

Managing an extensively drug-resistant tuberculosis outbreak: the public health face of the medal

To the Editor:

We read with interest the letter by ESPOSITO *et al.* [1], reporting on the clinical management of a paediatric case of extensively drug-resistant tuberculosis (XDR-TB) in Milan, Italy, who faced a life-threatening condition [2, 3] that required access to an electronic Consilium [4]. The article is important as it describes a complex epidemic originated by a really difficult-to-treat case who had an intensive social life in a large city, thus making it necessary to perform a vast tracing of contacts, stratified into circles at different risk of exposure.

In the context of tuberculosis (TB) elimination [5–7], when TB incidence decreases and health services are obliged, based on cost-effectiveness considerations, to abandon the old-style vertical approach and integrate prevention, clinical and control functions, several difficulties gradually emerge [8, 9]. First, a central authority, explicitly empowered to coordinate the outbreak management, is not generally available [5, 10]. Secondly, coordination between the different services involved (clinical and preventive medicine), between themselves and with local/regional/national health authorities, are usually not regulated. Last but not least, a trained focal point with a mandate to deal with media is usually missing [10]. A recent European Centre for Disease Prevention and Control (ECDC) survey clearly demonstrated the limited capacity of European Union countries in dealing with TB outbreaks and advocated for further public health research in this area [10].

Milan and the Lombardy region (the most populated region in Italy), due to specific epidemiological features (large population, important migrant community, TB incidence higher than the national rate, previous experience in managing TB outbreaks, and historical leadership in TB control through the establishment of a regional coordination group) has established a permanent task force to deal with outbreaks/micro-epidemics [8]. The group includes the Regional Office for Public Health (Milan, Italy), the Reference TB Centre and Laboratory (Milan), plus the public health districts and clinicians involved in the various outbreaks. In the present case, the National Centre for Molecular Surveillance of *Mycobacterium tuberculosis* (Milan) performed the extra-regional laboratory investigations, and Stop TB Italy (a local nongovernmental organisation member of the Stop TB Partnership) was involved in the counselling of contacts and communication with the press.

We will describe here how the Milan XDR-TB outbreak was managed, from the public health perspective, to complete the information provided in the letter by ESPOSITO *et al.* [1], and to quantify by cost-description its direct costs.

All activities performed in order to investigate the index and secondary cases [1], to provide educational and counselling services to cases (the majority being children), relatives, healthcare workers and other individuals involved, to perform contact-tracing and to deal with the media are reported in table 1.

The average gross hourly cost (€28.10), as derived from official Italian figures for 2013 [11], has been applied to all direct costs related to activities performed by healthcare workers involving relatives employed in the different circles evaluated during contact-tracing, and any other person involved. In addition, the costs of performing microbiological examinations (sputum smears, cultures, drug susceptibility testing, *etc.*) and diagnosis for latent infection (Mantoux tests and interferon- γ release assays (IGRAs)) have been also added (table 1). In total, five cases were involved in the outbreak. Of these, two were microbiologically confirmed: the index case (an Italian 12-yr-old male with pulmonary and laryngeal TB) and one of his classmates (a Romanian male of the same age, with pleural effusion). Three were not confirmed: the two younger siblings of the index case (with minimal pulmonary lesions) and another classmate (a female from Morocco who was independently diagnosed with initial TB and successfully treated with a standard regimen in another hospital). Contact tracing has been organised in five different circles, and included screening of 320 individuals. Out of the 55 who were positive for the Mantoux test (Tubertest 5 UT;

TABLE 1 Costs of activities performed in order to investigate the index and secondary cases in the extensively drug-resistant TB outbreak in Milan, Italy

