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ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use

To the Editor:

The European Respiratory Society (ERS) and the World Health Organization (WHO) Regional Office for Europe implemented a consultation body, the ERS/WHO Tuberculosis (TB) Consilium, in late April 2013 [1–4]. This is a novel, high-priority initiative, as part of the 2012–2013 Presidential plan, to face the growing problem of drug-resistant TB in Europe and globally to support clinicians in managing difficult-to-treat TB cases.

Clinicians are increasingly challenged by difficult-to-treat cases of multidrug-resistant (MDR)-TB (*i.e.* TB caused by *Mycobacterium tuberculosis* strains resistant to isoniazid and rifampicin) and extensively drug-resistant (XDR)-TB (*i.e.* TB caused by MDR-TB strains that are also resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug) [5–8]. MDR/XDR-TB is seriously hampering TB control and elimination in Europe [9–11], as patients require long and expensive regimens with significant adverse effects, while cure rates remain low [7, 8, 12–14].

Clinicians can upload a case description and queries *via* the ERS/WHO TB Consilium website (www.tbconsilium.org), the process of which takes up to 20 minutes. The case is then assigned to global experts who provide feedback to the clinician's questions in a limited timeframe, free of charge. At the time of writing, the TB Consilium has provided expert opinion on 51 cases (and two outbreaks from 11 countries), with an average response time of 36 h. The most frequently posed questions are related to the design and duration of the most appropriate regimens for difficult-to-treat patients [4].

In the absence of a sufficient number of medicines to which a strain is sensitive *in vivo*, life-saving treatment may rely on the use of new medicines (bedaquiline or delamanid) either under conditional or through compassionate use [15–18].

We describe the contribution of the TB Consilium e-platform to the management of the first case accessing delamanid for compassionate use, with an overview of the epidemic context.

The patient (male; 12 years old; native Italian; no comorbidities or risk factors for TB) was diagnosed in October 2013 in Milan (Italy) with both laryngeal and pulmonary TB. The patient reported progressive dysphonia, including aphonia, associated with hearing loss of the right ear as well as asthenia and weakness since May 2013. A chest radiograph showed multiple nodular infiltrates in both lungs with fibrotic and calcified areas suggestive of pulmonary TB. A tuberculin skin test (TST) was negative but an interferon-γ release assay (IGRA) (QuantiFERON Gold; Qiagen GmbH, Hilden, Germany) was positive. Direct gastric aspirate smear microscopy for acid-fast bacilli was positive as was gastric aspirate culture for *M. tuberculosis*. The *M. tuberculosis* isolate (Haarlem strain) was resistant to all first-line drugs, as well as ethionamide, the fluoroquinolones and all injectable agents.

Based on early detection of rifampicin resistance by Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) the patient was initially prescribed (October 4) ethambutol, pyrazinamide, high-dose isoniazid and moxifloxacin. On October 30, when complete drug susceptibility test (DST) results became available (showing resistance to all first- and second-line drugs except para-aminosalicylic acids (PAS) and linezolid), the regimen was re-designed (fig. 1). Following clinical and radiological (chest radiography and computed tomography (CT)) improvement, and bacteriological conversion of the gastric aspirate smear microscopy (the culture remaining positive), the patient was discharged on December 12.

Despite good treatment adherence, on January 27, 2014, direct smear aspirates reverted to positive (the culture remaining positive) and the patient experienced progressive clinical deterioration with loss of 4 kg body weight (down to 37.9 kg from 42 kg at discharge). His haemoglobin decreased from 11 $g \cdot dL^{-1}$ to 8.5 $g \cdot dL^{-1}$. The patient was re-hospitalised on February 2 and the treatment regimen modified, with further adjustment on February 9 (fig. 1). The patient received a blood transfusion and parenteral nutrition was started.

In order to select the most appropriate treatment regimen for the young patient, the TB Consilium platform was used and four different world experts in paediatric MDR/XDR-TB management were consulted. All of them recommended inclusion of one of the newly approved TB drugs (either bedaquiline or delamanid; not both, because of lack of safety data with concomitant use or the drug–drug interaction) in a regimen that included meropenem and clofazimine.

Following the experts' recommendations, delamanid was procured in 10 days *via* the manufacturer (Otsuka Europe, Wrexham, UK) and treatment initiated on March 1, with close monitoring of the patient. The Consilium experts' opinion played a crucial role in the manufacturer's decision to create a name-based compassionate programme for delamanid. Initial clinical, laboratory and radiological improvement was observed, including bacteriological conversion (gastric aspirate as well as smear and culture; provisional result at week 3).

Contact screening revealed a complex pattern of infection and likely transmission. Within the household, the index case's sister (6 years old) and brother (10 years old) were diagnosed with smear- and culture-negative TB (from gastric aspirates) with pathological images on CT. They were prescribed a regimen including isoniazid, pyrazinamide, moxifloxacin and linezolid from October, remaining symptom free. The mother had latent TB infection (LTBI), being TST and IGRA (QuantiFERON) positive, whereas the father was negative for both tests.

