 300,000 (range: 230,000-380,000) MDR-TB cases and approximately 210,000 (range: 130,000-290,000) deaths from MDR-TB. In spite of the notable progress in case detection, we still rely on estimates: 3.5% of new cases and 20.5% of previously treated cases are estimated to be affected by MDR-TB at the global level².

The prevalence of MDR-TB is dramatically high in several countries belonging to the former Soviet Union, where 9-35% of new cases and $\geq 50\%$ of previously treated cases harbor MDR-TB strains² (Table 1).

XDR-TB had been reported by 100 countries worldwide by the end of 2013. A total of 75 countries and five territories reported representative data from continuous surveillance or special surveys regarding the proportion of MDR-TB cases affected by XDR-TB. Combining these data, the average proportion of MDR-TB

cases harboring XDR-TB strains of *M. tuberculosis* was 9% (95% CI: 6.5-11.5%); they correspond to the 2012 9.6% estimates. Fifteen of 75 countries reported 10 or more XDR-TB cases in the most recent year for which data were available. Among those countries, the proportion of MDR-TB cases affected by XDR-TB was highest in Georgia (20%), Kazakhstan (22.7%), Latvia (21.7%), Lithuania (24.8%) and Tajikistan (Dushanbe city and Rudaki district: 21%)².

In response to the alarming rates of MDR- and XDR-TB in former Soviet Union countries, the 53 Member States of WHO European Region have endorsed the five- year Consolidated Action Plan to Prevent and Combat M/XDR-TB 2011-2015⁶.

The clinical outcome of MDR-TB cases is largely unsatisfactory^{2,7-10} (Figure 2). In the largest ever-published cohort of 9,153 MDR-TB cases from 32 observational cohorts supporting an individual data meta-analysis, the clinical outcomes were unacceptably poor (treatment success 54%; default 23%; failure/relapse 8%; death 15%)¹¹. In XDR-TB cases and cases with resistance patterns beyond XDR the outcomes were even worse, with treatment success ranging from 19% to 40%, failure/relapse from 15% to 54% and death from 15% to 35%^{12,13}.

The challenge of providing proper treatment to M/XDR-TB patients has been identified in several countries globally. Due to frequent occurrence of adverse events, limited availability of second-line anti-TB drugs, the eminent risk of acquiring further mycobacterial resistance, associated conditions such as alcohol and drug abuse and problems in patients' adherence, physicians often face major challenges to successfully treat their patients.

WHO recommends that management of MDR-TB cases is supported by a specialized team, including complementary medical professionals able to cover diverse perspectives (clinical, both for adults and children; surgical; radiological; public health; psychological; and nursing, among others). Implementation of such a body (known as Consilium in most of the former Soviet Union countries) is often a pre-requisite to apply for international TB control funding and concessionally priced medicines to treat M/XDR-TB cases.

The Green Light Committee (GLC), a WHO-hosted committee provides technical assistance on MDR-TB management to countries through yearly country visits and on-distance support via email or telephone. GLC ensures that MDR-TB patients are prescribed treatment in line with the WHO guidelines, the latest scientific evidence and country experiences. Thank to GLC's technical assistance, several high MDR-TB burden countries in

Table 1

Estimated proportion of MDR among pulmonary TB cases in Eastern Europe countries reported in the period 2011-2013.

Country	Estimated proportion of MDR-TB among new cases	Estimated proportion of MDR-TB among retreatment cases
Armenia	9.4	43
Azerbaijan	13	28
Belarus	35	55
Bulgaria	2.3	23
Estonia	17	48
Georgia	11.0	38
Kazakhstan	25	55
Kyrgyzstan	26	55
Lithuania	11	44
Republic of Moldova	24	62
Russian Federation	19	49
Tajikistan	13	56
Ukraine	14	32
Uzbekistan	23	62

TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis
Source: (Reference #2, WHO Global TB report 2014)

