



EDITORIAL

Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium

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Multidrug-resistant tuberculosis (MDR-TB), defined as active TB cases infected by *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampicin (the two most important anti-TB drugs currently in use), and extensively drug resistant tuberculosis (XDR-TB), defined as active TB cases caused by infection with strains that are resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug in addition to resistance to isoniazid and rifampicin, attract interest at different levels [1–5]. In recent years the alarming rates of MDR- or XDR-TB in Eastern Europe and some other parts of the world, have resulted in strong expressions of concern from national and international partners, health authorities, and professional societies.

At the media level, the key words MDR-TB and XDR-TB attract spikes of citations and consistent interest, as a simple Google search can testify (fig. 1).

From the public health point of view, MDR- and XDR-TB is considered a serious threat for TB control and elimination. Therefore, the international community and national governments prioritise monitoring and evaluating prevalence rates and trends of drug resistant TB at both the global and the regional level [2, 3].

Recent evidence suggests that of the estimated 310,000 MDR-TB cases among notified TB patients with pulmonary TB in 2011, 60% occurred in India, China and the Russian Federation. XDR-TB is, at present, notified in 84 countries, although representative data on these difficult-to-treat cases are only available in 13 of them [2, 3].

The proportion of MDR-TB cases harbouring XDR-TB strains of *M. tuberculosis* was highest in Azerbaijan, Belarus, Estonia, Latvia, Lithuania and Tajikistan.

The prevalence of MDR-TB is dramatically high in several countries of the former Soviet Union, where 9–32% of new TB cases and $\geq 50\%$ of previously treated cases harbour MDR-TB strains [2, 3] (table 1). In response to these alarming rates, the

53 member states of the World Health Organization (WHO) European Region have endorsed a five-year consolidated action plan to prevent and combat MDR- and XDR-TB in 2011–2015 [6].

In spite of the notable progress in case detection (the number of cases reported by the 27 high MDR-TB burden countries almost doubled between 2009 and 2011) we still rely on estimates: 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB at the global level [2, 3].

As of today, the world record in terms of prevalence of MDR-TB was observed in Minsk, Belarus, where it was identified in 35.3% of new cases and in 76.5% of those previously treated: this means that about half of the cases diagnosed in that setting harbour MDR-TB strains. This finding was also confirmed at the national level.

The clinical outcome of MDR- and XDR-TB cases is largely unsatisfactory [7–10] (table 2). In the largest ever published cohort of 9,153 MDR-TB cases from 32 observational cohorts supporting an individual data meta-analysis, the outcomes of these cases were unacceptably poor (success 54%; default 23%; failure/relapse 8%; death 15%) [11]. In XDR-TB cases and in those harbouring *M. tuberculosis* strains with resistance patterns beyond XDR, the outcomes were even worse, with success ranging from 40% to 19%, failure/relapse from 15% to 54% and death from 15% to 35%, respectively [12, 13].

Due to the frequent occurrence of adverse events, limited availability of second-line anti-TB drugs, the eminent risk of acquiring further resistance, associated conditions such as alcohol and drug abuse and problems in patients' adherence, physicians often face major challenges to successfully treat their patients.

The WHO recommends that management of MDR-TB cases is supervised by a specialised team, including complementary medical professionals able to cover several perspectives (clinical, both for adults and children; surgical; radiological; public health; psychological; and nursing, among others). Implementation of such a body (known as a consilium in some countries belonging to the former Soviet Union) is a requisite to apply for international TB control funding and concessional pricing of medicines to treat MDR- and XDR-TB cases.

The Green Light Committee for Europe, a WHO-hosted committee ensuring technical assistance to countries during yearly country visits and on an *ad hoc* basis via email or telephone, ensures that MDR-TB patients are prescribed

