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Active case-finding of tuberculosis in Europe. A TBNET (Tuberculosis Network European Trials Group) survey

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Short title: Active case-finding of tuberculosis in Europe.

Abstract

Tuberculosis control depends on successful case-finding and treatment of individuals infected with *Mycobacterium tuberculosis*. Passive case-finding is widely practised: we wanted to ascertain the consensus and possible improvements in active case-finding across Europe.

Recommendations from national guidelines were collected from 50 countries of the WHO-European Region using a standard questionnaire.

Contacts are universally screened for active tuberculosis and latent tuberculosis infection (LTBI). Most countries (>70%) screen those with HIV-infection, prisoners and inpatient contacts. Screening of immigrants is related to their contribution to national rates of tuberculosis. Only 25/50 (50%) advise a request for symptoms in their guidelines. 36/50 (72%) countries recommend sputum examination for those with a persistent cough; 13 countries do not, even if the chest radiograph suggests tuberculosis. Nearly all countries (49/50) use tuberculin skin testing (TST); 27/50 (54%) countries also perform chest radiography irrespective of the TST result. Interpretation of the TST varies widely. All countries use 6-9 months of isoniazid as treatment of LTBI, with an estimated median uptake of 55% (range 5-92.5%).

Symptoms and sputum examination could be used more widely when screening for active tuberculosis. Treatment of LTBI might be better focused by targeted use of interferon-γ release assays. (195 words)

Key words: active case-finding, contacts, Europe, screening, tuberculosis

Introduction

Despite investment to control tuberculosis (TB) in Europe, the incidence of TB has increased from 2000 through 2005 in countries such as Norway, the United Kingdom and Ireland, as well as Romania, Turkey, Macedonia and Bulgaria and all except Kyrgyzstan and Turkmenistan in the eastern part of the World Health Organization (WHO) European Region[1]. Passive case-finding is standard and consistent with the WHO-recommended Stop TB Strategy[2]. Active case-finding includes all methods to identify and then treat those with TB who have not reported to health care systems of their own accord. The aim is to reduce the transmission of TB by screening high risk populations (i.e. those at an increased risk of exposure to TB infection, most notably contacts of infectious cases) and detect and treat active disease earlier than would otherwise occur[3,4]. At the same time, latent tuberculosis infection (LTBI) may be detected and treated, and thereby prevent the later development of active TB.

In 2006 the Tuberculosis Network European Trials Group (TBNET) was established to conduct clinical trials and surveys on TB in Europe. Within the TBNET, this survey was undertaken to determine whether national guidelines or policies within Europe recommend screening of the same high risk groups, the methods used and locations for screening and the nature and estimated uptake of preventive treatment. We expected to see differences related to local epidemiology, such as screening for migrants only in those countries where immigrants represent a significant proportion of cases of TB[5]. Discrepancies between local epidemiology and national guidelines might encourage the redirection of resources to improve the treatment success rate of active TB, currently less

than the World Health Assembly target of 85%. Our aim was to help clinicians and inform national committees creating guidelines of: i) consensus, which would define the minimum standard of active case-finding for TB across Europe; ii) variations, affected by local epidemiology; iii) guidelines of historical or sociological significance, that are no longer necessary and iv) differences in the treatment of LTBI (TLTBI).

Methods

The questionnaire

A questionnaire was developed, consisting of three sections: who should be screened, what screening methods are used and the nature of preventive treatment (see e-file). The questions regarding a positive tuberculin skin test (TST) were based on the American Thoracic Society guidelines interpretation of the available evidence[6], whereby the clinical circumstances determine the cut-off value. Questions included BCG vaccination policy as a check for replies to TST screening. Locations for screening were requested as an indication of the variety of screening programmes available. Questionnaires were in English and Russian; the Russian version was re-translated into English to confirm accuracy of translation.

Data collection

Representatives from each European country were selected on the basis of their official position in their own country's TB programme: all were participants in the TBNET, EuroTB correspondents and/or members of the Tuberculosis Section of the European Respiratory Society (ERS). They were required to have sufficient command of English

or Russian to understand the questionnaire, to have access to their national guidelines and to answer the questionnaire from these. The only personal opinion that was invited was their estimate of the uptake of TLTBI compared to the number eligible under their national guidelines. One year after data collection, the questionnaire was returned to each respondent, who was then required to confirm that they had answered each question from their national guidelines and no personal opinions were expressed, except for the estimate of uptake of TLTBI. Any corrections made at this stage were then incorporated into the final manuscript.