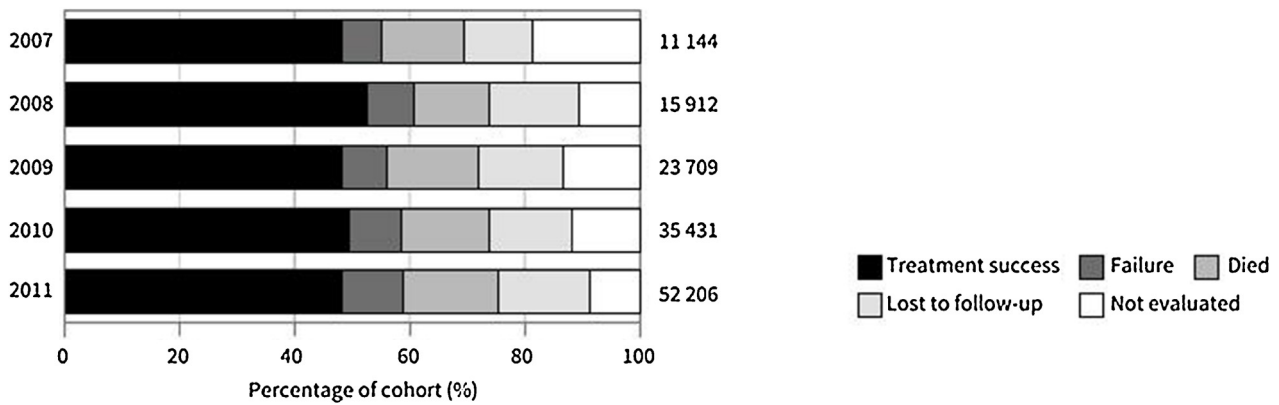


Figure 2. Patients diagnosed with MDR-TB: treatment outcomes, 2007–2011 cohorts (global data). The total number of cases with outcome data is shown beside each bar. MDR-TB: multidrug-resistant tuberculosis. Source: (Ref.#2, WHO Global TB report 2014).

the different WHO Regions have introduced the Consilium at the national level to reach consensus on the best treatment approach for M/XDR-TB patients. However, before launching the ERS/WHO electronic Consilium in September 2012, there were no online mechanism to facilitate peer-to-peer consultation for individual patient at supranational level.

However, most of these Consilia have limited experience or cover only a fraction of the patients in the country. On the other hand, the majority of low TB incidence countries do not have a similar consultation body, even though, expertise to manage M/XDR-TB cases in these settings is often limited and concentrated in main MDR-TB reference centres.

A recent European Respiratory Society (ERS)/European Centre for Disease Control and Prevention (ECDC) study¹⁴ highlighted several clinical and public health MDR-TB management shortcomings in some of the low TB incidence countries of the European Union (EU). The existence of WHO guidelines and European Standards of TB Care seems apparently insufficient to guarantee appropriate treatment of M/XDR-TB, while rapid advice from a multidisciplinary team with clinical and management experience at a national or supranational level would help ensure proper treatment^{15–17}. In countries without a formal system of consultation, specialised staff from MDR-TB reference centres spend a significant proportion of their working time responding to phone or e-mail clinical queries from all over the country and without any formal recognition, monitoring or support for the service offered.

The WHO Regional Office for Europe, ECDC, the UNION and documents originating from the Wolfheze workshops (i.e. periodic expert meeting setting the scene for improved TB control and elimination in Europe) and national TB control programme managers' meetings¹⁸ recognized the significance of national and supranational consultation from clinical and public health's perspectives.

The ERS has increased its commitment towards TB control and elimination in Europe^{19–22} through different initiatives, including a public health initiative focused on the Presidential TB plan²³, the European Forum for TB innovation²⁴, and, more recently, the Rome consultation on TB Elimination which produced the global consensus document "Framework for tuberculosis elimination in low-incidence countries"¹⁹.

To this extent and after consultation with WHO/Europe and ECDC, and under the ERS Presidential initiative, the ERS-WHO Electronic TB Consilium has been launched during the 30th ERS Congress in Vienna, on September 6th, 2012. The WHO Regional Office for Europe signed a Memorandum of Understanding with ERS to co-ordinate and co-manage this initiative, which has also

the support of ECDC in public health and monitoring and evaluation aspects.

