Title

Management of child MDR-TB contacts across countries in the WHO European Region: a survey of current practice

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Management of MDR-TB child contacts in Europe

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Summary

The World Health Organization European Region has one of the highest rates of multidrug-resistant (MDR) tuberculosis (TB) in the world, resulting in many vulnerable children getting exposed each year. Evidence for preventive therapy following MDR-TB exposure is limited and current guidance is conflicting. An online survey was performed to determine clinical practice in this region. Seventy-two clinicians from 25 countries participated. Practices related to screening and decision-making were highly variable. Just over half were providing preventive therapy for MDR-TB-exposed children; the only characteristic associated with provision was practice within the European Union (adjusted odds ratio: 4.07; 95% confidence interval: 1.33-12.5).

Background

Multidrug-resistant (MDR) tuberculosis (TB) is caused by *Mycobacterium tuberculosis* with resistance to isoniazid and rifampicin.[1] In the World Health Organization (WHO) European Region (defined at: http://www.who.int/about/regions/euro/en/) 16% of new TB cases and 48% of retreatment cases were estimated to be MDR-TB in 2015.[2] Over 40,000 cases were notified that year,[2] many of whom had contact with children. Young children are at high risk of progression to TB, including MDR-TB, following exposure.[3,4] MDR-TB treatment is long, expensive and associated with significant adverse events.

There is good evidence for the effectiveness of drug therapy for child contacts of drug-susceptible TB to prevent progression to TB disease.[5] However, the evidence base for the management of child contacts of MDR-TB cases is less robust. National and international guidance is inconsistent and conflicting, with clinicians facing difficult management choices. To date, only limited data exist regarding the current management of paediatric MDR-TB contacts in clinical practice. We therefore aimed to document current practice across different countries in the WHO European Region.

Methods

From March-July 2014 a web-based survey was conducted to explore variations in the management of MDR-TB-exposed children.[6] We developed an online questionnaire in English and Russian capturing the following: respondent characteristics, screening practices, preventive therapy (PT) practices, and follow-up (Supplementary Materials). Participants were asked to define patient groups considered for PT, the PT regimens used and treatment duration. The questionnaire was piloted among five clinical experts within the Paediatric Tuberculosis Network European Trials Group (ptbnet).[7]

A list of clinicians likely to be managing child MDR-TB contacts in the WHO European Region was compiled using the membership lists of ptbnet, the International Union Against Tuberculosis and Lung Disease Childhood TB Working Group, and the Childhood Subgroup of the WHO Stop TB Partnership. Each clinician was sent a personalised email requesting their participation, with the request to forward the invitation to relevant colleagues. Three reminder emails were sent during the study period (Supplementary Materials). To assess factors associated with PT provision, we used a multivariable stepwise logistic regression model. Variables with $p<0.15$ in the univariable analysis were included in the model. Statistical analyses were undertaken using Stata version 14.0 (StataCorp, College Station, U.S.).

Ethics Approval

Under current UK National Research Ethics Service (NRES) regulations, Research Ethics Committee review is not required for research involving healthcare staff recruited as research participants by virtue of their professional role (Governance Arrangements for Research Ethics Committees, paragraph 2.3.13). Participation in the survey was voluntary. Participants were aware that they were participating in research, and that the results may be published.

Results

Of 176 specialists from 44 countries approached, 72 (41%) respondents from 25 countries participated in the survey, including 28 from 6 countries outside the EU/EEA (Figure 1). Of all respondents, 66/72 (92%) had >5 years of experience working with TB; 59/72 (82%) were at senior level and 41/72 (57%) managed ≥3 child MDR-TB contacts a year. To guide the management of the contacts, in addition to clinical history and examination, most respondents used imaging: 42/72 (58%) chest x-rays, 21/72 (29%) both chest x-rays and computer tomography, 4/72 (6%) computer tomography only; the remaining 5/72 (7%) did not routinely use imaging. Nearly half (32/72;44%) stated routinely collecting respiratory specimens in asymptomatic children. Variable combinations of interferon-gamma release assays (IGRA) and skin tests were used to diagnose TB infection: 45/72 (63%) used both IGRA and skin tests, 23/72 (32%) skin tests only, 2/72 (3%) IGRA only and 2/72 (3%) neither. Of the skin tests, the tuberculin skin test (TST) was most frequently used; the Diaskintest (using recombinant CFP-10/ESAT-6; Generium Pharmaceuticals, Moscow) was used by 11 respondents based in the Russian Federation, Belarus, Estonia and Ukraine.