| Activities | Persons involved and examinations performed n | Average estimated time per person involved h | Total work time h | Total estimated cost calculation € |
|---|---|--|-------------------|---|
| Contact recruitment and counselling [#] | 320 | 1 | 320 | 28.1×320 = 8992 |
| Educational meetings with relatives and adult contacts [¶] | Relatives: 16 Adult contacts: 3 | Relatives: 2 Adult contacts: 1 | 35 | 28.1×35 = 983.50 |
| Mantoux TST [*] | 430 | 2 | 860 | (5×430 = 2150) +(28.1×860 = 24 166) = 26 316 |
| Chest radiography [§] | 138 | 1 | 138 | (80×138 = 11 040) +(28.1×138 = 3877.80) = 14 917.80 |
| Quantiferon test ^{f,##} | 60 | | | 62×60 = 3720 |
| Cultures and species identification ^{f,¶¶} | 3 | | | 193×3 = 579 |
| Drug susceptibility test ^{f,¶¶} | 3 | | | 81×3 = 243 |
| MIRU-VNTR ^{plus} ^{f,¶¶} | 3 | | | 173×3 = 519 |
| GeneXpert ^{f,¶¶} | 3 | | | 86×3 = 258 |
| Whole genome sequencing ^{f,++} | 6 | | | 200×6 = 1200 |
| Total | | | | 57 728.30 |

TB: tuberculosis; TST: tuberculin skin test; MIRU: mycobacterial interspersed repetitive units; VNTR: variable number of tandem repeats. [#]: the estimated time to trace and provide initial information to each contact is 1 h; the total cost of these activities has been calculated by multiplying the average labour cost by the total working hours lost by the relatives involved. [¶]: the estimated time needed for educational activities is 2 h with each relative of infected schoolmates and 1 h with each infected adult; the total cost of educational activities has been calculated by multiplying the average labour cost by the total working hours lost by the relatives involved. ^{*}: the cost of the test has been calculated by including: 1) the labour cost for the staff performing the Mantoux TST and the material cost of the vial and associated consumables, and 2) the working hours lost by the relatives involved, which have been estimated at 2 h each (time needed to reach the public health service, to perform the test and to wait for the results); the total number of tests includes those who repeated the test at follow-up. [§]: the cost has been calculated by including: 1) the personnel costs for medical technical assistants and physicians plus material costs, and 2) the working hours lost by the relatives involved, which have been estimated at 1 h each (time needed to reach the TB centre, to perform the test and to wait for the results); the total number of radiographs includes the initial examination for TST positives and repetitions at follow-up. ^f: the cost of these tests includes the labour cost for the staff performing the test plus the material costs. ^{##}: the total number of tests includes those with previous bacille Calmette–Guerin vaccination and/or dubious TST results. ^{¶¶}: these tests include the three confirmed active TB cases. ⁺⁺: the total number includes the strains of the national collection and the children's strains.

Sanofi Pasteur MSD, Paris, France), 36 underwent confirmation with the Quantiferon test (Qiagen, Valencia, CA, USA) and eight were positive. Patients with negative Mantoux or IGRA were retested after 2 months, while those who were positive started a follow-up with controls at 3, 6, 12 and 24 months at the Reference TB Centre.

Molecular epidemiology on 24 samples obtained from the culture-positive children unexpectedly demonstrated that the two strains isolated were identical to two strains previously isolated in Italy. The Regional Office for Public Health requested whole genome sequencing (WGS) to achieve a higher level of discrimination. WGS showed almost complete identity between one of the two strains of the national collection and the children's strains.

Overall, the direct costs of similar epidemics are relevant. The figures presented here are conservative because: 1) they do not consider the fact that the hourly cost of healthcare staff (medical doctors in particular) and of several of the relatives involved are higher than the average national cost; 2) other direct costs (transportation, *etc.*) were not added; and 3) indirect costs (patients' and relatives' stress and suffering, and loss of productivity related to the working hours lost, *etc.*), as well as the costs of admission and treatment, have not been calculated.

This experience demonstrates that: 1) TB outbreaks absorb important resources that might otherwise be devoted to other health-related activities; 2) correct clinical management and adequate coordination among prevention, clinical and control health services might prevent TB outbreak occurrence and/or minimise their effects; 3) in large cities, a stable mechanism of coordination is advisable to ensure preparedness to deal adequately with TB outbreaks [9]; and 4) national molecular surveillance is an important tool for outbreak management.



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XDR-TB outbreaks absorb important resources and public health/clinical coordination is essential to minimise effects <http://ow.ly/B5Mqh>

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ERS/WHO Tuberculosis Consilium assistance in extensively drug-resistant tuberculosis

To the Editor:

We read with interest the article by Esposito *et al.* [1], whereby they emphasised the role of the European Respiratory Society (ERS)/World Health Organization (WHO) Tuberculosis (TB) Consilium [2–4] in the management of an extensively drug-resistant (XDR)-TB case. The creation of this e-platform brings