Epidemiological Analysis of Tuberculosis Treatment Outcome as a Tool for Changing TB Control Policy in Israel*

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Abstract

Background: Sensing an inadequacy of tuberculosis control due to an influx of TB associated with immigration, we analyzed TB treatment outcome in Israel by population groups.

Objectives: To provide an epidemiological basis necessary for any new national TB control policy, and to bring it to the attention of the medical profession in Israel and abroad since its results led to a change in Israel's TB control policy.

Methods: We reviewed all TB cases notified during the period 1990 to September 1992. "New cases" (820 cases, 93.5%) and "re-treatment cases" (57 cases, 6.5%) were analyzed according to three mutually exclusive groups: "successful outcome," "death," and "potentially unsatisfactory outcome" (according to WHO/IUATLD definitions).

Results: Of 820 "new cases," 26.6% had a "satisfactory outcome," 68.5% had a "potentially unsatisfactory outcome" and 4.9% died; compared to 47.4%, 45.6% and 7% among 57 "re-treatment cases," respectively. Using logistic regression analysis, outcome was associated with the district health office ($P < 0.0001$), the TB "experience" of the notifying clinic ($P < 0.0001$), and the form of TB ($P = 0.02$). No significant relationships were obtained for population groups, gender and age, interval between arrival in Israel and TB notification, and bacteriological results.

Conclusions: Non-supervised TB treatment resulted in poor outcomes regardless of population groups. Better outcomes occurred in the larger TB clinics. Therefore, in addition to measures such as adequate drug supplies, reorganization of TB laboratories and training of TB personnel, we recommend the "directly observed treatment short-course" for all cases as well as reducing the number of treatment centers thereby increasing their case load.

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Tuberculosis has re-emerged as an important public health issue in western countries [1,2]. In the early 1990s practitioners and public health physicians in Israel noted the increasing difficulty of treating tuberculosis. This was due to a number of factors: the systematic dismantling of TB clinics and dispersal of their highly trained personnel (following the decrease in TB rates from 204 per 100,000 in 1952 to less than 5 in 1987 [3]) on the one hand, and the influx of new cases due to mass immigration from Ethiopia in 1985 and 1991 and from the former Soviet Union since 1990, on the other. TB rates more than doubled from 4.2/100,000 in 1987 to 10.2/100,000 in 1991 [4]. In order to provide epidemiological data as a basis for TB health policy decisions, we conducted – for the first time in Israel – a national study of the therapy completion rate for all TB cases for the period January 1990 to September 1992 [5]. This epidemiological analysis was part of an overall quantitative [5] and qualitative [6,7] re-evaluation of the TB treatment process in Israel, as described elsewhere [5–7]. The aim of this article is to bring this analysis to the attention of the medical profession, both in Israel and abroad, since this was the epidemiological rationale that led to a change in government policy concerning TB control [8, and submitted for publication].

Materials and Methods

This study can be viewed as both an historical prospective study and a retrospective cohort study [9]. Between May 1993 and June 1994 we reviewed *all* (900) TB cases notified to the

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TB = tuberculosis
WHO/IUATLD = World Health Organization/International Union Against Tuberculosis and Lung Disease

Tuberculosis National Register for the study period (January 1990 to September 1992). A first analysis was done in 1995 [5,10] – according to operational definitions described elsewhere [5], in line with those of the American Thoracic Society [11] – which directly influenced the 1996 decision for a new TB policy [6]. Our previous data enabled us to re-analyze the outcome of treatment according to the main categories of the treatment outcome classification recommended by a working group of the WHO and the European Region of the Inter-national Union Against Tuberculosis and Lung Disease [12].

Tuberculosis in Israel is a notifiable disease for both clinicians and laboratories. The same physician validated all notifications according to the WHO/IUATLD definitions [13] and we used the TB case notifications from the National Register. We asked all 15 district health offices to obtain information on case management from the medical records of all the lung clinics and/or departments treating TB, with an emphasis on the documentation of completion of treatment in *all* TB cases. In addition to 900 notifications, 27 cases for the study period were revealed by the DHOs as a result of our study. For technical reasons we did not receive any updated data from 2 of the 15 DHOs (accounting for 50 cases). Thus the study population comprised 877 cases.

