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Multidrug-resistant tuberculosis: eight years of surveillance in France

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Multidrug-resistant tuberculosis: eight years of surveillance in France. J. Robert, D. Trystram, C. Truffot-Pernot, V. Jarlier. ©ERS Journals Ltd 2003.

ABSTRACT: The aim of this study was to evaluate the annual prevalence of multidrug-resistant tuberculosis (MDRTB) and to describe the characteristics of the patients with MDRTB in France.

Annual questionnaire surveys from 1992–1999 were mailed to all French microbiological laboratories performing mycobacterial cultures. A total of 264 distinct patients were reported to the National Reference Centre for Resistance of Mycobacteria to Antituberculosis Drugs during the 8-yr surveillance period resulting in a mean annual prevalence of MDRTB of 0.6%.

A mean of 16% of the MDRTB patients were reported over several subsequent years. The majority of patients were male (69.7%), foreign-born (55.7%), with a previous history of treatment (65.9%), and pulmonary involvement (92.8%) with smear-positive results (59.1%). Human immunodeficiency virus (HIV) coinfection was present in 20.8% of the patients. Strains were resistant only to isoniazid and rifampin in 37.9% of the cases, and additional resistance to both streptomycin and ethambutol was present in 25.8%. HIV coinfection and female status were statistically associated with primary resistance, whereas smear-positive results were associated with secondary resistance. Foreign-birth and smear-positive results were associated with a chronic status.

The prevalence of multidrug-resistant tuberculosis is low in France (<1%). However, a substantial proportion of patients remain positive for several years, suggesting nonoptimal management. Therefore, as recommended by the World Health Organization, a few reference teams, working in collaboration with national associations of physicians and microbiologists, should be established to improve the outcome of multidrug-resistant tuberculosis.

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Acquisition of resistance to antituberculosis agents in *Mycobacterium tuberculosis* was described soon after their clinical use. In 1999, the prevalence of resistance to any of the first-line drugs (rifampin (RIF), isoniazid (INH), ethambutol (EMB) and streptomycin (SM)) reached >30% among new cases of tuberculosis (TB) in several countries (Estonia, Thailand), and >40–50% among previously treated cases (China, Estonia, Italy) [1]. Multidrug-resistant tuberculosis (MDRTB), defined as resistance of *M. tuberculosis* to at least INH and RIF, is especially worrisome because of its potential impact on the control of TB. Indeed, INH and RIF are the two major drugs in the treatment of TB, and resistance to both of them and particularly to RIF represents a major risk factor for treatment failure [2, 3]. MDRTB has been reported in most parts of the world but it is more prevalent in countries where TB and human immunodeficiency virus (HIV) coinfection are endemic [4]. In the 1980s, because of a steady decline of the total number of cases, TB and especially MDRTB was abandoned as a public health priority in industrialised countries. TB became the focus of attention again in the early 1990s because of outbreaks of MDRTB in healthcare and correctional facilities in the USA, and because of a stop in the downward trend in TB prevalence in some industrialised countries [5–9].

In France, surveillance of drug resistance is not linked to the case notification system. National surveillance of TB drug resistance was discontinued in the early 1970s [10] but resumed in the 1990s. Surveillance of MDRTB was established in France at the national level in 1992 in order to evaluate the annual prevalence of MDRTB, and to describe the characteristics of patients with MDRTB. The present report gives the results of the surveillance for an 8-yr period, from the beginning of the programme in 1992, up to 1999.

Methods

Definitions

MDRTB was defined as resistance of *M. tuberculosis* to at least INH and RIF. According to previous history of treatment [11] at the time of MDRTB diagnosis, patients were classified into three groups: 1) previously untreated patients, or new patients, who had never taken any anti-TB drug or had taken anti-TB drugs for <4 weeks; 2) previously treated patients who had taken anti-TB drugs for ⩾4 weeks; and 3) unknown, all patients for whom the treatment history was unknown or doubtful. Chronic status was defined according to the World Health Organization (WHO). Foreign status was defined as place of birth.

Antimicrobial susceptibility tests to first-line drugs were initially performed by reporting laboratories. Confirmation of multidrug resistance and susceptibility tests to second-line drugs were performed on request by the National

Reference Centre for Resistance of Mycobacteria to Antituberculosis Drugs (NRC-RAD) using the proportion method of Löwenstein-Jensen.

