Drug-resistant tuberculosis in Israel: risk factors and treatment outcomes

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SUMMARY

SETTING: All culture-positive tuberculosis (TB) isolates in Israel.

OBJECTIVES: To outline the magnitude of drug-resistant TB in Israel, describe treatment outcomes and identify risk factors.

DESIGN: Retrospective study of laboratory data of all strains of adult TB patients tested for resistance to first- and second-line anti-tuberculosis drugs between 1999 and 2010.

RESULTS: Of 4652 reported TB cases, 3552 (76.3%) underwent culture (annual range 73–81%); 445 (12.5%) were resistant to one or more first-line drugs, while 207 (5.8%) had multidrug-resistant TB (MDR-TB). Risk factors for MDR-TB included being male, age 30–59 years, migrants (mainly from the former Soviet Union [FSU]) who had stayed in Israel 2 years, and having pulmonary TB, human immunodeficiency virus (HIV) infection and sputum smear positivity. Of all MDR-TB patients, 71.0% achieved treatment success, while 19.8% died. Twelve Israeli citizens had extensively drug-resistant TB (5.8% of MDR-TB cases). All had emigrated from the FSU and had pulmonary TB; 1 was HIV-infected. Seven (58.4%) achieved treatment success and 5 (41.6%) died.

CONCLUSIONS: Drug-resistant TB in Israel is influenced by migration, especially from the FSU, where the patients were probably infected. Rapid sputum sampling performed in the early stages of the disease, patient isolation and drug susceptibility testing should be the standard of care to avoid further transmission and improve TB control.

KEY WORDS: drug resistance; immigration; laboratory; mycobacteriology; tuberculosis

TUBERCULOSIS (TB) remains a major public health threat, and it was estimated that in 2012 about 8.6 million individuals were diagnosed with TB worldwide.1 The initial phase of treatment for TB includes the administration of four drugs: isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and either ethambutol (EMB) or streptomycin (SM). The first two are the most potent drugs and are critical in achieving treatment success, while the other drugs are added to shorten the duration of treatment and prevent the emergence of drug resistance.2 Drug resistance is defined as the capacity of the mycobacteria to remain viable or multiply in the presence of critical concentrations of each anti-tuberculosis drug, which would otherwise destroy or inhibit susceptible mycobacterial growth.3

*Mycobacterium tuberculosis* that is resistant to at least INH and RMP is defined as multidrug-resistant TB (MDR-TB). MDR-TB requires lengthy, prohibitively expensive and less effective treatment, while exposing patients to various side effects.4 In addition to the more complex treatment at the individual level, it also complicates community TB control, as close contacts of an MDR-TB index case may acquire the drug-resistant strain.

The global estimated proportion of MDR-TB in untreated cases in 2012 was 3.6% (range 2.1–5.1),1 and the public health significance of MDR-TB is increasing.5 The highest global proportion was reported from the World Health Organization (WHO) European region (22.2% of all culture-positive cases), mainly in countries that belonged to the former Soviet Union (FSU).1,6

Israel is an industrialised country with a population of ~8 million, of whom ~2.5 million are non-Israeli-born, having arrived mostly from the FSU and eastern Europe, in addition to ~200 000 work migrants.7 The TB burden is considered low: the average annual adult TB incidence among Israeli-born citizens, non-Israeli-born citizens and migrant workers were respectively 0.86, 11.9 and 27.0 per 100 000 population during the period 1999–2010.7

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The present study aims to describe for the first time the magnitude and secular trends in drug-resistant TB in Israel over 12 years, describe treatment outcomes, and identify potential risk factors for infection with drug-resistant strains, an important step in strengthening the National TB Control Programme.