Data analysis

Using the recent WHO/IUATLD recommendations [14], we defined two mutually exclusive groups: "new cases" (820 cases, 93.5%) and "re-treatment cases" (57 cases, 6.5%). The 57 re-treatment cases were mainly relapses. We performed our analysis in both groups according to three mutually exclusive categories: "successful outcome," "death," and "potentially unsatisfactory outcome." According to the WHO/IUATLD definition [14], "successful outcome" was applied to patients who were cured or had completed treatment within 12 months after the start of treatment. All the other notified cases, with the exception of those known to have died during treatment, were defined as "potentially unsatisfactory outcome" irrespective of whether any follow-up information was available. The WHO/IUATLD definition "completion of the protocol of treatment" corresponds to "clinical outcome." We examined the TB treatment outcome among both "new cases" and "re-treatment cases" according to numerous parameters, including population group, gender and age, DHO of residence, interval between arrival in Israel and TB notification, notifying clinics, form of TB (i.e., pulmonary vs. extra-pulmonary), duration of TB treatment, and bacteriological examinations. Chi-square analysis was performed with SPSS software. A multivariate analysis (logistic regression analysis) was also performed.

Validation of data

In an attempt to assess the validity and completeness of our data we extracted two random samples (25 cases in each) and contacted the patient directly. The information on outcome of treatment was similar in these samples to that obtained by Ministry of Health sources. The very high notification rate (97%) (see Materials and Methods regarding the 900 notifications and additional 27 cases revealed by the DHO as a result of our study) during the period of our study provides further evidence that our data are valid [5].

Results

The study population of 877 included 467 males (53%). There were five major population groups: 66 native non-Jews (7.5%), 62 native Jews (7%), 166 Jews from the former Soviet Union (18.9%), 371 Jews from Ethiopia (42.3%) and 207 other foreign-born Jews (23.6%). Five cases were of unknown origin (0.6%). We analyzed the 820 new cases and the 57 re-treated cases separately.

Table 1 presents the outcome data by diagnostic category (i.e., newly diagnosed and re-treatment cases) according to the different population groups. Among the 820 new cases, 26.6% (218 cases) had a satisfactory outcome, 68.5% (562 cases) had a

DHO = District Health Office

Table 1. Outcome data by diagnostic category (i.e., newly diagnosed and re-treatment cases) and by population group, Israel 1990 – September 1992

	No. of new cases (% by country of birth)**				No. of re-treatment cases (% by country of birth) ***				
Treatment outcome	**Success**	**Potentially unsatisfactory**	**Death**	**Subtotal**	**Success**	**Potentially unsatisfactory**	**Death**	**Subtotal**	**Total**
Ethiopian Jews	106 (29.0)	250 (68.5)	9 (2.5)	365 (100.0)	1 (16.7)	5 (83.3)	0	6 (100.0)	371 (42.3)
Former USSR Jews	30 (20.7)	103 (71.0)	12 (8.3)	145 (100.0)	11 (52.4)	8 (38.1)	2 (9.5)	21 (100.0)	166 (18.9)
Native Jews	20 (32.3)	40 (64.5)	2 (3.2)	62 (100.0)	0	0	0	0	62 (7.0)
Foreign-born Jews	38 (21.0)	129 (71.3)	14 (7.7)	181 (100.0)	13 (50.0)	11 (42.3)	2 (7.7)	26 (100.0)	207 (23.6)
Non-Jews	23 (35.4)	39 (60.0)	3 (4.6)	65 (100.0)	0	1 (100.0)	0	1 (100.0)	66 (7.5)
Total	**217** (26.5)	**561** (68.6)	**40** (4.9)	**818*** (100.0)	**25** (46.3)	**25** (46.3)	**4** (7.4)	**54** *(100.0)	**872*** (99.4)

* This table does not include the five cases (0.6%) of unknown origin (2 new cases and 3 re-treatment cases).
** $P < 0.01$ (value = 19.819)
*** Not significant (value = 5.289)

potentially unsatisfactory outcome, and 4.9% (40 cases) died. Among the re-treatment cases, the percentages were 47.4%, 45.6% and 7% respectively. Among the new cases, the gender ratio was 1.11 (M/F = 1.7 in the re-treatment cases) and there was no association between outcome and gender. No association was found between outcome and age among the re-treated cases, but it was present among the new cases (three-quarters of the deaths occurred among persons older than 64, and a higher rate of successful outcome was observed among children aged 0–14 and adults aged 30–64) ($P < 0.001$).