Surveillance

Surveys were conducted annually from 1992–1999 by standardised questionnaires sent by mail to a network of laboratories covering the entire French territory and including the hospital laboratories, Pasteur Institutes, and private laboratories performing mycobacteria cultures. These laboratories have been extracted from the national roster of all French laboratories performing medical analysis.

The total number of patients with culture yielding *M. tuberculosis* and, among them, the number of patients harbouring multidrug-resistant strains were recorded from each laboratory. For each patient with MDRTB, additional data were collected by mail or by phone by the microbiologist and the physician in charge of the patient. Data included age, sex, place of birth, site of infection, HIV coinfection, date of first diagnosis of MDRTB, smear result and susceptibility to first-line drugs. Duplicate reports were identified throughout the surveillance period by using initials of first and last name, date and place of birth. No additional information were recorded for non-MDRTB patients.

Data were entered into computer and analysed using Epi-Info 6 software (Centers for Disease Control, Atlanta, GA, USA; WHO, Geneva, Switzerland). The Chi-squared test or Fisher′s exact test was used to compare proportions. The Chi-squared test for linear trend was used to assess trends over time. Logistic regression was used for multivariate analysis.

Results

Response rate

During the 8 yrs of surveillance, the number of laboratories reporting cases to the NRC-RAD decreased from 363 to 338. The decrease was mainly due to discontinuation of mycobacterial activities by some laboratories or to fusion of laboratories. In all cases, the new laboratories resulting from these fusions participated in the network. The mean response rate to the questionnaire was 97% during the 8-yr period (range 95–99%). Missing data always originated from laboratories reporting less than five patients per year.

Annual prevalence and incidence rates

The number of MDRTB patients reported each year ranged 26–58 accounting for a total of 328 patients. The annual prevalence of MDRTB among the total number of patients with culture-positive TB ranged 0.4–0.9% (table 1).

A substantial proportion (mean 16%) of the MDRTB patients were reported during several subsequent years, *i.e.* chronic patients (table 2). Consequently, the total number of distinct patients with MDRTB was 264 during the 8-yr surveillance period and the mean annual incidence rate (distinct patients) was <0.5%. At least one case of MDRTB was reported in 22 of the 23 regions of France (including the overseas countries) during the 8-yr period. One-half of the 264 patients were reported in the Paris area (Ile de France region), compared with nine other regions reporting one or two cases each.

Table 2. – Year of the first report of multidrug-resistant (MDR) tuberculosis patients, 1992–1999

Year	Total MDR patients n	Cases reported for the first time n							
		1992	1993	1994	1995	1996	1997	1998	1999
1992	48	48							
1993	40	7	33						
1994	58	8	6	44					
1995	40	3	7	4	26				
1996	29	1	0	3	3	22			
1997	26	2	1	1	0	4	18		
1998	39	1	0	2	1	1	3	31	
1999	48	1	0	0	1	0	0	2	44
Total	328								

Characteristics of multidrug-resistant tuberculosis cases

The characteristics of the 264 distinct MDRTB patients reported during the 8-yr surveillance period are shown in table 3. The majority of patients were male (69.7%), and more than one-half were foreign-born (55.7%). Among the latter group, 27.9% were born in Northern Africa, 37.4% in sub-Saharan Africa, 16.3% in Asia, 5.5% in Southern America, and 12.9% in Europe. Moreover, 30.6% of foreign-born patients came to France especially for management of their MDRTB. Patients aged 25–44 yrs represented 54.9% of all cases and HIV-coinfected patients represented 20.8%. HIV coinfection was more frequent among males (p=0.02), but not more frequent among foreign-born patients (p=0.69). Foreign-born patients were younger than French-born patients (median age 34 yrs *versus* 49 yrs, respectively, p<0.01). However, there was no difference regarding sex.

The site of TB was only pulmonary in 78.4% of the cases, only extrapulmonary in 7.2% and both pulmonary and extrapulmonary in 14.4%. Extrapulmonary TB, either alone or associated with pulmonary TB, was associated with HIV coinfection (45% in HIV-coinfected and 15% in non-HIV-coinfected patients, p<0.01). The smear result was positive in 59.1% of the patients. Smear-positive results were slightly more frequent among HIV-coinfected patients (70% *versus* 60%) but the difference was not statistically significant (p=0.21).