METHODS

This retrospective study included all cases diagnosed with TB in Israel aged >18 years between 1999 and 2010. A TB case was defined as a patient with disease due to M. tuberculosis complex confirmed using culture from sputum, body fluid or tissue, or on the basis of the clinician’s decision to treat with a full course of anti-tuberculosis treatment if the patient’s clinical or radiological signs and/or symptoms were suggestive of TB.1 Pulmonary TB was defined as TB affecting the lung parenchyma, the tracheo-bronchial tree or the larynx. Extra-pulmonary TB was defined as TB affecting any site other than those causing pulmonary TB. Concomitant pulmonary and extra-pulmonary TB and disseminated TB were classified as pulmonary TB.

Treatment outcomes were defined as set down in the WHO guidelines,8 and patients who were cured or completed treatment were considered ‘treatment success’; ‘failure’ was defined as a patient who was initially sputum smear-positive and who remained positive at month 5 or later or progressed to MDR-TB during treatment. An MDR-TB patient was considered cured if he/she was smear- or culture-negative in the last month of treatment and on at least one previous occasion. If a new TB patient was smear- or culture-positive at month 5 or later during treatment, he/she was considered having failed treatment.1 Relapse was defined as a patient who was diagnosed with M. tuberculosis in Israel before the current episode and her/his previous treatment outcome had been recorded as ‘success’.

All patients with suspected pulmonary TB in Israel are requested to provide sputum or other biological specimens for culture, while most suspected extra-pulmonary cases undergo tissue biopsy for histopathology examination and culture.9 All cultures processed in Israel are sent to the National TB Laboratory (NTBL), in Tel Aviv, Israel. At the NTBL, smears from samples and TB cultures are stained using Ziehl-Neelsen staining and cultured on Löwenstein-Jensen (LJ) media using standard methods10 and in MB/Bact bottles (BacTAlert System, Biomérieux, Marcy l’Etoile, France) or BACTEC™ MGIT™ 960 (BD, Sparks, MD, USA). The species are identified using conventional biochemical methods11,12 and the commercially available strip DNA probe test (Hain Lifesciences, Nehren, Germany). Mycobacteria other than M. tuberculosis complex were excluded from the analysis.

Drug susceptibility testing (DST) was performed at the NTBL using the resistance ratio method11,12 against INH, RMP, SM and EMB. PZA was tested using Mark’s stepped pH method.13 DST against second-line drugs was performed as for first-line drugs, using the resistance ratio method,11,12 for ciprofloxacin, clarithromycin, capreomycin (CPM), cycloloserine, ethionamide, ofloxacin (OFX) and clofazimine and amikacin (AMK). Extensively drug-resistant TB (XDR-TB) was defined as MDR-TB that was also resistant to any fluoroquinolone and to one or more of the injectable drugs AMK, CPM or kanamycin (KM).13

Treatment regimens for patients presumed to have TB included four of the first-line drugs (INH, RMP, PZA and EMB or SM) daily for 6 months by directly observed treatment (DOT). The regimen was later individualised according to the DST results in case of mycobacterial resistance. MDR-TB cases were treated under DOT for a minimum of 18 months.

In this study, any drug resistance and MDR-TB were the primary outcome variables, which were associated with other independent attributes, including demographics and behavioural and clinical data, as reported by the treating physicians. Categorical variables of patients with resistant and those with non-resistant strains were compared using the $\chi^2$ test. Variables significantly associated with two-tailed tests ($P < 0.05$) were included in multivariable logistic regression to predict resistance to any first-line drug or MDR-TB using the Enter technique after assessing for collinearity and normal distribution, generating odds ratios (ORs) and 95% confidence intervals (95%CIs). The $\chi^2$ test was also used to evaluate year-by-year trends. All analyses were performed using the SPSS® programme, version 18.0 (Statistical Package for the Social Sciences, Chicago, IL, USA).

As the study involved only routine epidemiological analysis of non-nominal data from a standard public health database reporting system, ethics approval was not required.