Population groups and country of birth

Gender was not significantly predominant in any of the five population groups. No significant association was seen between the TB treatment outcome and the two population groups – Jews and non-Jews – in both new cases and re-treatment cases (successful outcome in new cases was obtained for 25.8% and 35.4% of cases, respectively; $P = 0.48$). Among the new cases, the association of TB treatment outcome with the five population groups (Ethiopian Jews, former-USSR Jews, native Jews, other foreign-born Jews, and non-Jews) was significant ($P < 0.01$) [Table 1]. In the new cases, the "best" levels of TB treatment outcome were obtained among the non-Jewish (35.4%) and the native Jewish (32.3%) population groups, and the worst level among the former USSR Jewish population group (20.7%). This latter group also had the highest level in the death category (8.3%). In the re-treatment cases, no significant association was found between TB treatment outcome and the four population groups ($P = 0.5$; there was no native Jew among the re-treated cases). In both new and re-treated cases, there was a significant association between age and population group, with Ethiopian Jews and native Israeli Jews being younger than the two other foreign-born groups (former USSR Jews and other foreign-born Jews) ($P < 0.001$ and $P < 0.01$ respectively) [Table 2].

Distribution by DHOs and local clinics

Table 3 shows the TB treatment outcome in new cases of each subdistrict, coded in a decreasing order according to successful outcome. The association of TB treatment outcome with DHO is significant in both new cases and re-treatment cases ($P < 0.001$ and $P < 0.01$ respectively).

Table 4 shows the TB treatment outcome for the 28 notifying clinics/or hospital departments; this table does not include 280 cases – some 30% of the new cases and re-treated cases – notified only by non-specialized clinics or DHOs. These clinics are grouped according to the number of patients notified by each clinic during the study period, as a *proxy variable* for the "TB experience in case management" of the notification clinic. The best results in terms of treatment outcome were obtained by the five clinics that notified 40 cases or more (range 47–121) during the study period [Table 4] ($P < 0.001$).

Pulmonary TB and culture results

Pulmonary TB was found among 685 new cases (83.5%) and 48 re-treated cases (84.2%). Pulmonary TB in new cases was more common among former USSR Jews, Ethiopian Jews and other foreign-born Jews (88.3%, 87.5% and 77.9%, respectively) than among native Jews and non-Jews (74.2% and 72.3%, respectively) ($P < 0.001$). Successful outcome was observed in 24.4% of pulmonary TB and in 37% of extra-pulmonary TB ($P < 0.01$). Overall, less than 30% of the pulmonary TB cases were "definite" cases (with a culture-confirmed disease due to *Mycobacterium tuberculosis* complex). A positive culture was notified only in 196 pulmonary TB new cases and 10 re-treated ones (28.6% and 20.8% respectively). Treatment outcome was not associated with culture positivity in both new and re-treated cases.

Extra-pulmonary TB

A total of 144 cases was classified as extra-pulmonary TB (16.4% of the study population, almost equally divided among new and re-treated cases). Regarding the site of extra-pulmonary TB, lymph glands accounted for a third of the cases (35.7%), followed by renal tract and genitourinary system (25.1%) and bones or joints (14.7%). Seven cases of TB meningitis were reported during this period (4.9%).