The overarching aim of this initiative is to provide scientifically sound and evidence-based advice to national Consilia and individual clinicians on how to manage drug-resistant TB and other difficult-to-treat TB cases, including co-infection with HIV and paediatric cases. Through technical guidance provided to clinicians, the main contribution and outcome of the initiative will be a public health response aimed at achieving correct management of affected patients and prevention of further drug resistance development. Its secondary objective is to ensure monitoring and evaluation of clinical practices on the ground (diagnosis, treatment and prevention). On top of supporting clinicians, the system will also allow evaluating the trends in key challenges and pitfalls which can be addressed through human resources capacity building, including M/XDR-TB management practices (e.g. diagnostic and prescription habits), and clinician's compliance with WHO and other international, evidence-based guidelines.

The Electronic TB Consilium is particularly relevant for ERS and ECDC, as evaluation on how the recently published EU Standards for TB Care^{16,17,25} are applied is considered a priority.

The ERS/WHO TB Consilium ensures a free-cost, multi-lingual (English, Portuguese, Russian and Spanish) internet-based consultation system able to provide suggestions on clinical management of complicated TB cases in less than 3 working days. The launch of the initiative has been preceded by a call for experts (including TB clinicians, but also other professionals relevant for patient management). The expert applications have then been reviewed and validated by a ERS/WHO/ECDC Review team based on strict technical criteria. The electronic TB Consilium platform has been then presented to different countries, national TB programme managers and individual clinicians. The Consilium had been advertised via WHO channels to National TB Programme Managers and a presentation was done at TB STAG (Strategic Technical Advisory Group) in Geneva; ERS addressed chest specialists through its own publications (newsletter, European Respiratory Journal) and its website. The Consilium has been also included in the curriculum of the WHO Course for managers and consultants conducted twice a year in Cepina/Sondalo, Italy, and replicated in different continents in different languages.

Recently, a first evaluation of the e-platform's utilization has been published after completing the first 10 cases²⁶.

The study evaluated: origin of the expert consultation's request (country generating the request, patient's country of birth), clinical questions and clinical features of the case, performance of the platform (time to load the case, response time, need for additional

request for details, problems encountered, etc), as well as client satisfaction (evaluated through a structured questionnaire).

The study conclusions were the following:

1. Requests came from different regions of the world, confirming that there is a global need of clinical advice for MDR-TB and difficult-to-treat-cases. Requests came mainly from Europe – with the United Kingdom being predominant (5 requests out of 10) but also from India and Vietnam;
2. Requests were mainly for adult patients (mean age: 27.9 years; range:12–40), with 2 out of 10 cases being of pediatric interest (a 14 year old girl from Vietnam and a 12 year old girl from India, respectively);
3. Out of the 10 cases evaluated, one was drug susceptible while 9 cases were MDR-TB (of whom 2 were XDR-TB and one pre-XDR, e.g. MDR-TB with additional resistance to a fluoroquinolone or aminoglycoside);
4. Six cases were pulmonary TB, while 3 were extrapulmonary and one was both pulmonary and extrapulmonary. All of them were bacteriologically confirmed.
5. In most of the cases the clinician requested experts' opinions about the most suitable treatment regimen, validation of the treatment regimen prescribed and suggested treatment duration. In a complicated case from the United Kingdom the clinical question requested experts' opinion for the management of cachexia, muscle wasting and the appropriateness of surgical treatment. In other cases, specific guidance on possible drug interactions was requested. In one of the extrapulmonary cases the question specifically requested how to monitor the response to treatment and when to stop it.
6. The time needed for the clinician to upload the case into the electronic platform was usually less than 30 minutes, with a mean value of 20 minutes and the average response time was 40 hours. In 2 cases the experts asked the clinician to provide further details in order to finalise their report.
7. All clinicians reported to be satisfied by experts' advice.
8. Experts provided useful comments to improve the system's functionality. The main suggestion was aimed at improving reporting of the new diagnostics and radiological findings, and a better location for the (open) spaces where the clinician is allowed to add descriptive clinical details.
9. The coordinators identified the need to allow a consolidation of the 2 experts' reports, in order to provide the clinician with a perspective for the best interpretation and use of the experts' reports. In addition the client's satisfaction survey was added, together with the option to invite a third expert if necessary or to disengage an expert not providing a rapid reply. The reviewers' pop-up directory was improved, making details available to facilitate the choice (e.g. language spoken, specialty: pediatrician, surgeon, HIV/infectious disease expert, etc).