All definitions used (except otherwise mentioned) were derived from WHO documents and ERS guidelines[2, 3,4,7]. Epidemiological data for TB in Europe were taken from the EuroTB website. These included proportion of cases due to foreign-born, most recent cure/completion rate and proportion with concurrent human immunodeficiency virus (HIV) infection.

Results

Respondents

Replies were obtained from 50 out of 53 countries of the WHO European Region (all except Monaco, S. Marino and Andorra, Table 1). Two countries have no national guidelines for TB and each gave an expert opinion on current practice (Greece) or guidelines to be issued in late 2008 (Austria). Five countries (10%) had two respondents: in the first survey, replies from four countries were identical, but one differed by 27/65

items; differences were resolved by referral to a TB expert from that country. Twelve respondents (24%) provided a copy of national guidelines (8 with a translation of the relevant portions in English) which were used to check the accuracy of the replies; no discrepancies were identified. One year later, 8 countries provided modifications when prompted to reassess their responses against national guidelines and exclude personal opinion. In one, there were 9 changes due to revised guidelines (Montenegro), another added missing data (Tajikistan) and the remaining 6 countries made one, two or three changes (two, three and one countries respectively).

Contacts

Six out of 50 (12 %) countries limit screening to contacts of sputum smear-positive pulmonary TB (Table 1). The remaining countries are equally divided between those who screen contacts of just pulmonary or all TB cases.

Immigrants

Twenty-eight (56 %) countries screen immigrants. In 16/50 (32 %) countries, foreign-born persons contribute >40% of all TB and only two in this category (Denmark and Austria) do not carry out screening of new immigrants. In countries with a moderate contribution (11-40%) of immigrants to TB (n=7/50; 14 %), three have no screening programme, two carry out selective screening and two screen all new entrants. Six countries with ≤1% and four countries with <5% of TB due to foreign-born subjects have screening programmes for immigrants.

Other high risk groups

Most countries screen for TB in those who are HIV-positive (42/50, 84%), prisoners (37/50, 74 %) and hospital contacts of inpatients (35/50, 70%). In 32/50 (64%) countries information on HIV co-infection was available: two out of 16 countries with an estimated co-infection rate of >5% and 2/13 countries with a rate of 1-5% have no policy for screening patients with HIV infection for TB. Screening of laboratory staff (33/50 countries, 66%), the homeless (24/50, 48%), teachers (19/50, 38%) and the elderly in long term care facilities (16/50, 32%) occurs less often. Three replies mention screening for TB before the use of anti-tumour necrosis factor treatments and in those whose immunity is depressed for whatever reason. Individual countries also screen intravenous drug users (Belgium, Macedonia, Portugal, Serbia), selected Roma people (Macedonia, Serbia), the mentally ill (Macedonia, Serbia), prostitutes (Austria) and food handlers (Moldova, Poland).

Process of screening

Half of the countries specify questioning for symptoms of TB in those who are screened. Almost three-quarters (36/50, 72 %) ask for a sputum smear where someone reports cough lasting more than 3 weeks. Only one country screens all those at risk of TB with chest radiography alone, while the majority (49/50) use tuberculin skin testing (TST) and 27 of these (55 %) obtain a chest radiograph irrespective of the TST result. Twelve countries of 50 (24 %) have access to mass radiography screening and 7/50 (14 %) recommend its use in guidelines. Thirteen out of 50 (26%) guidelines do not stipulate the need for sputum examination when a chest radiograph suggests TB. Legal provisions to

screen individuals for TB are available in 20/50 (40 %) countries, but we did not invite comments as to how often this was used.

Many guidelines recommend screening for active TB in a larger group than that eligible for TLTBI. Twenty-three of 50 (46%) guidelines recommend TST in the same population that will receive TLTBI if positive (1 for 0-5 yr, 12 for age 0-16 yrs, 5 for those up to 35 years of age and 4 for older age groups), using other tests to exclude active TB. The median estimated uptake of TLTBI in these countries is 55% (data available for 17 countries, range 10-90%), but lower (40%) in countries where TST is used indiscriminately (data available for 14 countries, range 5-92.5%).