Of all 72 respondents, 42 (58%) stated they were providing PT to MDR-TB-exposed children. For children with evidence of TB infection, 18/42 (43%) clinicians were providing PT if additional risk factors were present (age <2 or <5 years, HIV-infection or immunocompromise); 24/42 (57%) were treating all TB-infected children. For children without evidence of TB infection, the majority of respondents (26/42;62%) were doing follow-up without PT, 12/42 (29%) were providing PT if risk factors were present, and 4/42 (10%) were treating all contacts. For PT, 31/42 (74%) used regimens tailored to the drug susceptibility pattern of the source case's isolate, 9/42 (21%) used standardised regimens (i.e. independent of susceptibility results), and two used variable approaches depending on situation. Approximately half of the respondents (22/42;52%) were using two-drug regimens, fewer used ≥3 drugs (8/42;19%) or monotherapy (10/42;24%), and the remaining two decided on case by case. Variable combinations of ethambutol, pyrazinamide, high-dose isoniazid and levofloxacin/moxifloxacin were the most commonly reported regimens. Most respondents (30/42;71%) stated treating for 6 or 9 months (50% and 21%, respectively). Most clinicians were following

children up for two years or longer regardless of PT being used or not (30/42;71% and 61/72;85% respectively) (Supplementary Materials).

In the multivariable model the only factor associated with the provision of PT was practice within the EU/EEA (vs. outside the EU/EEA) with an adjusted odds ratio of 4.07 (95% CI: 1.33-12.5; p=0.014; Table 1).

Discussion and Conclusions

The results highlight a wide spectrum of practice in the management of children exposed to MDR-TB in countries of the WHO European Region. Over half of clinicians reported using PT with varying indications and drug regimens. Practices regarding PT differed significantly between clinicians based within the EU/EEA and those based outside. The observed difference between EU/EAA and non-EU countries may be due to a more individualised approach to patient management in EU/EAA countries versus a more programmatic approach in non-EU countries with greater reliance on official national guidelines and WHO recommendations.

In addition to marked heterogeneity regarding provision of PT, our data also indicate high variation in investigations performed in children with MDR-TB contact with somewhat surprisingly high proportion of CT scans and collection of respiratory specimens in asymptomatic children. These findings may be a reflection of the paucity of data to guide standard diagnostic approaches in these children, and indicate that clinicians may have a tendency for more 'aggressive' investigation strategies in MDR-TB contacts.

A key component of the WHO End TB Strategy is the identification and treatment of TB infection,[8] with modelling exercises suggesting that without addressing TB infection it will be impossible to eliminate TB globally.[9] This is as true, if not more so, for MDR-TB as it is for drug-susceptible TB, as a smaller proportion of MDR-TB cases are identified and treated, and outcomes are much poorer. At least three funded trials investigating the treatment of MDR-TB contacts are currently underway, but results are not expected for several years. Observational studies suggest that the use of PT for MDR-TB can be safe and effective,[10] but existing guidelines are highly variable. It is therefore not surprising that current practice across the WHO European Region is so inconsistent, and it appears likely that these inconsistencies will persist until international and national guidelines are harmonised.

The survey was limited to clinicians managing child MDR-TB contacts in the WHO European Region who were identified and responded to the survey. Although we contacted a wide range of clinicians and included flexible answer options, it is likely that not all possible practices were captured. The survey only documents

reported practice, rather than capturing individual patient management. Despite these limitations, the results provide insight into the current management of paediatric MDR-TB contacts in EU/EAA and non-EU, countries and highlight the urgent need for stronger evidence to guide clinical decisions.

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Conflicts of Interest

All authors – none.

Authors' contributions:

The study was coordinated by JAS. AT, JAS designed the study. All authors piloted and critically appraised the questionnaire. JAS, AT emailed the questionnaire and JAS collated the results. AT and JS undertook the analysis and drafted the paper with input from MT. All authors contributed to the revision of the manuscript and approved the final version.

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Table 1. Association between respondent characteristics and the provision of preventive therapy (n=72)

		PT given (n)	PT not given (n)	Odds ratio (95% CI)	P value	Adjusted Odds ratio (95% CI)	P value
Experience of treating TB patients	<10 years	13	10	Ref	0.83		
	≥ 10 years	29	20	1.12 (0.41-3.06)			
Specialist TB doctor	No	28	13	Ref	0.05	Ref	0.51
	Yes	14	17	0.38 (0.14-1.04)		0.69 (0.23-2.09)	
Consultant level doctor	No	6	7	Ref	0.33		
	Yes	36	23	1.83 (0.54-6.22)			
Number of MDR-TB child contacts managed per year	<3 per year	19	12	Ref	0.66		
	≥3 per year	23	18	0.81 (0.31-2.10)			
Country of respondent	Outside EU/EEA	10	18	Ref	0.002	Ref	0.014
	Within EU/ EEA	32	12	4.80 (1.59-14.5)		4.07 (1.33-12.5)	

CI: confidence interval; EEA: European Economic Area; MDR-TB: multidrug-resistant tuberculosis; PT: preventive therapy Ref: reference value; TB: tuberculosis.