Here we provide further update about utilization of the Consilium platform. Seventy cases benefited from the ERS/WHO Consilium as of October 28th, 2014. There were 46 cases of active TB requesting individual advice. In addition advice was requested for additional 24 cases, including 4 active TB and 20 individuals latently infected in two epidemics. In 3 cases more than one opinion was requested to the experts, in order to ensure adequate treatment monitoring at different stages of the patients' roadmap towards cure^{27,28} (Table 2).

India, United Kingdom and Italy are the top 3 countries requesting the TB Consilium services, the majority of patients (37%) being born in India. The patients were young (mean age: 31 years), with a significant proportion of paediatric cases (32.7%), extrapulmonary TB forms (13.4%) and M/XDR-TB cases (56.5%).

The male to female ratio was 1:1.

The majority of the clinical queries are, again, focused on the correct selection of the treatment regimen and on its duration in M/XDR-TB cases, TB/HIV co-infected individuals and other difficult-to-treat cases which included extrapulmonary and paediatric TB cases^{27,28}.

The time necessary to load the cases remained stable at 20 minutes, while the average time necessary to provide the clinical answer to the queries by two top global TB experts has slightly increased with the increasing number of consultations, being now 41.6 hours. This time includes also week-ends and non-working days, as several requests were sent on Fridays. Clients confirmed their satisfaction.

There are plans to add the translation of the platform into French.

In addition, ERS is working to further expand the platform functionality in different areas.

In collaboration with the WHO Regional Office for Europe, a new function related to trans-border migrants has recently completed pre-testing and will be launched in 2015. It is aimed at supporting clinicians treating trans-border migrants affected by TB. The system will allow clinicians managing a patient in a given country to liaise with the country where the patient is planning to migrate during TB treatment, so that data can be exchanged and continuum of care can be ensured. This functionality will contribute to prevent management errors related to lack of information on the previous patient's medical history as well as early treatment interruptions after the patient's migration to a different country/destination.

Furthermore, a new functionality is under development in collaboration with the civil society organizations, aimed at allowing patients to directly request specific advice for their TB infection or disease to a physician, a nurse, a psychologist, and/or to ask motivational support by other patients who survived the disease.

Table 2

Summary evaluation report of the first 70 cases seeking expert advice through the ERS/WHO Consilium

Indicator	Categories	Proportion/ratio
Country requesting (top 3)	India	27.2%
	Italy	22.7%
	United Kingdom	16%
Country of birth (main)	India	37%
Sex	Male/female ratio	1.1
Age (mean)	31 years	
Age (range)	1–68 years	
Paediatric cases (number)	10 active TB	14.2%
	13 Latent TB Infection	18.5%
	Susceptibility of the M. tuberculosis strain	Susceptible
M. tuberculosis strain	Poly-resistant	6.5%
	Mono-resistant	4.3%
	M/XDR-TB	56.5%
	Not classifiable	6.5%
	Pulmonary (P) and extrapulmonary (EP) TB	Pulmonary TB
Core clinical questions	Extra-Pulmonary TB	13.4%
	P/EP TB	23.9%
	Not classifiable	2%
	Treatment regimen	81.3%
	Treatment duration	8.3%
Mean time to case-load	Other	10.4%
	20 minutes	
	41.6 hours	
Average response time	3 cases	6.25%
Repeated requests on the same case	70 cases	100%
Clinician satisfaction		

TB: tuberculosis; ERS: European Respiratory Society; WHO: World Health Organization

Last but not least, a new functionality is under preparation to support clinicians and public health specialists in managing index cases' contacts and latently infected individuals (including those generated by outbreaks and micro-epidemics).

A plan has been developed to increase the number of experts serving the Consilium in its different functionalities based on the increasing workload expected in the coming months. To cope with the new challenges, new experts speaking Spanish, Portuguese and Russian have been recently added to the initial pool of TB Consilium consultants. In addition a coordinator has been identified to run the patients' branch, in collaboration with ELF (European Lung Foundation), the patients' voice supported by ERS.

At present two co-directors manage the Consilium, with the support of one area coordinator. The number of area coordinators will increase over time, to ensure timely response to the query posed.

All the TB Consilium functionalities have been developed based on the requirements of the Swiss legislation in force.

This new system will represent an effective instrument able to support the new WHO End -TB Strategy focused on the concept of TB pre-elimination (defined as <10 TB cases per million population) and TB elimination (defined as <1 TB case per million)^{19–21}.

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