Interpretation of the TST varies widely across the European Region (Table 2). Twenty-eight out of 50 (56 %) countries do not modify interpretation of the TST according to the presence or absence of a BCG scar; two comment that BCG vaccination is compulsory and five have no BCG programme. In the latter five countries, immigration contributes significantly to the incidence of tuberculosis (median 44%, range 9-60%). Most countries set a positive TST for those with concurrent HIV infection (70%) and BCG-negative contacts (17/17 where mentioned) at 5 mm. Ten millimetres of induration was the commonest cut-off value for healthy subjects at risk of tuberculosis (25/47, 54%), immigrants (20/49, 41%) and BCG-positive contacts (9/17, 53% where specified).

All countries offer TLTBI consisting of either 6 or 9 months of isoniazid. Thirteen out of 50 (26 %) countries offer alternative regimens in specified circumstances: 11 offer 3

months of rifampicin and isoniazid, 8 four months of rifampicin and 4 two months of rifampicin and pyrazinamide. One country (Portugal) permits the use of 2 months of rifampicin, isoniazid and pyrazinamide.

TLTBI is required in 26/50 (52 %) countries, while radiographic follow-up is recorded as an option in 27/50 (54 %) countries. Most countries will recommend TLTBI for HIV-positive contacts of patients with sputum smear-positive pulmonary TB (40/50, 80 %) and for babies born to mothers with pulmonary TB (42/50, 84 % – one only if the mother is not on treatment at the time of delivery).

Discussion

This study is the first survey of national guidelines comparing screening for active and latent TB across the WHO European region. There is a general consensus which advocates screening of TB contacts and offering treatment for individuals with LTBI. Discrepancies between a low detection rate and excessive screening suggest that some programmes could be improved.

Priorities in contact tracing

The two main reasons for contact tracing are identification of active cases and those infected who are at risk of developing active TB later in life. Most patients with active TB have symptoms like cough, fever, night sweats and weight loss[8], yet only half of European countries recommend asking for symptoms of active TB in those who are screened. Indeed, a productive cough for more than three weeks can be used as a simple

tool to refine the investigation of those with suspected contagious TB[9,10]. The evidence supports both screening of contacts of only pulmonary (especially sputum smear-positive, which is the most contagious form) TB[11,12] and of non-pulmonary TB, the latter on the grounds that they represent an especially high risk group[12,13,14,15,16]. Indeed, DNA fingerprinting has shown that strains of *Mycobacterium tuberculosis* found in contacts may differ from, rather than be the same as the strain obtained from the index case[17,18].

The recognition of LTBI before developing TB is uncertain. A positive TST is most frequent in contacts of those with smear-positive TB[11,19]. Even when the index has non-pulmonary TB, a positive TST is still more common than in any of the other high risk groups screened[12]. We would therefore advocate that after effective treatment of active TB is established, contacts of all TB patients are screened before any other high risk group.

Other high risk groups

Active screening is expensive and indiscriminate screening is inefficient[5]. Several countries had high TB incidence and poor treatment success rates despite extensive screening – higher efficacy and lower cost programmes seem feasible[4,20]. However, mathematical models suggest that active case-finding can have a significant impact on the incidence of TB[21], especially in those co-infected with HIV[22]. There is a general consensus supporting the screening of patients with HIV infection for TB[1,7,12,23]. TLTBI reduces the risk of active tuberculosis in HIV-positive individuals with positive TSTs, in countries with high[24] and low[25] incidences of TB, although the absolute number of

prevented cases in low incidence countries is small. This policy is not yet implemented widely, especially in countries from the Eastern European Region where the TB/HIV co-infection rate is increasing. The newer T-cell interferon-γ release assays (TIGRAs) may be more helpful than the TST in detecting LTBI in individuals infected with HIV[26].

A survey of several European countries has confirmed that the prevalence of TB in prisons is nearly 100 times that of the general population[27], especially in those with HIV infection[28]. The risk of TB in intravenous drug-users, prostitutes and those with mental illness is also associated with concurrent HIV infection[29,30,31]. Tuberculosis is spread by aerosols and not by food; the inclusion of food handlers in TB guidelines is therefore an historical anomaly[32].