Considering the first-line drugs (INH, RMP, EMB and SM), 37.9% of the MDR strains were resistant only to INH

Table 1. – Number of multidrug-resistant (MDR) tuberculosis (TB) and culture-positive TB cases, 1992–1999

	Year of report							
	1992	1993	1994	1995	1996	1997	1998	1999
MDR	48	40	58	40	29	26	39	48
Total culture-positive	8441	8539	7751	7119	6441	5917	5766	5597
MDR prevalence	0.6 (0.4–0.7)	0.5 (0.3–0.6)	0.7 (0.5–0.9)	0.6 (0.4–0.8)	0.5 (0.3–0.6)	0.4 (0.3–0.6)	0.7 (0.5–0.9)	0.9 (0.6–1.1)

Data are presented as n or % (95% confidence interval).

Table 3. – Characteristics of the 264 patients with multidrug-resistant tuberculosis reported from 1992–1999

Characteristic	Total	Previously treated patient		Patient reported more than once[#]	
		Yes	No	Yes	No
Total cases	264 (100)	174 (100)	88 (100)	42 (100)	222 (100)
15–24 yrs	20 (7.6)	12 (6.9)	8 (9.1)	3 (7.1)	17 (7.7)
25–34 yrs	78 (29.5)	44 (25.3)	34 (38.6)	11 (26.2)	67 (30.2)
35–44 yrs	67 (25.4)	46 (26.4)	20 (22.7)	13 (31.0)	54 (24.3)
45–64 yrs	61 (23.1)	44 (25.3)	16 (18.2)	12 (28.6)	49 (22.1)
⩾65 yrs	38 (14.4)	28 (16.1)	10 (11.4)	3 (7.1)	35 (15.8)
Male	184 (69.7)	128 (73.6)	54 (61.4)	26 (61.9)	158 (71.2)
Female	80 (30.3)	46 (26.4)	34 (38.6)	16 (38.1)	64 (28.8)
Country of birth					
France	115 (43.6)	76 (43.7)	39 (44.3)	14 (33.3)	101 (45.5)
Other country	147 (55.7)	96 (55.2)	49 (55.7)	28 (66.7)	119 (53.6)
Unknown	2 (0.8)	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.9)
Place of residence					
France	218 (82.6)	142 (81.6)	76 (86.4)	36 (85.7)	182 (82.0)
Other country	45 (17.0)	31 (17.8)	12 (13.6)	6 (14.3)	39 (17.5)
Unknown	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)
HIV-positive	55 (20.8)	29 (16.7)	24 (27.3)	5 (11.9)	50 (22.5)
HIV-negative	169 (62.9)	114 (65.5)	55 (62.5)	33 (78.6)	136 (61.3)
HIV unknown	40 (16.3)	31 (17.8)	9 (10.2)	4 (9.5)	36 (16.2)
Site of disease					
Pulmonary	207 (78.4)	144 (82.8)	61 (69.3)	36 (85.7)	171 (77.0)
Extrapulmonary	19 (7.2)	10 (5.7)	9 (10.2)	5 (11.9)	33 (14.9)
Both	38 (14.4)	20 (11.5)	18 (20.5)	1 (2.4)	18 (8.1)
Microscopy					
Positive	156 (59.1)	110 (63.2)	45 (51.1)	29 (69.0)	127 (57.2)
Negative	94 (35.6)	52 (29.9)	41 (46.6)	10 (23.8)	84 (37.8)
Unknown	14 (5.3)	12 (6.9)	2 (2.3)	3 (7.1)	11 (5.0)
Resistance to other first-line drugs					
None	100 (37.9)	70 (40.2)	30 (34.1)	15 (35.7)	85 (38.3)
SM alone	78 (29.5)	50 (28.7)	28 (31.8)	10 (23.8)	68 (30.6)
EMB alone	18 (6.8)	10 (5.7)	8 (9.1)	4 (9.5)	14 (6.3)
SM and EMB	68 (25.8)	44 (25.3)	22 (25.0)	13 (31.0)	55 (24.8)

Data are presented as n (%). [#]: patient reported more than once (at least for 2 yrs) during the 1994–1998 period. All information were missing for one case in 1999 and two cases had no information on history of treatment. HIV: human immunodeficiency virus; SM: streptomycin; EMB: ethambutol.

and RMP. In addition, 29.5% of the strains were resistant to SM, 6.8% to EMB, and 25.8% to both SM and EMB. Resistance to both SM and EMB was less frequent among French-born patients than among foreign-born patients (29% *versus* 50%, p<0.01), even after stratification of previous history of treatment.

