ERS/WHO Tuberculosis Consilium: reporting of the initial 10 cases

To the Editor:

As part of the 2012–2013 European Respiratory Society (ERS) Presidential plan, the ERS/World Health Organization (WHO) Tuberculosis (TB) Consilium was implemented as a novel high priority initiative to face the growing global multidrug-resistant (MDR) TB pandemic, which is also very much a European problem [1–3].

This priority is largely due to the alarming rates of MDR-TB (*i.e.* active TB cases infected by *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampicin) and extensively drug-resistant (XDR) TB (*i.e.* TB caused by strains that are resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug, in addition to isoniazid and rifampicin) [4–7]. MDR/XDR-TB are considered serious threats for TB control and elimination in Europe as their clinical outcomes are largely suboptimal, as the regimens are very toxic and expensive and taken for much longer [6–9]. The largest available meta-analysis, assessing 9153 MDR-TB cases, has shown treatment success as low as 54% (with 15% dying, 8% failing/relapsing and 23% defaulting). In cases whose disease is caused by *M. tuberculosis* strains with resistance patterns beyond XDR-TB the outcomes are much lower: treatment success ranges from 19% to 40%, failure/relapse from 15% to 54% and death from 15% to 35% [6, 7].

Due to the clinical complexity (frequent occurrence of adverse events, lack of clinical experience, limited availability of adequate diagnostics and second-line anti-TB drugs in some countries), the real risk for acquiring further resistance and problems in patients' adherence to treatment, clinicians face a greater challenge to successfully manage their patients. The ERS and the WHO Regional Office for Europe implemented a consultation body (the ERS/WHO TB Consilium) in late April 2013 [1, 2]. Clinicians can upload a case description *via* the website (www.tbconsilium.org). The case is then sent to two experts belonging to the Consilium roster, who are expected to respond within a few days. The aim of the present article is to evaluate the e-platform's functionality after it has supported the clinical management of the first 10 cases as of July 15, 2013.

The following parameters have been taken into consideration in this first report of evaluated cases: the origin of the expert consultants request (country generating the request and patients' country of birth); clinical questions and clinical features of the case; performance of the platform (time taken to load the case, response time, the need for an additional request for details, any problems encountered, *etc.*); and client satisfaction (evaluated through a structured questionnaire). The results are summarised in table 1.

Based on the initial experience with the ERS/WHO TB Consilium, the following issues were found to be of relevance.

1) The need for clinical advice is global. Requests came mainly from Europe, with the UK being predominant (five out of 10 cases), but also from India and Vietnam.

2) Seven out of the 10 cases were born in Moldova and/or in India.

3) More female patients are represented (seven out of 10 cases).

4) The patients are young (mean age: 27.9 years; range: 12–40 years), two out of 10 cases were paediatric (both females, a 14 year-old from Vietnam and a 12 year-old from India).

5) Out of the 10 cases, one is susceptible and nine are MDR-TB, of whom two are XDR-TB and one is pre-XDR-TB (*i.e.* MDR-TB with additional resistance to a fluoroquinolone or aminoglycoside).

6) Interestingly, while six cases were pulmonary, three were extrapulmonary and one was both pulmonary and extrapulmonary. This proportion exceeds the general proportion of notified extrapulmonary cases in the global context [3]. They are all bacteriologically confirmed, in contrast to what is usually reported through surveillance systems.

7) In all cases, the clinical question was related to the treatment regimen. In seven cases, the question specifically focused on the drug choice, the validation of the treatment regimen prescribed and treatment duration. In one case from the UK, the clinical question was more complicated, including a request for expert opinion on the management of cachexia, muscle wasting and possible surgery. In other cases, specific

TABLE 1 Summary evaluation report of the first 10 cases seeking expert advice through the European Respiratory Society/World Health Organization Consilium

Country of request origin	Country of birth	Sex	Age years	Clinical question to the expert	Time to load request min	Response time h	Strain susceptibility	P/EP	Request for second opinion from the experts	Clinician satisfied	Experts' reported problems
Italy	Moldova	F	29	Treatment regimen (after 9 months, still bacteriologically positive; when to stop it)	20	24	Susceptible	P	Yes	Yes	No
Vietnam	Vietnam	F	14	Treatment regimen (drug choice)	20	24	MDR-TB	P	Yes	Yes	No
Moldova	Moldova	M	34	Treatment regimen (drug choice)	20	24	XDR-TB	P	No	Yes	No
India	India	F	12	Treatment regimen (drug choice)	20	24	Pre-XDR-TB	P/EP (lymph node)	No	Yes	No
UK	India	F	19	Treatment regimen (drug choice)	20	24	XDR-TB	EP (cervical and mediastinal lymph node)	No	Yes	No
UK	Romania	F	36	Treatment regimen and drug interactions	20	24	MDR-TB	P	No	Yes	No
Italy	Moldova	F	28	Treatment duration (drug choice)	20	24	MDR-TB	P	No	Yes	No
UK	Somalia	M	40	Treatment regimen, advice for monitoring the response and when to stop treatment	20	144[#]	MDR-TB	EP (mediastinal lymphadenopathy)	No	Yes	No
UK	India	M	35	Advice for management of cachexia, muscle wasting and possible surgery; confirmation of MDR-TB treatment plan	20	48	MDR-TB	P	No	Yes	No
UK	India	F	32	Treatment regimen, advice for surgery, advice for PET	20	24	MDR-TB	EP (chronic abscess on left thigh)	No	Yes	No

P: pulmonary; EP: extrapulmonary; F: female; M: male; MDR: multidrug-resistant; TB: tuberculosis; XDR: extensively drug-resistant; pre-XDR-TB: MDR-TB with additional resistant to a fluoroquinolone drug; PET: positron emission tomography. [#]: one expert took 6 days to respond.

guidance on possible drug interactions was requested. In one of the extrapulmonary cases, the question was a specific request regarding how to monitor the response to treatment and when to stop it.