The problem of the effectiveness of active case-finding has particularly exercised national experts in regard to immigrant screening. Whilst immigration can account for a significant percentage of a country's TB notifications, the denominator can be so large that the likelihood of finding a case of TB for an individual clinic or entry point to the country can be vanishingly small[33]. However, the yield may vary depending on the subgroup of immigrants screened. For example, in Belgium, the incidence of tuberculosis was significantly higher in asylum seekers than in other immigrants[34]. In Israel, Ethiopians and those from the former Soviet Union have more intensive screening[35]. Many countries have adopted a selective screening policy based on incidence of TB in the country of origin (Table 1). Most immigrants are healthy when they arrive and therefore screening by chest radiography is of little benefit. National surveys have

shown that most immigrants present with active TB >5 years after arrival[36,37]. Programmes with continued screening of immigrants, even on a voluntary basis, can be effective[38], but still most transmission is from individuals who do not attend for screening[39]. Many have argued that the detection of LTBI can make screening for TB among immigrants cost-effective, but only if TLTBI is completed and set-up and administrative costs are excluded[33]. Where multi-drug resistant (MDR-) and extensively drug resistant (XDR-) TB is likely[40,41] , screening can be cost-effective in treating active disease and permitting follow-up to recognize early the development of drug-resistant TB[42]. Selection of immigrants most likely to have TB (e.g. in deprived city areas)[43] or to adhere to TLTBI[44] may be more effective than general screening.

Latent tuberculosis infection (LTBI)

The average number of secondary TB cases acquired from a primary case is affected most by those who develop tuberculosis after a latent period[45]. TLTBI holds the greatest benefit in controlling TB after treatment of active, infectious cases. However, few contacts with positive TSTs are offered and even fewer adhere to TLTBI[46].

TST is widely undertaken, but surveys to define the best cut-off point to discriminate between those most likely to develop disease and those in whom LTBI is unlikely are rare in Europe[47], the best such survey being from Mexico[48]. There is general consensus that a TST induration diameter of >5 mm should be the cut-off value for those without BCG vaccination or with HIV co-infection (Table 2). However, in HIV infection anergy may be an all-or-none phenomenon, so that the size of induration is not helpful[49]. Most

countries considered TST >10 mm positive in those with a BCG vaccination, but a meta-analysis suggested that 15 mm might be a better cut-off[50].

TIGRA and LTBI

Large longitudinal studies of TIGRAs have yet to define their role in assessing who will benefit from TLTBI. However, contacts with a positive TIGRA may have a higher risk of developing TB than contacts with a positive TST[51]. As merely 1.7% of tuberculin-positive contacts develop active TB[52], the UK NICE guidelines limit those offered TLTBI by requiring a TST of ≥15 mm and a positive TIGRA[12]. Transient TIGRA responses have been observed in TST-negative contacts, suggesting the possibility of resolving acute infection[53]. The use of a TIGRA should be prioritised to those most likely to benefit from treatment of LTBI (contacts <16 years, HIV co-infected individuals and those receiving anti-TNF treatment)[54].

TLTBI

Treatment of individuals with TST conversion is cost-effective and is important to decrease the global incidence of TB[54]. However, completion rates are unsatisfactory in the countries that were surveyed and the relative benefit of TLTBI is very low (to prevent one case of active TB, 72 subjects (95% confidence intervals 50-143) need to be treated[52], although this is comparable to the benefit of secondary prevention in myocardial infarction[55]). Adherence is often as low as 11-30%[33,37,46]. While we cannot argue against the individual benefit of completing a course of TLTBI, the public health benefit of the strategy relies critically on large acceptance and completion rates. Clearly,

if TLTBI is not going to be undertaken (e.g. where the risks from drug-induced hepatitis outweigh the benefits or indeed the individual does not agree to take any treatment after the risks have been explained clearly to them, unless follow-up is important as in the instance of contact with drug-resistant TB), then TST or TIGRA need not be done and active TB should merely be excluded (e.g. by symptoms and sputum smear) at the first visit and by appropriate follow-up.

Conclusion

The minimum standard for active case-finding is screening all contacts of patients with sputum smear-positive TB. In addition, screening contacts of those with TB but without a positive sputum smear and individuals with HIV infection is broadly supported. To improve the detection of active TB, symptoms should be sought and sputum sent for analysis from all those with an abnormal chest radiography suggestive of TB. Many guidelines could be improved by using TIGRA to confirm LTBI and limit testing to those who would agree to be treated. Selective screening, especially of immigrants, should be guided by local epidemiology. While a 6-9 month regimen of isoniazid monotherapy is widely recommended for TLTBI in Europe, *Mycobacterium tuberculosis* resistance to isoniazid is increasing and alternative well tolerated short term regimens need to be explored. (2935 words)

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Table 1. Who is screened for tuberculosis?