The results of the *in vitro* susceptibility tests were considered separately for pyrazinamide because of uncertainties of interpretation [12]. Indeed, unequivocal results were available for only 154 strains, 39 (25.3%) being reported as resistant.

Susceptibility data to second-line drugs were not reported for all strains. Susceptibility rates to these drugs were 89.6% to kanamycin or amikacin (112 of 125 strains), 94.1 to capreomycin (96 of 102 strains), 67.5% to thioamides (81 of 120 strains), 90.5% to fluoroquinolones (either ofloxacin or sparfloxacin, 114 of 126 strains), 64% to tiacetazone (64 of 100 strains), 95.7% to cycloserine (111 of 116 strains), and 92.2 to para-aminosalicylic acid (94 of 102 strains).

Among the 264 patients, 174 (65.9%) had been previously treated, and 88 (33.3%) were classified as new patients (previous history of treatment was unknown for two patients). Compared with new patients, previously treated patients were more likely to be male (73.6% *versus* 61.4%, p=0.04), to have only pulmonary TB (82.8% *versus* 69.3%, p=0.02), and to be smear-positive (63.2% *versus* 51.1%, p=0.02). In addition, previously treated patients were slightly older than new patients (median age 39 yrs *versus* 35 yrs, p=0.03). In contrast, new patients were more likely to be HIV coinfected (27.3% *versus* 16.7%, p=0.09). New and previously treated patients were not statistically different regarding foreign-born status and place of residence.

Multivariate analysis

Country of birth, age, sex, HIV coinfection, site of TB and smear result were introduced in a backward logistic regression model to assess characteristics independently associated to primary or secondary multidrug resistance. HIV coinfection (odds ratio (OR) 2.02, 95% confidence interval 1.04–3.95) and female status (2.01, 1.12–3.62) were statistically associated with primary resistance. On the contrary, a smear-positive result was associated with secondary resistance (0.50, 0.29–0.86).

In a second multivariate model assessing characteristics independently associated with the risk of being reported more than once to the NRC-RAD (chronic status), foreign-birth (1.91, 0.91–3.99) and a smear-positive result at MDR diagnosis (1.98, 0.91–4.30) remained associated with chronic status, but the association was not statistically significant (p=0.08 for both).

Trend over time

There was no significant linear trend over time when considering the overall proportion of MDRTB patients reported each year, the proportion of HIV-coinfected patients, and the

proportion of foreign-born patients. However, from 1993–1999, there was a significant increase in the proportion of patients reported for the first time to the NRC-RAD (p=0.03), in the number of new patients, *i.e.* those with no previous history of treatment (p=0.002), and in the proportion of foreign patients coming to France for the management of their MDRTB (permanent residence outside France; p=0.02). There was no significant increase in the annual number of patients originating from Eastern Europe.

Discussion

The results of the ongoing surveillance of MDRTB in France between 1992–1999 shows that a laboratory-based surveillance system obtaining data recommended by the WHO and International Union Against Tuberculosis and Lung Disease yields high added value. First, the system allowed the measurement of the magnitude of the problem and the evaluation of trends over time; the prevalence of MDRTB remains low in France (<1%). Secondly, it acquired data that allows the evaluation of the quality of the TB programme; the fact that 16% of the patients were reported at least twice suggests that they were not cured. Thirdly, it confirmed that foreign-born patients were at higher risk of MDRTB and drew attention on the recent trend toward an increase in the proportion of foreign-patients coming to France to be treated. Finally, and as expected, it showed that HIV coinfection is related to MDRTB, but that it is true in France only for patients with no history of treatment (OR 2.0).