RESULTS

Of 4652 adult TB patients diagnosed in Israel during the study period, 3552 (76.3%) had their initial isolates cultured (annual range 73–81% for the study period); 445 (12.5%) isolates were resistant to at least one first-line drug: 361 (10.2%) were resistant to SM, 355 (10.0%) to INH, 222 (6.3%) to RMP, 131 (3.7%) to EMB and 116 (3.3%) to PZA. MDR-TB was diagnosed in 207 (5.8%) (annual range 1.8–355 (10.0%) to INH, 222 (6.3%) to RMP, 131 (3.7%) to EMB and 116 (3.3%) to PZA. MDR-TB was diagnosed in 207 (5.8%) (annual range 1.8–8.5% for the study period); of these, 166 (80.2%) were resistant to at least one additional first-line drug; 75 (36.2%) to any injectable drug (AMK, KM or CPM) and 93 (44.9%) to any fluoroquinolone. Of all MDR-TB patients, 71.0% ($n = 147$) achieved
treatment success, while 19.8% ($n = 41$) died. XDR-TB was detected in 12 Israeli citizens (5.8% of all MDR-TB, i.e., 0.34% of all isolates obtained during the study period). All were migrants from the FSU and had pulmonary TB; one was HIV-infected. Treatment success was recorded for seven (58.4%) of the XDR-TB cases; five died (41.6%).

Patients whose isolates were resistant to at least one first-line drug were more likely than patients with susceptible isolates to be males aged 30–59 years. They were also more likely to originate from countries other than Israel (especially the FSU), be migrants who had stayed in Israel for longer periods, have pulmonary TB, be HIV-co-infected and demonstrate smear sputum positivity. Multivariate analysis suggested that being male, originating in countries other than Israel, being HIV-infected and being smear-positive were factors predicting resistance to at least one first-line drug (Table).

Drug resistance showed fluctuations throughout the study period (Figure 1). While the proportion of resistance to at least one of the first-line drugs was elevated throughout the study period ($P = 0.04$), the proportion of MDR-TB decreased ($P = 0.02$) (Figure 2). Factors associated with MDR-TB included being male, age 30–59 years, having Israeli citizenship, being born in countries other than Israel (especially the FSU), being a migrant with a longer duration of stay in Israel, having pulmonary TB, being a relapse case, HIV-infected and sputum smear-positive. In multivariate analysis, being a young adult, male, migrant born in countries other than Israel, migrants who had stayed in Israel for >2 years, having pulmonary TB, being a relapse case, HIV-infected and sputum smear-positive were factors predictive of MDR-TB in TB patients (Table).

As shown in Figure 3, the 35–44 year age group showed the highest proportion of resistance to at least one first-line drug and MDR-TB (respectively 14.0% and 7.1% of all patients), while the ≥65 year age group had the lowest rate, at respectively 5.2% and 2.2% of all patients.

As shown in Figure 4, the proportion of resistance to at least one first-line drug among migrants decreased with length of stay in Israel, from 14.3% within the first year after arrival to 5.7% among all migrant patients who had stayed in Israel for >15 years ($P = 0.02$).

**DISCUSSION**

This study describes a 12-year national surveillance of drug-resistant TB in Israel, a country that receives migrants from high TB prevalence countries. The proportion of MDR-TB in our study (5.8%) was higher than reported by a study performed in Israel during the years 1983–1992, showing 5.3% MDR-TB and 7.3% resistance to any single drug,\textsuperscript{14} and was also higher than those reported from western European Union (EU) countries (4.5%),\textsuperscript{6} the United States (1.3%)\textsuperscript{15} and the global average (3.6%).\textsuperscript{1} Population mobility has been found to encourage TB transmission dynamics across international borders. The majority (~75%) of all Israeli MDR-TB patients had emigrated from the FSU; this is in agreement with previous Israeli publications on MDR-TB.\textsuperscript{14,16–19} The high prevalence of MDR-TB among migrants from the FSU is indicative of a larger epidemic, and other countries hosting migrants from FSU have reported a similar phenomenon.\textsuperscript{20} It was suggested that the anti-tuberculosis treatment among these migrants during their residence in the FSU was incomplete due to previous mismanagement and lack of DOT.\textsuperscript{1,20–22} The collapse of the public health infrastructure in the 1990s, the unreliable supply of anti-tuberculosis drugs, deterioration in socio-economic conditions and transmission in congested institutions all contributed to the emergence of MDR-/XDR-TB in the FSU.\textsuperscript{22} Furthermore, the process of immigration may have disturbed anti-tuberculosis treatment and follow-up in patients who emigrated during the treatment period.\textsuperscript{16}