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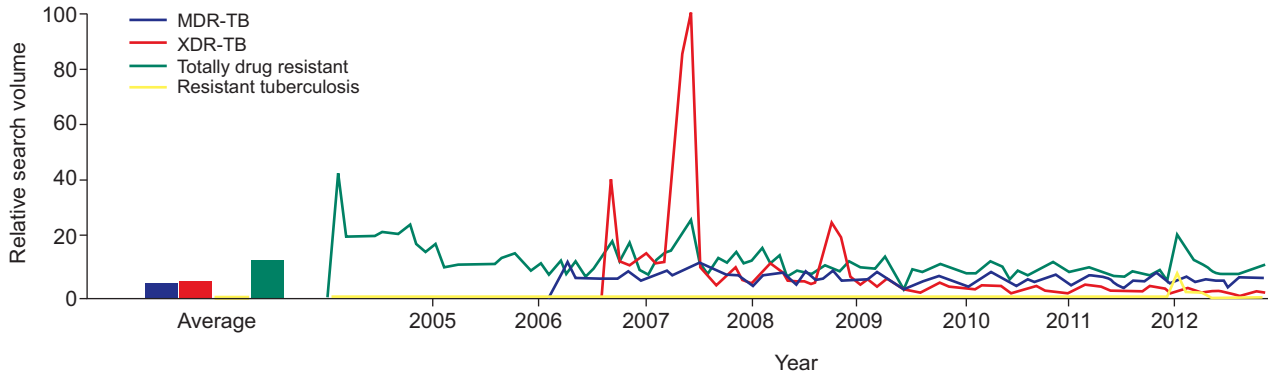


FIGURE 1. Web search interest for “MDR-TB”, “XDR-TB”, “totally drug resistant” and “resistant tuberculosis” worldwide from 2004 to present (source: Google Trends). On the y-axis the number 100 represents the peak search volume.

treatment in line with the WHO guidelines, the latest scientific evidence and country experiences. Through its technical assistance, several high MDR-TB burden countries in the WHO European Region have introduced these mechanisms at the national level. However, to date, no online mechanism exists to facilitate peer-to-peer consultation at supranational level.

The majority of low TB incidence countries, which do not need to apply for donor funding, do not have a similar consultation

body, even though expertise to manage MDR- or XDR-TB cases in these settings is often limited. The challenge of providing proper treatment to MDR- or XDR-TB patients has been identified in several countries in the region. In these countries, consilia or similar structures have been established to reach a consensus on the best treatment approach for MDR- or XDR-TB patients. However, most of these consilia have limited experience or cover only a fraction of the patients in the country.

TABLE 1 Estimated proportion of multidrug-resistant tuberculosis (MDR-TB) cases among TB notified cases and absolute number of MDR-TB cases notified, 2011

Country	Estimated proportion of notified TB cases with MDR-TB % [#]		Notified pulmonary MDR-TB cases n [#]	
	Newly treated	Previously treated	Newly treated	Previously treated
High MDR-TB burden countries in the WHO European Region				
Armenia	9.4 (7.1–12)	43 (38–49)	86 (65–110)	170 (140–190)
Azerbaijan	22 (19–26)	55 (52–60)	930 (790–1100)	2500 (2300–2700)
Belarus	32 (30–35)	76 (72–79)	1200 (1100–1300)	810 (780–850)
Bulgaria	2.0 (1.1–3.2)	26 (19–33)	28 (16–46)	91 (66–120)
Estonia	23 (17–29)	58 (43–71)	56 (43–72)	44 (33–54)
Georgia	11 (9.6–12)	32 (28–35)	340 (300–390)	420 (370–460)
Kazakhstan	30 (29–32)	51 (50–53)	3800 (3600–3900)	4500 (4300–4600)
Kyrgyzstan	26 (23–31)	52 (45–58)	970 (830–1100)	550 (490–620)
Latvia	13 (10–16)	29 (20–40)	89 (70–110)	28 (19–39)
Lithuania	11 (9.2–13)	49 (44–54)	170 (140–200)	190 (170–210)
Moldova	19 (17–22)	64 (60–67)	660 (570–760)	940 (890–980)
Russian Federation	20 (18–22)	46 (41–52)	19000 (17000–21000)	25000 (23000–29000)
Tajikistan	13 (9.8–16)	54 (48–59)	540 (420–670)	500 (450–550)
Ukraine	16 (14–18)	44 (40–49)	4400 (3800–5100)	5100 (4600–5600)
Uzbekistan	23 (18–30)	62 (53–71)	2400 (1800–3000)	670 (560–760)
High MDR-TB burden countries in other WHO regions (top 3)				
China	5.7 (4.6–7.1)	26 (22–30)	49000 (39000–61000)	12000 (10000–14000)
India	2.1 (1.5–2.7)	15 (13–17)	21000 (15000–27000)	45000 (40000–50000)
Philippines	4.0 (2.9–5.5)	21 (14–29)	7700 (5500–10000)	2900 (2000–4000)

[#]: ranges represent uncertainty intervals. WHO: World Health Organization. Data are taken from [2].

