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Infection control, genetic assessment of drug resistance and drug susceptibility testing in the current management of multidrug/extensively-resistant tuberculosis (M/XDR-TB) in Europe: A tuberculosis network European Trialsgroup (TBNET) study

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ABSTRACT

Aim: Europe has the highest documented caseload and greatest increase in multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) of all World Health Organization (WHO) regions. This survey examines how recommendations for M/XDR-TB management are being implemented.
Methods: TBNET is a pan-European clinical research collaboration for tuberculosis. An email survey of TBNET members collected data in relation to infection control, access to molecular tests and basic microbiology with drug sensitivity testing.
Results: 68/105 responses gave valid information and were from countries within the WHO European Region. Inpatient beds matched demand, but single rooms with negative pressure were only available in low incidence countries; ultraviolet decontamination was used in 5 sites, all with >10 patients with M/XDR-TB per year. Molecular tests for mutations associated with rifampicin resistance were widely available (88%), even in lower income and especially in high incidence countries. Molecular tests for other first line and second line drugs were less accessible (76 and 52% respectively). A third of physicians considered that drug susceptibility results were delayed by > 2 months.
Conclusion: Infection control for inpatients with M/XDR-TB remains a problem in high incidence countries. Rifampicin resistance is readily detected, but tests to plan regimens tailored to the drug susceptibilities of the strain of *Mycobacterium tuberculosis* are significantly delayed, allowing for further drug resistance to develop.

1. Introduction

The World Health Organization (WHO) 2015 report observed that the European Region had the highest caseload of documented patients and greatest increase in multidrug/extensively drug-resistant tuberculosis (M/XDR-TB) [1]. TBNET reported on the outcome of a review of the management of M/XDR-TB in 2010, noting that there were significant departures from the International Standards of Care for Tuberculosis and their European adaptation [2]. Most notably, there were deficiencies in recording patient outcomes, infection control [3], bacteriological analysis and laboratory support, as well as regimen selection and treatment duration. TBNET has also noted the problems of availability and cost of drugs in the management of M/XDR-TB [4].

In a consensus statement regarding the management of M/XDR-TB, it was identified that infection control measures should include a prompt diagnosis and isolation of patients in a well-ventilated single room with upper room ultraviolet germicidal irradiation [5]. Prompt diagnosis requires phenotypic drug susceptibility testing (DST) and genotypic tests for rifampicin resistance in those at risk of multidrug-resistant tuberculosis (MDR-TB), with further molecular testing for those with rifampicin resistance, especially for resistance to fluoroquinolones or injectable drugs. This survey aims to describe the current situation with regard to these basic recommendations.

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2. Methods

2.1. Study design

A cross-sectional survey.

2.2. Setting

Any hospital within the WHO European Region where physicians manage tuberculosis (TB).

2.3. Participants

The Tuberculosis Network European Trialsgroup (TBNET) has >650 members who are engaged in the management of tuberculosis. From October 2015 to January 2016, a standardized questionnaire was sent to TBNET members by e-mail to collect information about their management of patients with M/XDR-TB. Reminders were sent at weekly intervals after the first communication until more than 100 replies had been obtained. Members who were from the same hospital were considered to give a single answer and, where there were any differences in information, were contacted to confirm which answer was correct.

2.4. Variables

The questionnaire consisted of 7 identifiers, a confirmation of consent to participate in the study, 10 questions regarding inpatient and outpatient facilities, 19 questions regarding access to microbiology laboratories and 8 questions regarding participation in clinical research. The full questionnaire is available on request; included in the e-supplement are the questions relevant to this publication.

2.5. Bias

The title of the survey indicated an interest in MDR-TB. The responders were therefore less likely to reply if they had not seen patients with drug-resistant TB. Some replies were subjective and in particular all replies regarding the frequency of drug sensitivity testing results, which were received more than two months after the start of treatment, were rechecked by repeated email correspondence.

2.6. Statistical methods

Frequencies were compared using a chi-squared test and if a cell had <5, then Yates' correction [6] was employed, using the GraphPad free software (https://graphpad.com/quickcalcs/contingency1.cfm). High income (>$12,475 pa) and middle income ($1026-12,475) were based on the 2015 Gross National Income per capita from data collated by the World Bank website (http://data.worldbank.org/indicator/).

2.7. Ethics

The study did not require ethical approval after consultation with the Health Research Authority decision tool and Integrated Research Application System websites.

3. Results

3.1. Description of the sample

From 650 members, 105 replies were received. The data included 13 duplicates and 2 triplicates and replies without any information apart from the initial identification (Fig. 1). There were therefore 79 valid responses, of which 68 were from within the WHO European Region.

Twenty-four countries gave replies, of which 9 were from a single site, several of which were the major referral centres for that country (e.g. Belarus). The remainder had 2 or more site responders (Table 1; Fig. 2). Five countries had included all notified MDR-TB cases for 2015 and a further five covered >72% of all cases. If countries with a population <1 million and those with no MDR-TB cases per year were excluded, the significant omissions for the WHO Region were Bulgaria, Estonia, Hungary, Lithuania, Armenia, Azerbaijan and Georgia and the Central Asian republics Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. However, the survey covered countries having 96% of all MDR-TB cases within the WHO European Region, excluding the Central Asian republics. In terms of cases of MDR-TB, the survey participants had seen 15% of the recorded number for 2015 in the WHO region, excluding the Central Asian republics and 16% of those countries with a response.

Ten of the 68 responding sites had no MDR-TB cases in the period covered by the survey (Fig. 2). However, their responses indicate the preparedness for such cases. In one case, the responder had responsibility for MDR-TB, but had apparently not supervised their care (DC, Moldova). In other instances, another site in the same city could provide data, apart from Denmark, where there were few cases of MDR-TB.

In most cases, the responder was the head of department (57/68, 84%). The majority were pulmonary physicians (40/68, 59%), but there were significant contributions from infectious diseases physicians 20/68, 30%) and paediatricians (4/68, 6%). Specialist or university hospitals provided most responses (54/68, 80%), but some considered themselves district general hospitals even though they were the highest tier of health care for their area (e.g. Mathilde Jachym, at the national MDR-TB centre outside Paris). This is evidenced by the data in Table 1, noting that the percentage of the national figures for MDR-TB was generally high.

In order to assess consistency, replies were examined in detail. Repeated replies either gave the same information or only one reply contained complete information. The hospital with four responses differed according to the personal responsibilities of the individual physicians for inpatient facilities; the junior doctor's answers on this occasion were at variance with the other three physicians' and were therefore discarded. With regard to countries where more than one hospital replied (Table 1), inpatient, outpatient and local laboratory facilities differed, as would be expected, but regional and supra-regional laboratory access was consistent.

3.2. Facilities for treating M/XDR-TB

Five responding hospitals, located in Austria, Greece, Moldova and two in Spain had no inpatient facilities for treating patients with M/XDR-TB. The physicians indicated that inpatient facilities were accessed by referral to another specialist unit.

Table 2 shows the range of inpatient beds and the availability of different measures for infection control. Most notably, as the incidence of MDR-TB increases, the number of single rooms fails to follow accordingly (Fig. 3A and B). If there is any infection control in these hospitals managing large numbers of M/XDR-TB, this is through the occasional use of UV light irradiation, but single room isolation and negative pressure are rarely available.

Negative pressure was frequently used in multi-occupancy rooms in hospitals with more than 10 M/XDR-TB patients a year (Fig. 2C). Infectious disease physicians had greater access to negative pressure single rooms (15/19) compared to pulmonologists (16/34; χ^2 with Yates' correction $P = 0.049$).