Investigations of the index case's school-related contacts identified two schoolmates affected by TB. A girl born in Morocco had sputum-negative pulmonary TB (negative culture from bronchoalveolar lavage but positive histology from hilar lymph node biopsy). She completed 6 months of the standard first-line regimen with a good treatment response. A second case, a boy born in Romania, had monolateral pleurisy with modest symptoms, reflecting recent infection (most likely by the index case). He was prescribed the same regimen as the index case (moxifloxacin, amoxicillin-clavulanate, terizidone, clarithromycin, linezolid

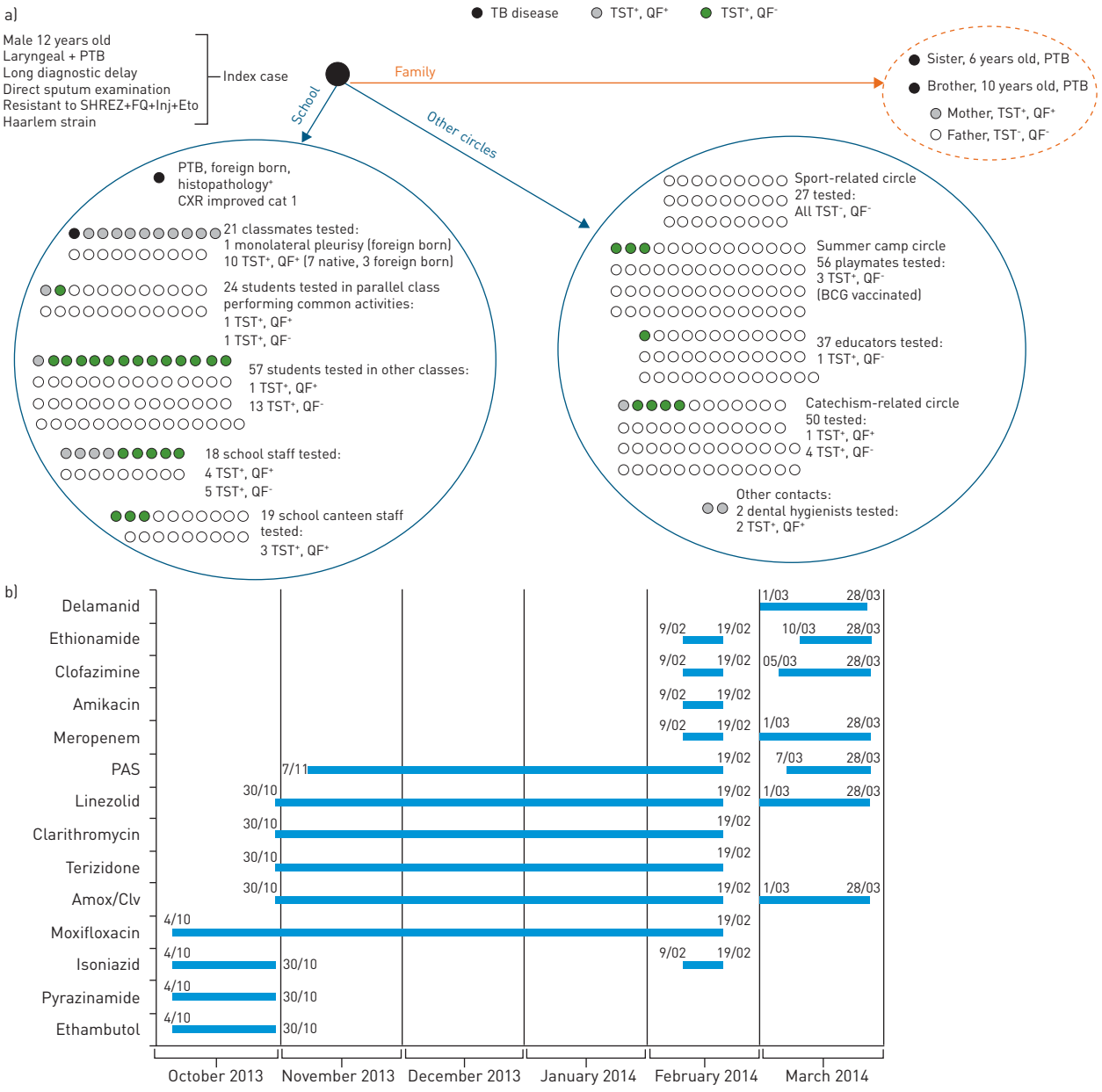

FIGURE 1 a) Evaluation of the Milan extensively drug-resistant tuberculosis epidemic (2013) managed through the European Respiratory Society/World Health Organization Consilium's expert advice and b) summary of drugs included in the treatment regimen of the index case. Numbers in b) represent date/month. The dosages were as follows. October 4, 2013 (start): ethambutol 400 mg twice daily *p.o.*, pyrazinamide 700 mg twice daily *p.o.*, high-dose isoniazid 400 mg twice daily *p.o.* and moxifloxacin 550 mg once daily *p.o.* October 30, 2013 (complete drug susceptibility test available): moxifloxacin 550 mg once daily *p.o.*, amoxicillin-clavulanate (Amox/Clv) 1 g three times per day *i.v.*, terizidone 750 mg once daily *p.o.*, clarithromycin 300 mg twice daily *p.o.* and linezolid 600 mg twice daily *i.v.*; linezolid and Amox/Clv were administered *i.v.* for 6 weeks and then were given orally at the same dosage. November 7, 2013: para-aminosalicylic acid (PAS) 6 g once daily *p.o.* was added. February 2, 2014: Amox/Clv 1 g three times per day *i.v.*, linezolid 600 mg twice daily *i.v.*, oral moxifloxacin 550 mg once daily *p.o.*, terizidone 750 mg once daily *p.o.*, clarithromycin 300 mg twice daily *p.o.* and PAS 6 g once daily *p.o.* February 9, 2014: clofazimine 200 mg once daily *p.o.* and ethionamide 750 mg once daily *p.o.* were added, the treatment including linezolid 600 mg twice daily *i.v.*, meropenem 1 g three times per day *i.v.*, amikacin 750 mg OD *i.v.*, Amox/Clv 1 g three times per day *i.v.*, moxifloxacin 550 mg once daily *p.o.*, PAS 550 mg once daily *p.o.* and high-dose isoniazid 400 mg twice daily *p.o.* February 19, 2014: all the drugs were stopped due to acute pancreatic insufficiency. March 1, 2014: delamanid 100 mg twice daily *p.o.* was added with linezolid 300 mg twice daily *i.v.*, meropenem 1 g three times per day *i.v.* and Amox/Clv 700 g three times per day *i.v.* March 5, 2014: clofazimine 100 mg once daily *p.o.* was added to the regimen. March 7, 2014: PAS 8 g once daily *p.o.* was added to the regimen. March 10, 2014: ethionamide 500 mg once daily *p.o.* was added to the regimen. PTB: pulmonary tuberculosis; SHREZ+FQ+Inj+Eto: streptomycin, isoniazid, rifampicin and ethambutol, plus fluoroquinolone, all second-line injectables (amikacin, kanamycin and capreomycin) and ethionamide; TST: tuberculin skin test; QF: QuantiFERON; CXR: chest radiography; cat: category; BCG: bacille Calmette–Guérin.