Interval between arrival in Israel and TB notification

Eighty-five percent of all TB cases occurred among the foreign-

Table 2. Population groups by age, Israel 1990 – September 1992

	Number of new cases (% by country of birth)**					No. of re-treatment cases (% by country of birth)***				
Age (yr)	0–14	15–29	30–64	65+	Subtotal	0–14	15–29	30–64	65+	Subtotal
Ethiopian Jews	107 (29.3)	86(23.6)	130 (35.6)	42 (11.5)	365 (100.0)	0	3 (50.0)	2 (33.3)	1 (16.7)	6 (100.0)
Former USSR Jews	3 (2.1)	15 (10.3)	45 (31.0)	82 (56.6)	145 (100.0)	1 (4.8)	1 (4.8)	8 (38.1)	11 (52.4)	21 (100.0)
Native Jews	20 (32.3)	11 (17.7)	20 (32.3)	11 (17.7)	62 (100.0)	0	0	0	0	0
Foreign-born Jews	3 (1.7)	7 (3.9)	77 (42.5)	94 (51.9)	181 (100.0)	0	0	14 (53.8)	12 (46.2)	26 (100.0)
Non-Jews	7 (10.9)	10 (15.6)	32 (50.0)	15 (23.4)	64 (100.0)	0	0	1 (100.0)	0	1 (100.0)
Subtotal	140 (17.1)	129 (15.8)	304 (37.2)	244 (29.9)	817 *(100.0)	1 (1.9)	4 (7.4)	25 (46.3)	24 (44.4)	54* (100.0)

* This table does not include the five cases of unknown origin and the one of unknown age (3 new cases and 3 re-treatment cases).
** $P < 0.001$ (value = 234.510)
*** $P < 0.01$ (value = 21.731)

Table 3. TB treatment outcome (in percentage) in new cases, by subdistrict of residence, Israel 1990 – September 1992

Subdistrict	Successful outcome	Potentially unsatisfactory outcome	Deaths	Total cases No. (%)
1	72.2	25.9	1.9	54 (100.0)
2	54.5	43.9	1.5	66 (100.0)
3	47.4	52.6	0	19 (100.0)
4	39.4	45.5	15.2	33 (100.0)
5	35.1	52.6	12.3	57 (100.0)
6	32.9	65.1	2.1	146 (100.0)
7	25.3	72.2	2.5	79 (100.0)
8	17.5	79.8	2.6	114 (100.0)
9	15.4	76.9	7.7	26 (100.0)
10	9.1	68.2	22.7	22 (100.0)
11	3.9	90.3	5.8	154 (100.0)
12	2.4	95.2	2.4	42 (100.0)
13	0	100.0	0	5 (100.0)
Unknown	0	66.7	33.3	3 (100.0)
Total	26.6	68.5	4.9	820 (100.0)

Note that the study was not performed in 2 of the 15 district health offices. $P < 0.001$ (value = 205.384)

Table 4. TB treatment outcome by notifying clinics (*) according to the number of TB cases, Israel 1990 – September 1992

	No. of patients per clinic		Total
	1–39	40+	
No. of lung clinics and/or hospital dept.	23	5	28
No. (%) of cases with successful outcome	62 (24.0)	158 (46.6)	220 (36.8)
No. (%) of cases with probably unsatisfactory outcome	179 (69.4)	170 (50.2)	349 (58.5)
No. (%) of deaths	17 (6.6)	11 (3.2)	28 (4.7)
Total no. (%) of cases	258 (100.0)	339 (100.0)	597(*) (100.0)

* This table does not include the 280 cases (264 new cases and 16 re-treated cases, 32.2% and 28% of total new and retreated cases respectively) notified only by non-specialized clinics or directly by the district health office. $P < 0.001$

born. Their cases, disease was notified 2 years after immigration in 50% and more than 20 years after arrival in Israel in 25%.

Multivariate analysis

Among the numerous parameters included in the logistic regression analysis of the new cases, significant results were obtained for the following variables: DHO of residence ($P < 0.0001$), notifying clinics ($P < 0.0001$), and form of TB ($P < 0.01$). This means that "infrastructure," DHO as the organizing center, and the number of notified cases per notifying clinic (representing the clinic case load, a proxy of the experience of the TB clinic) greatly influenced the outcome of treatment.

No significant relationships were obtained in the multivariate analysis for the following variables: population groups, gender and age, interval between arrival in Israel and TB notification, and bacteriological examinations.