The declining trend in drug-resistant TB in Israel during the study period corresponded with a reduction in the flux of migration from the FSU to Israel. Between 1990 and 2001, an average of ~74 000 FSU migrants arrived in Israel each year and were naturalised, while between 2002 and 2010, the average annual inflow to Israel declined to ~7 500, following a decreasing trend throughout the study period.\textsuperscript{23}

The 0.3% XDR-TB rate found in our study was twice as high as reported from Germany (0.15%)\textsuperscript{20} and the EU (0.09%),\textsuperscript{6} and is regarded as a global problem. The high mortality rate among XDR-TB cases in this study highlights the importance of rapid and reliable DST and the need for strict treatment adherence and close monitoring of patients.

The proportion of treatment success among MDR-TB patients in our study (71.0%) was higher than reported in Germany (59.3%)\textsuperscript{20} and a recent meta-analysis from 32 countries (54.0%),\textsuperscript{24} as well as the average rate globally (60.0%),\textsuperscript{25} and is not far from the 75% treatment success rate recommended by the WHO.\textsuperscript{25} This high treatment success may be attributed to the well-functioning National TB Control Programme in Israel,\textsuperscript{7} adapting drug regimens to DST results and the practice of providing strict DOT for the entire duration of treatment, the high hospitalisation rate among MDR-TB patients,\textsuperscript{16} and individual migrants’ desire to assimilate into Israeli society, resume work and preserve routine social cycles.\textsuperscript{26}

The frequency of MDR-TB was much higher in young adults and peaked at 35–44 years; this was similar to findings from MDR-TB surveillance data from other countries.\textsuperscript{27,28} This pattern suggests that
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resistance to any drug (n = 445)</th>
<th>Susceptible strain (n = 3107)</th>
<th>OR (95% CI)*</th>
<th>aOR (95% CI)*</th>
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<td>137 (30.8)</td>
<td>1308 (42.1)</td>
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<td>Male</td>
<td>308 (69.2)</td>
<td>1799 (57.9)</td>
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<td>38 (8.6)</td>
<td>360 (11.6)</td>
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<td>1</td>
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<td>Former Soviet Union</td>
<td>245 (55.0)</td>
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<td>2.8 (2.1–3.7)</td>
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<td>87 (19.5)</td>
<td>814 (26.2)</td>
<td>2.2 (1.7–2.8)</td>
<td>2.3 (1.6–3.3)</td>
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<td>Other</td>
<td>75 (16.8)</td>
<td>886 (28.5)</td>
<td>2.2 (1.5–3.1)</td>
<td>2.4 (1.8–3.2)</td>
</tr>
<tr>
<td>Years in Israel from arrival to diagnosis†</td>
<td>0.005</td>
<td></td>
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<td>1</td>
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<tr>
<td>≤ 2</td>
<td>155 (34.8)</td>
<td>873 (28.1)</td>
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<td>1</td>
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<tr>
<td>&gt;2</td>
<td>252 (64.8)</td>
<td>1874 (61.9)</td>
<td>5.4 (4.6–6.2)</td>
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<td>3071 (98.8)</td>
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<td>7 (1.6)</td>
<td>36 (1.2)</td>
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<td>HIV status</td>
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<tr>
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<td>410 (92.1)</td>
<td>2952 (95.0)</td>
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<tr>
<td>Positive</td>
<td>35 (7.9)</td>
<td>155 (5.0)</td>
<td>1.5 (1.2–2.1)</td>
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<td>History of incarceration</td>
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<td>3052 (98.2)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Yes</td>
<td>13 (2.9)</td>
<td>55 (1.8)</td>
<td>1.7 (0.8–3.1)</td>
<td>5 (2.4)</td>
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<td>Sputum smear status</td>
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<td>1417 (45.2)</td>
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<tr>
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<td>301 (67.8)</td>
<td>1690 (54.4)</td>
<td>1.7 (1.4–2.2)</td>
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<td>Treatment outcomes</td>
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<tr>
<td>Success</td>
<td>354 (79.6)</td>
<td>2607 (83.9)</td>
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<tr>
<td>Death</td>
<td>66 (14.8)</td>
<td>384 (12.4)</td>
<td>1.5 (0.9–2.7)</td>
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<td>Stopped treatment</td>
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<td>Referred/failed</td>
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<td>77 (2.4)</td>
<td>0.9 (0.4–2.2)</td>
<td>83 (2.6)</td>
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</table>