8) The time taken for the clinician to load the case onto the electronic platform was <30 min, with a mean value of 20 min. No clinician reported problems in using the system.

9) The average response time was 40 h, although in eight cases it was within 24 h, in one case 48 h, and in a single case 6 days as one of the two experts, after accepting the request, temporarily had no access to an internet connection and needed some time to complete the report. In two cases the experts asked the clinician to provide further details in order to finalise their report. The mail exchange was rapid and did not delay the time to the final answer.

10) All clinicians reported they were satisfied with the experts' advice.

11) No problems were reported by the experts, who provided useful comments for improving the system functionality. All these suggestions were captured by the Consilium coordinators. The main suggestions were aimed at improving reporting of new diagnostics and radiological findings, and a better location for the spaces where the clinician is allowed to add descriptive clinical details.

12) The coordinators identified a need to allow consolidation of the two 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 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 reviewer pop-up directory was improved, making further details available to facilitate the choice of expert, for example language spoken and speciality (HIV, paediatrician, surgeon *etc.*).

Preliminary analysis indicates that 2 months after its launch, the e-platform has achieved a satisfactory functionality, thanks to adequate pretesting. Useful operational conclusions can be drawn from this initial analysis, including: 1) regimen selection appears to be the predominant query from clinicians, *vis-à-vis* the need for rational prescribing of regimens with maximised clinical effectiveness; and 2) extrapulmonary and paediatric TB cases raise questions regarding both management and monitoring of therapy.

A rapid response to each request is possible if the Consilium director and area coordinator provide an immediate reaction following the upload of a case into the system. Next steps will include the full activation of the Russian translation of the system interface, which will be followed by translation into Spanish, Portuguese and French.

In addition to providing clinical advice, the system also allows monitoring and evaluation of the adherence to existing guidelines [10], as well as the transborder follow-up of TB cases throughout Europe [10]. An *ad hoc* analysis will be planned when a sufficient number of cases have been stored in the database, under the stringent rules of the Swiss legislation with regard to confidentiality and data protection (the server is hosted by the ERS in Lausanne).

The ERS Consilium platform aims to provide clinicians world-wide with a tool that assists care providers in formulating individualised treatment plans for their MDR-TB patients, hence guaranteeing better guideline adherence, improved treatment success rates, tolerability and prevention of further resistance.

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Evaluation of the TB consilium e-platform based on the first 10 cases (TB strain, question, response time, satisfaction) http://ow.ly/pP9K4

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Bedaquiline in MDR/XDR-TB cases: first experience on compassionate use

To the Editor:

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are recognised as global emerging public health priorities [1, 2], with 310 000 MDR-TB cases notified to the World Health Organization (WHO) in 2011, 9% of them being XDR. MDR/XDR-TB testify to the failure of National TB Programmes to use available first- and second-line drugs correctly [3], and generate clinical dilemmas for clinicians managing these difficult-to-treat cases.

The chances of achieving treatment success, or even sputum smear and culture conversion, are largely suboptimal in these cases [1, 2]. In the largest MDR-TB cohort ever analysed [1, 2], the proportion of cases treated successfully was 54%, with 8% failing or relapsing, 15% dying and 23% defaulting. In the XDR-TB subgroup, 40% achieved treatment success, 22% failed treatment or relapsed, 15% died, and 16% defaulted.

The reason for this is simple: treatment of MDR/XDR-TB is expensive [4], more toxic [5, 6], and, as of today, takes up to 2 years of therapy according to current WHO guidelines [3]. The therapeutic armamentarium is limited in XDR-TB cases, where, by definition, the strains of *Mycobacterium tuberculosis* are resistant to the two most powerful anti-TB drugs (rifampicin and isoniazid, defining MDR-TB) plus any fluoroquinolones and to at least one second-line injectable (amikacin, capreomycin and kanamycin). The remaining treatment options available are the ''old'' bacteriostatic drugs and the not well-known WHO group 5 drugs [3, 5–7].

The real clinical dilemma clinicians face in managing these cases is how to ensure the fourth active drug during the intensive phase and/or the third active drug during the continuation phase of treatment, as recommended by WHO [3]. From this dark perspective, the present availability of new drugs in the development pipeline represents a possible solution. While delamanid is still completing the necessary registration procedures [5, 8], bedaquiline [5, 9] (a new diarylquinoline, formerly known as TMC207) has recently received US Food and Drug Administration approval and ''compassionate'' use in several European countries. While it is still undergoing phase III trials, phase I, II and IIb trials have shown the drug to be safe and effective, although an excess mortality has been identified in the treatment arm and will need further evidence [9].

In a multidrug treatment regimen, bedaquiline increased sputum culture conversion from 9% to 48% and reduced the time to sputum-negative conversion by 58%, suggesting its potential capacity to significantly reduce the treatment period as well as the debilitating and dangerous adverse effects associated with some of the existing second-line anti-TB drugs.