Discussion

Our historical prospective study is based on data of TB cases as reported on a standard form verified from existing medical records. This type of study is commonly used in health-planning services despite its inherent biases (selection and information biases) and difficulties controlling for confounding variables [9].

"Successful outcome" was defined as documentation in the medical chart of the completion of treatment, or cured for one year after beginning treatment. However, other data may have been incomplete, particularly the record of bacteriological confirmation of disease. For example, rates of confirmed disease are much higher and are underestimated due to the delay in notifying the Ministry of Health, and to the lack of emphasis on obtaining this information at the time of chart review (monitors from DHO focused more on documentation of treatment completion than on clinical features of the cases).

Multivariate analysis of our data showed a significant association between the outcome of TB treatment and DHO of residence, TB "experience" of the notifying clinics, and form of TB, but not with age, ethnic origin or recent immigration. This study refuted our assumption that treatment outcome would be worst among recent immigrants. In fact, the outcome of TB treatment was poor regardless of the population group. We found that self-administered treatment prescribed at clinics lacking adequate facilities and personnel resulted in unacceptably low rates of completion of treatment. We also found that the larger the TB clinic in terms of number of patients seen, the better the outcome of treatment, indicating that small units with a low turnover of TB patients are less able to successfully manage TB patients.

On average only 26.6% of the "new cases" had a "successful outcome." Had we studied compliance rather than successful outcome, the former being a much more stringent requirement [14], our results would likely have been worse.

Many studies, using criteria other than the WHO/IUATLD classification for completion of treatment, show that about one-third to one-half of patients with TB do not adhere to non-supervised TB treatment [15–18] and that health practitioners are unable to predict compliance [18–20], which leads to poor completion rates. However, comparison among different studies, including our own, are hindered by differences in the definition of "successful outcome." Indeed, when our results were previously analyzed according to the definition of the American Thoracic Society [11], we obtained a completion rate of 43% (with an additional 11.5% of cases still under treatment) [5,10]. With the WHO/IUATLD classification [12] used in the current study, we obtained a 26.6% successful outcome rate among the new cases. Reporting on treatment results is not mandatory in low incidence countries (except Norway) and only a few of these countries have introduced a monitoring system for treatment outcome [12]. As mentioned by the working group that recommended standardized treatment monitoring in

Europe, standardization will allow comparisons both within and between countries [12]. For instance, it will be possible for us in Israel to compare treatment outcome before and after the implementation of a new national TB program [submitted].

The WHO's global target for infectious TB cases is a cure rate of 85%, and the WHO/IUATLD classification stipulates not more than 10% of "probably unsatisfactory outcome" cases [12]. Using these criteria, our findings in Israel were very far from what are considered acceptable results. In the subsequent years 1993– 1995 we noted a 9.6% rate of re-treatment cases, which is perhaps a reflection on the findings of this study. We attributed the dismal results described above to the cuts in public funding for TB control and to reduced services devoted to tuberculosis that were implemented in Israel and in many developed countries during the last two decades [1,21,22].

We subsequently formulated a new approach to TB control and management to rectify the shortcomings described above [8, and submitted for publication]. We decided to adopt the WHO recommendation of 1995 urging that the "directly observed treatment short-course become the priority for TB control in communities where the disease is endemic" [23]. While Israel is not located in a highly endemic TB region, more than 65% of our new cases are new immigrants from such regions. We felt that by improving compliance through DOTS (including the progressive use of "enhancers" and "enablers" as the program developed) we would certainly improve our rates of successful treatment outcome. Based on the better performance of the larger centers in managing TB as demonstrated above, we also decided to limit TB management to nine specialized centers [8, and submitted for publication].

An influx of new cases due to immigration is not unique to Israel. Other countries in Western Europe have had a similar experience [24]. Our approach of centralization of treatment associated with universal DOTS may be applicable to problematic areas in larger countries other than Israel, implemented on a regional and not necessarily a national basis. In Israel it has enabled the Ministry of Health to monitor the treatment of TB more closely and efficiently. We can now address problems such as poor drug supplies or difficult cases, in a timely fashion, and provide epidemiological and clinical information on a regular basis to the participating centers.

DOTS = directly observed treatment short course.

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