* Adjusted for age, sex, country of origin, years of stay in Israel for foreigners, site of infection, HIV status, sputum smear.
† Among non-Israeli born.

MDR-TB = multidrug-resistant TB; TB = tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; NA = not applicable; HIV = human immunodeficiency virus.
MDR-TB is a relatively recent transmission and that young adults shoulder the highest burden. It is possible that the lifestyle at this age is more intense and involves greater social interaction, thus exposing young adults to infection, MDR-TB and susceptible strains alike. The high incidence of MDR-TB in the 35–44 year age group should increase physicians’ index of suspicion when treating patients in this age group. These patients should be kept in isolation until culture conversion. Physicians should also identify social problems and cultural concerns likely to undermine patient confidence in or disrupt adherence to treatment, as this may be common among migrant TB patients.29

HIV-infected TB study patients were at higher risk for MDR-TB. HIV is the strongest risk factor for the development of active TB.22 It has been suggested that HIV infection may lead to gastrointestinal malabsorption of anti-tuberculosis drugs and acquired RMP resistance. Furthermore, the poly-pharmacy prescribed to HIV-infected TB patients may lead to lower treatment adherence, increasing the possibility of primary MDR-TB.

Relapse cases in our study were at higher risk for MDR-TB, in agreement with other studies.16,25 Relapse was also found to be the strongest risk factor for MDR-TB in Europe.30 Previous exposure to anti-tuberculosis drugs during incomplete treatment is a well-established risk factor for drug resistance, as shown in surveillance data worldwide.1,6,15

Figure 1  Annual proportion of first-line drug-specific resistance from all first positive tuberculosis cultures, Israel, 1999–2010.

Figure 2  Annual proportion of first-line, multi and extensive drug resistance from all first positive tuberculosis cultures, Israel, 1999–2010.

Figure 3  Aggregated age-specific proportion of first-line, multi and extensive drug resistance from all first positive tuberculosis cultures, Israel, 1999–2010.
The study is subject to several limitations. First, only 76.3% of all TB patients in Israel were diagnosed using positive culture. Second, information on behavioural risk factors, such as homelessness, smoking, alcohol or drug use, was not available in the national registry. Third, we did not have data regarding previous treatment prescribed to patients who relapsed during the study period or their adherence to treatment if they were diagnosed in other countries before migration to Israel.

In conclusion, the proportion of MDR-TB in Israel declined between 1999 and 2010; the majority of the patients with drug-resistant or MDR-TB strains were young adult migrants, most of whom had arrived from the FSU. The average success rate of MDR-TB treatment was 71.0%, and it is probable that migrants acquired the disease in their countries of origin. Physicians in Israel and other industrialised countries should increase their level of suspicion when treating young adult migrants from the FSU, and should advise rapid sputum sampling for appropriate treatment and isolation of the patient at the initial stages of the disease.

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Conflict of interest: none declared.

References
TB drug resistance in Israel


**CONTEXTE :** Tous les isolats de culture positive de *Mycobacterium tuberculosis* en Israël.

**OBJECTIFS :** Evaluer la magnitude de la tuberculose (TB) pharmaco-résistante en Israël, décrire les résultats du traitement et identifier les facteurs de risque.