Geographic area Country	Incidence per 100,000 pop. in 2005	Contacts of	% of TB among foreign born	New immigrants†
Georgia	144.1	S+PTB	0#	None
Ukraine	93.3	S+PTB	0#	None
Turkey	28.1	S+PTB	0#	None
Italy*	7.1	S+PTB	44	>40 per 100,000
Finland*	6.9	S+PTB	10	Asylum seekers & immigrants from the former Soviet Union
Iceland	3.7	S+PTB	64	Non-EU
Romania*	135.2	Pulmonary	0	None
Tajikistan	109.8	Pulmonary	0#	>40 per 100,000
Uzbekistan	108.6	Pulmonary	0#	None
Armenia	77.0	Pulmonary	0#	None
Turkmenistan	68.1	Pulmonary	0#	None
Portugal*	33.7	Pulmonary	12	None
Macedonia, F.Y.R.	32.3	Pulmonary	0#	None
Montenegro	27.3	Pulmonary	1#	>40 per 100,000
Croatia	25.1	Pulmonary	9	None
Albania	17.3	Pulmonary	0#	None
Slovakia*	14.1	Pulmonary	4	Asylum seekers
Slovenia*	14.1	Pulmonary	17	>40 per 100,000
Austria*	11.6	Pulmonary	44#	None
Ireland*	11.1	Pulmonary	31	None
Belgium*	11.0	Pulmonary	51#	>50 per 100,000
France*	8.6	Pulmonary & children	45	>40 per 100,000
Switzerland	7.8	Pulmonary	60	Asylum seekers; school children from >50 per 100,000
Germany*	7.3	Pulmonary	43	Asylum seekers
Greece*	6.9	Pulmonary	29	All
Norway	6.3	Pulmonary	78	Non-western Europe
Sweden*	6.3	Pulmonary	73	>100 per 100,000
Malta*	5.7	Pulmonary and child extrapulmonary	74#	>25 per 100,000
Kazakhstan	210.4	All TB	0#	All
Kyrgyzstan	128.5	All TB	0#	None

Moldova	149.3	All TB	1#	None
Russian Federation	109.0	All TB	1#	All
Azerbaijan	94.2	All TB	0#	None
Belarus	65.2	All TB	0#	All
Lithuania*	75.0	All TB	3	All
Latvia*	62.5	All TB	6	All
Bosnia & Herzegovena	55.3	All TB	0#	None
Bulgaria*	42.7	All TB	0#	All
Estonia*	39.0	All TB	16	None
Serbia	31.8	All TB	2#	>40 per 100,000
Poland*	24.1	All TB	0#	None
Hungary*	20.0	All TB	3	None
Spain*	18.2	All TB	19	All
United Kingdom*	14.2	All TB	64	>40 per 100,000
Czech Republic*	9.9	All TB	13	Asylum seekers
Luxemburg*	8.0	All TB	68	Non-EU
Denmark*	7.8	All TB	61	None
Netherlands*	7.1	All TB	66	High risk
Israel	6.0	All TB	82	>100 per 100,000
Cyprus*	4.4	All TB	68	Developing countries

TB: tuberculosis

S+PTB: sputum smear-positive pulmonary tuberculosis

*European Union member

#citizenship rather than place of birth

† where rates are shown immigrant screening is mandated/recommended if recent TB notification rates in the country of origin exceed this threshold.

Table 2. Positive tuberculin skin tests as specified in national guidelines for different screened groups of individuals at risk of tuberculosis.

Group	No. of countries which screen this group	Number of countries with:			
		Tuberculin cut-off value			No guideline
		5 mm	10 mm	15mm	
Contacts					
BCG status unspecified	28	12	10	3	3
BCG-negative	22	21	1	0	0
BCG-positive	22	0	14	8	0
Immigrants	27	1	20	1	5
Healthy persons at risk of tuberculosis	49	2	25	2	20
HIV-positive	40	35	1	2	2