In European countries without a formal system of consultation, specialised staff from reference centres spend a significant proportion of their working time responding to phone or e-mail clinical queries from all over the country on an *ad hoc* basis and without any formal recognition, monitoring or support for the service offered.

A recent European Respiratory Society (ERS)/European Centre for Disease Prevention and Control (ECDC) study [14] has demonstrated 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 is apparently insufficient to guarantee appropriate treatment of MDR- and XDR-TB. Rapid advice from a multidisciplinary team with clinical and management experience at national or supranational level will help ensure proper treatment [15, 16].

The WHO Regional Office for Europe, ECDC, the Union, documents originating from the Wolfheze workshops (periodic expert meetings setting the scene for improved TB control and elimination in Europe) and national TB control programme managers' meetings [17] have recognised the significance of national and supranational consultation from clinical and public health perspectives.

The ERS has increased its commitment towards TB control and elimination in Europe through different initiatives, including the European Respiratory Roadmap [18] initiative aimed at providing evidence on the need to support lung health. In 2012, at the ERS summit in Tallinn, the role and contribution of health inequalities in sustaining TB were discussed. In addition the European Forum for TB innovation has become part of the 2013 Presidential plan, and is focused on innovative interventions that can already be implemented based on the evidence that is presently available [19].

To extend this and after consultation with WHO/Europe and ECDC, and under the ERS Presidential initiative, the ERS-WHO Electronic Consilium was launched during the 22nd ERS Congress in Vienna, on September 6, 2012. The WHO Regional Office for Europe signed a Memorandum of Understanding with the ERS to coordinate and co-manage this initiative, which also has 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. Its primary objective 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 clinical action, the main contribution and outcome of the initiative will be a public health response aimed at preventing further development of drug resistance. Its secondary objective is to ensure monitoring and evaluation of clinical practices (diagnosis, treatment and prevention) in the WHO European Region; this will allow comparisons with established standards for designing interventions to address the common pitfalls. In addition the system will allow trans-border follow-up of difficult-to-treat cases moving from one country to another within Europe.

The ERS/WHO Consilium will provide a free-to-access, bilingual (English and Russian) internet-based consultation system able to provide suggestions on clinical management of complicated TB cases with a turnaround time of about 1 week. The launch of the initiative has been followed with 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 criteria.

As well as supporting clinicians in Europe (and eventually, in a second phase, outside of Europe), the system will also enable evaluation of the trends in key challenges and pitfalls which can be addressed through human resources capacity building, including MDR- and XDR-TB management practices (e.g. diagnostic and prescription habits), and clinicians' compliance with WHO and other international, evidence-based guidelines. The system will also enable evaluation of trends over time.

The Electronic Consilium is particularly relevant for the ERS and ECDC, as evaluation of how the recently published EU Standards for TB Care [16, 20] are applied is considered a priority.

We are particularly grateful to the European Respiratory Journal (a journal particularly committed to TB) for hosting this editorial and allowing a wider audience to become aware of this important initiative.

TABLE 2 Treatment outcomes (success and death) of the multidrug-resistant tuberculosis (MDR-TB) case cohort enrolled in 2007 in the high burden countries of the World Health Organization (WHO) European Region

Country	Treatment success %	Deaths %
High MDR-TB burden countries in the WHO European Region		
Armenia	53	11
Azerbaijan	56.5 [#]	8.7 [#]
Belarus	NA	NA
Bulgaria	25	45
Estonia	57	14
Georgia	38	20
Kazakhstan	77	4
Kyrgyzstan	50	5
Latvia	64	15
Lithuania	NA	NA
Moldova	52	8
Russian Federation	50.9 [#]	8.1 [#]
Tajikistan	NA	NA
Ukraine	NA	NA
Uzbekistan	55	10
High MDR-TB burden countries in other WHO Regions (top 3)		
China	NA	NA
India	NA	NA
Philippines	63	11

Data from [9], except [#]: country data from [10], 2008 cohort. NA: not available.

As this initiative requires a large consensus and significant support, all clinicians of goodwill are welcome to adhere and contribute, to the extent they can, to help their colleagues who need urgent suggestions to solve burning clinical dilemmas emerging from day-to-day practice.

The platform for the Electronic Consilium can be found on the ERS website and soon the links will be provided on the WHO/Europe and ECDC websites.

STATEMENT OF INTEREST

None declared.

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