**SCHEMA :** Étude rétrospective des données de laboratoire de toutes les souches de TB de patients adultes qui ont été testées pour la résistance aux médicaments antituberculeux de première et deuxième ligne entre 1999 et 2010.

**RÉSULTATS :** Sur les 4652 cas de TB rapportés, 3552 (76,3%) ont eu une culture (fourchette 73–81%). Sur tous les isolats, 445 (12,5%) étaient résistants à un ou plusieurs médicaments de première ligne et 207 (5,8%) étaient multi-résistants (TB-MDR). Les facteurs de risque de TB-MDR incluaient le fait d’être un homme, âgé de 30–59 ans, un migrant (surtout d’ex Union Soviétique [FSU]) ayant séjourné en Israël >2 ans, atteint de TB pulmonaire, virus de l’immunodéficience humaine (VIH) positif et avec un frottis de crachats positif. De tous les patients TB-MDR, 71,0% ont achevé leur traitement avec succès tandis que 19,8% sont décédés. Douze citoyens israéliens avaient une TB ultra-résistante (5,8% des TB-MDR). Tous avaient émigré de FSU et avaient une TB pulmonaire, tandis qu’un seul était infecté par le VIH. Sept (58,4%) ont achevé leur traitement avec succès et cinq (41,6%) sont décédés.

**CONCLUSIONS :** La TB pharmaco-résistante en Israël est influencée par la migration, surtout à partir de la FSU où les patients avaient probablement été infectés. Un échantillonnage rapide de crachats réalisé au début de la maladie, l’isolement des patients et le test de pharmacosensibilité devraient constituer la norme de prise en charge afin d’éviter la poursuite de la transmission et d’améliorer la lutte contre la TB.

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**RESUMEN**

**MARCO DE REFERENCIA: **Todos los aislados con cultivo positivo para *Mycobacterium tuberculosis* en Israel.

**OBJETIVOS:** Definir la magnitud de la tuberculosis (TB) farmacorresistente en Israel, describir los desenlaces terapéuticos y reconocer los factores de riesgo de aparición de resistencia.

**MÉTODO:** Fue este un estudio retrospectivo de los datos de laboratorio de todas las cepas obtenidas a partir de pacientes adultos con diagnóstico de TB, en las cuales se practicó la prueba de sensibilidad a los medicamentos antituberculosos de primera y segunda línea de 1999 al 2010.

**RESULTADOS:** De los 4652 casos de TB notificados, en 3552 se practicó el cultivo de las muestras (76,3%; variación anual de 73% a 81%). De todos los aislados, 445 exhibieron resistencia a uno o varios medicamentos de primera línea (12,5%) y 207 fueron multirresistentes (TB-MDR; 5,8%). Los factores de riesgo de presentar TB-MDR fueron el sexo masculino, la edad entre los 30 años y los 59 años, el ser inmigrante (sobre todo de la antigua Unión Soviética [FSU], la permanencia en Israel durante >2 años, la localización pulmonar de la TB, la serología positiva frente al virus de la inmunodeficiencia humana (VIH) y la baciloscopia positiva del esputo. De todos los pacientes con TB-MDR, el 71,0% logró el éxito terapéutico y el 19,8% falleció. Doce ciudadanos Israelíes presentaron TB extremadamente drogorrresistente (la proporción de TB-MDR fue 5,8%). Todos los habían emigrado de la FSU y presentaban TB pulmonar y un paciente presentaba coinfección por el VIH. Siete pacientes lograron el éxito terapéutico (58,4%) y cinco pacientes fallecieron (41,6%).

**CONCLUSIONES:** La migración modifica la tasa de TB farmacorresistente en Israel, especialmente que proviene de la FSU, donde probablemente los pacientes han contraído la infección. La norma de atención de estos casos debe ser una pronta recogida de muestras de esputo en una etapa temprana de la enfermedad, el aislamiento del paciente y la práctica de pruebas de sensibilidad a los antituberculosos, con el objeto de prevenir la transmisión de la enfermedad y mejorar el control de la TB.