The surveillance of MDRTB in France complies with most recommended standards, although the system was established before international recommendations for standardisation of drug resistance surveillance in Europe [13]. These results show that, in countries where anti-TB drug resistance surveillance is not linked to the TB case notification system, a system based on a national network of laboratories provides useful data. Such a network allows the reliable assessment of trends over time, as proven by its stability over the 8-yr period. Indeed, in order to ensure reliable data over time, it is important to use personal identifiers, since chronic patients may be reported by several laboratories over many years. In addition, changes in network members over time have to be carefully identified in order to ensure completeness of data. Of interest, the trend in the total number of cases with culture-positive TB reported to the network was similar to the trend of cases reported to the mandatory TB case notification system, with a mean decrease of 8.5% per year from 1993–1997 followed by a decrease of 3% per year compared with 9.2% and 1.5%, respectively. Since the source of the data is unrelated to the mandatory TB case notification system organised in France, and although it was not designed for this, the surveillance system described here could be used to assess completeness of both systems by techniques like capture-recapture.

This laboratory-based surveillance demonstrated that the size of the MDRTB problem is low and remains stable in France. The prevalence of MDRTB in France of <1% is comparable with figures reported in most Western European countries except Germany (prevalence 1.4%), Greece (5.1%) and Italy (6.3%) [14]. The low and stable number of MDRTB cases suggests that the global management of TB in France is satisfactory because very few cases of MDRTB are created each year. Indeed, no trends were observed with regards to the prevalence or incidence of MDRTB. However, the overall stable trend may be falsely reassuring. Indeed, in-depth analysis of data using personal identifiers pointed to a rather worrying proportion of chronic carriers. One epidemiological consideration could be made concerning the state of chronic carriers of MDR bacilli. If the pathogenicity of MDR strains were similar to that of fully susceptible strains, the number of primary MDRTB cases would increase in France and in other industrialised countries due to persistent exposure of the population to chronic carriers. It is not the case so far and a recent study may bring some light on this phenomenon [15]. Indeed, this study showed that nonimmunosuppressed patients harbouring INH-resistant strains (including MDR strains) are less likely to create clusters than patients harbouring INH-susceptible strains. However, this does not apply to immunosuppressed patients. This is in accordance with the association of HIV coinfection and MDRTB found for the new patients in the present study.

There was a shift toward a higher proportion of foreign-born patients in the recent years of the surveillance. In France, most of these originated from Africa. To date, an increase in the number of patients coming from Eastern Europe was not observed despite the political changes in this region in the 1990s, but such findings may vary from country to country [16]. Since MDRTB prevalence is worrying in some Eastern European countries, particular attention should be paid to this issue in the near future. The recent extension of the European Union towards the east may facilitate patient exchange and surveillance systems, which can alert health authorities on moving trends.

Results of molecular fingerprinting of a subset of MDR strains isolated in France has been previously published and few clusters were identified [17, 18]. This is not surprising according to the low number of MDRTB patients managed in France, their multiple geographic origins and diverse backgrounds. However, systematic molecular typing of MDR strains continues in France in order to compare results with the international MDR database.

The present surveillance system was not designed to monitor outcome of MDR patients. However, it brings two useful pieces of information together regarding the treatment of MDRTB in France. First, since a high proportion of strains are still susceptible to second-line drugs, antituberculosis drug regimens would be expected to cure the patients if properly designed and administered following WHO recommendations [19]. Indeed, following the WHO list of second-line drugs ordered by antibacterial activity, 70% of the MDR strains are still susceptible to amikacin, fluoroquinolones, pyrazinamide and EMB. Secondly, the cure rate may not be satisfactory because there are chronic cases reported over many consecutive years. Therefore, using the database, specific studies were performed focusing on outcome. The outcome of MDRTB patients reported to the NRC-RAD in 1994 were evaluated by a retrospective study. The results confirmed that the management of MDRTB patients was not optimal and that patient outcome was not satisfactory [3]. MDRTB patients were managed by >40 different sites disseminated throughout the territory. The relatively low number of patients managed each year in each centre precluded microbiological laboratories and clinicians to develop expertise in the management of these difficult-to-treat patients. Consequently, as recommended by the WHO and already implemented in some countries, one or a few reference teams working in collaboration with national associations of physicians and microbiologists should be established in France in order to improve the outcome of MDRTB patients. This is especially important in the prospect of the increase in the number of MDRTB patients coming to France and Europe from high prevalence areas.

The need for management and follow-up of multidrug-resistant tuberculosis patients by reference team(s) has been presented to the National Association Of Respiratory Physicians [20]. These recommendations are currently being implemented

in France and the first results are encouraging [21]. A decrease in chronic cases reported by the laboratory-based surveillance system and specific surveys assessing multidrug-resistant tuberculosis outcome will evaluate the impact of the implementation of these recommendations.

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