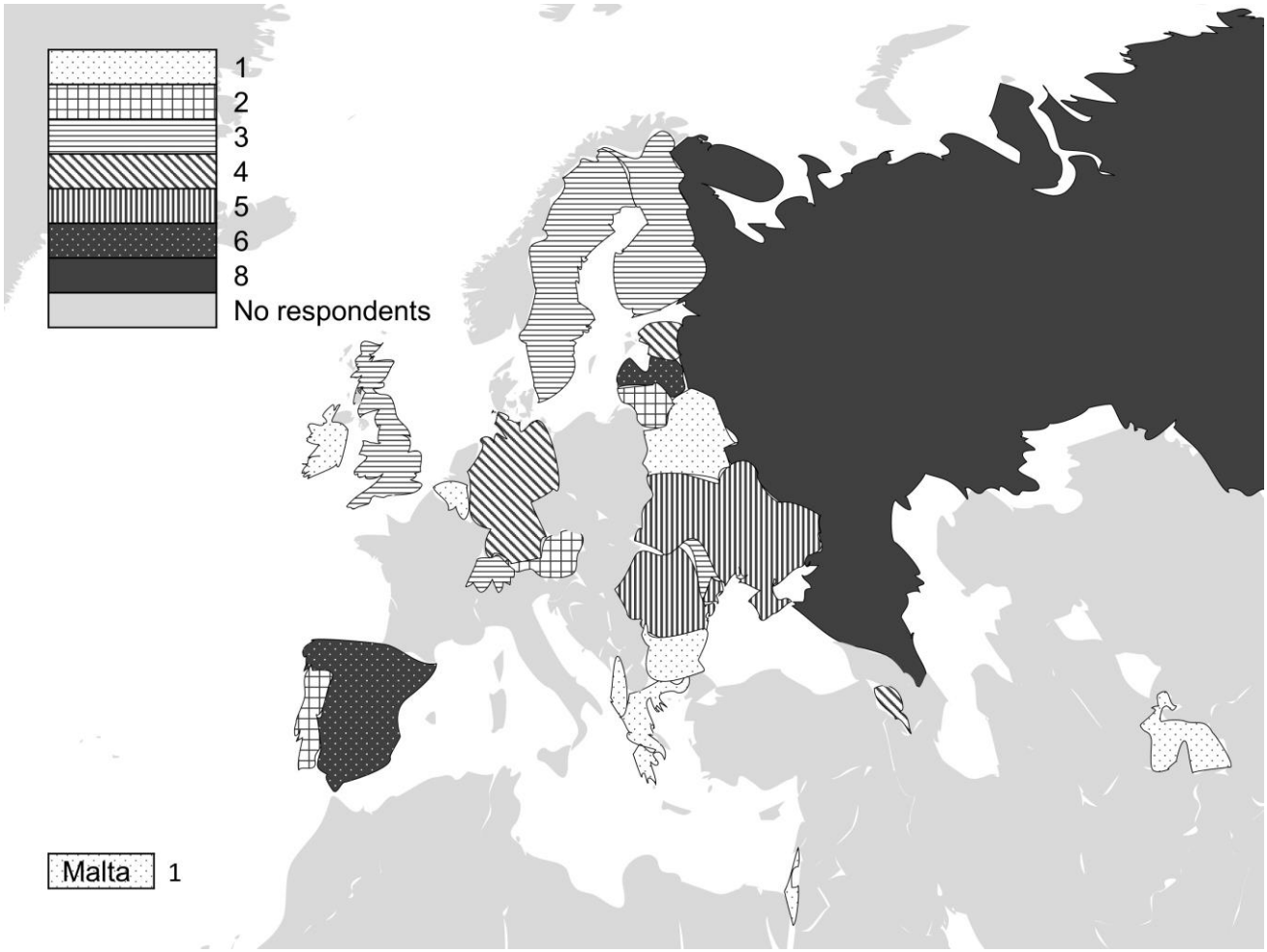

Figure 1

Figure Legend

Figure 1: Location of practice and number of survey respondents in countries in the World Health Organization European Region. Participating countries: Albania, Armenia, Austria, Belarus, Belgium, Bulgaria, Estonia, Finland, Germany, Greece, Ireland, Israel, Latvia, Lithuania, Malta, Moldova, Portugal, Romania, Russian Federation, Spain, Sweden, Switzerland, Tajikistan, UK, Ukraine