and PAS) and was improving clinically and radiologically at the time of writing. In addition, four members of the school staff, 10 schoolmates (seven native and three foreign born), two other students and another three individuals in the index case's other circles were found to have LTBI (QuantiFERON positive with no signs of TB). All LTBI individuals were undergoing clinical and radiological follow-up at the time of writing.

This is the first report on the compassionate use of delamanid involving a paediatric XDR-TB case. The TB Consilium platform is a functional instrument to rapidly provide (24 h) four expert opinions on how best to manage a complex case. The Consilium's recommendations facilitated the delamanid manufacturer's decision to make the drug available for compassionate use in a child. On the basis of this positive experience, the manufacturer has proposed to use the TB Consilium as a tool to provide rapid clinical advice guiding the release of the compound for compassionate use. In the absence of a pre-existing national authorisation process for the compassionate use of an unregistered drug (formally approved in Europe for adults only) the TB Consilium experts' opinion supported the treating team in obtaining clearance from Italian regulatory bodies (*e.g.* the hospital ethical committee and the National Drug Agency).

This experience shows the importance of defining a specific, consensus-based roadmap to guide the rational and authorised use of the new TB drugs. It is essential to ensure rapid access to the new drugs in selected cases (to save patients' lives and to break the transmission cycle), while the risk of cumulative resistance is minimised, and evidence about drug safety and effectiveness is collected.

The Milan outbreak was further complicated by a second case that was probably infected by a different strain (it was not possible to identify the second strain). Overall, there were five cases with TB and 19 with LTBI (12 out of 19 in children). The epidemic required coordination of different clinical and public health units. It illustrates that TB elimination would be difficult in low-incidence countries if TB remains endemic in areas from where refugees and immigrants originate [9–11].

The TB Consilium platform, in addition to providing expert opinion in four different languages (English, Russian, Spanish and Portuguese) to clinicians and patients (the patient's version being in preparation at the time of writing) and to support cross-border case management, proved to be effective in supporting compassionate use of new drugs for MDR/XDR-TB management.

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Evaluation of the e-platform in assessing appropriateness of delamanid (compassionate use) in a complex XDR-TB case http://ow.ly/vEfEW

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