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Izabela Siemion-Szcześniak, Jan Kuś

First Department of Lung Diseases, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
Head: Prof. J. Kuś

Treatment outcomes in culture-positive pulmonary tuberculosis

Abstract

Introduction: The aim of the study was to evaluate treatment outcomes in sputum culture positive patients with tuberculosis in three Polish provinces (Warsaw, Gdansk and Siedlce Provinces) in 1995 and again in 2000. We also assessed whether the implementation of the Directly Observed Therapy Short Course (DOTS) strategy in the former Gdansk Province led to improved outcomes compared to the outcomes observed in 1995, when this strategy was not being followed.

Material and methods: We started the study by reviewing microbiology registers covering the years 1995 and 2000 from all the tuberculosis laboratories in three provinces (Warsaw, Gdansk and Siedlce Provinces) and identified sputum culture positive patients. We then reviewed inpatient and outpatient medical records of patients who had been with pulmonary tuberculosis diagnosed and confirmed by bacteriology in 1995 and 2000. Treatment outcomes were evaluated in accordance with the World Health Organisation (WHO) recommendations and classified as: cure, treatment completed, default, treatment failure, death or other.

Results: A total of 708 patients were included in the study: 373 diagnosed in 1995 and 335 diagnosed in 2000. According to the WHO criteria, the treatment success rate (the sum of cures and treatment completions) in 1995 and 2000 was 58.8% and 54.0%, the default rate was 15.5% and 17.9%, the failure rate was 2.4% and 2.7% and the death rate was 5.6% and 6.3%, respectively. The rate of outcomes classified as "other" was 18.2% and 22.1%, respectively. Following the implementation of the DOTS strategy in Gdansk Province, treatment outcomes in significantly improved in 2000 compared to the year 1995. The treatment success rate was 89.6% vs 69.3% ($p = 0.0037$), the default rate was 0.0% vs 14.7% ($p = 0.0005$) and the death rate was 0.0% vs 9.3% ($p = 0.0184$).

Conclusions: The treatment success rate (the rate of cures and treatment completers) in 1995 and 2000 was 58.8% and 54.0% and was lower than that recommended by WHO (at least 85%). The results demonstrated that the treatment outcomes in the former Gdansk Province in 2000, following the implementation of the DOTS strategy, were significantly better than those in 1995, when the strategy was not being followed. Treatment success was observed in 89.6% and 69.3% of the patients, respectively ($p = 0.0037$).

Key words: culture-positive pulmonary tuberculosis, treatment outcome, adherence, DOTS strategy, cohort analysis

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Introduction

According to the World Health Organisation (WHO) experts, a tuberculosis control system is effective if it ensures that at least 70% sputum smear patients are detected and at least 85% of newly detected patients with microbiologically confirmed presence of mycobacteria in the sputum are cured [1]. Modern treatment of tuberculosis allows to achieve treatment success rates of more than 95% and to reduce the failure rate to 5% [2].

Given the unfavourable epidemiological situation of tuberculosis in the poorest countries and the increasing prevalence rates in the developing countries, WHO classified tuberculosis in 1993 as a global risk [3]. A year later, in collaboration with other international organisations involved in tuberculosis control, WHO announced a new strategy for the monitoring and treatment of patients with tuberculosis, the DOTS (Directly Observed Treatment, Short Course) strategy [4, 5]. It is a comprehensive strategy aimed to detect, treat and cure

Address for correspondence: prof. Jan Kuś, First Department of Lung Diseases, Institute of Tuberculosis and Lung Diseases, 26 Płocka St., 01–138 Warsaw, e-mail: j.kus@igichp.edu.pl

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patients with tuberculosis covered by healthcare schemes and should be at the core of tuberculosis control programmes in each country. This is confirmed by experiences of many countries, as the strategy has been demonstrated to result in very good treatment outcomes as well as being cost effective [6–10].

Patient adherence to treatment is an important problem affecting treatment outcomes. According to studies evaluating antituberculosis treatment outcomes, only directly observed treatment (DOT), which involves taking the drugs by the patient in the presence of a healthcare professional, such as a doctor, nurse or another specially trained person, ensures optimal treatment outcomes [6, 7, 11, 12]. Thanks to the inclusion of DOT in tuberculosis control programmes, a reduction in the incidence of tuberculosis has been observed in many countries [13].

WHO, in collaboration with other international organisations involved in tuberculosis control, has developed precise definitions of tuberculosis cases and treatment outcomes. These definitions are aimed to enable the correct recording, classification and counting of individual tuberculosis cases, to assess the percentage of new cases with sputum positivity and the percentage of recurrences among all the patients with pulmonary tuberculosis, and to determine the appropriate combination of antituberculosis drugs for an individual patient [5]. Appropriate systems for data collection are also provided by cohort analyses, which allow treatment outcomes to be evaluated in all the patients diagnosed with tuberculosis over a given period of time.

In Poland, thanks to the implementation of the tuberculosis control programme and the widespread adoption of the WHO treatment standards, the recent years have seen a consistent reduction in the incidence of tuberculosis. WHO monitors the implementation of DOTS in individual countries and in 1999 Poland was assigned category 3 and was one of the twelve countries to have subsequently improved its category.

According to WHO, cohort analyses are the best method of assessing the efficiency of tuberculosis control systems, which is why the aim of our study was to evaluate treatment outcomes in all patients with pulmonary tuberculosis confirmed by positive sputum cultures on the territory of three Polish provinces in 1995 and again in 2000. We also investigated whether the implementation of the DOTS strategy in the former Gdansk Province improved outcomes in 2002 versus 1995, when the strategy was not yet being followed.

Material and methods

The study was conducted on the territory of three Polish provinces (according to the administrative division of Poland as at 1995): Warsaw, Gdansk and Siedlce provinces.

We started the study by reviewing microbiology registers covering the years 1995 and 2000 from all the tuberculosis laboratories in each of the three provinces and identifying patients with positive sputum cultures for *Mycobacterium tuberculosis*.

Demographic data contained in the laboratory request forms made it possible to trace the healthcare facility that had sent the specimens for bacteriology.

In order to establish whether the patient who had been registered at the tuberculosis laboratory providing bacteriological confirmation of tuberculosis based on the positive sputum culture started antituberculosis treatment, we reviewed the patient's medical records at the healthcare facility which had provided specimens for bacteriology.

The following patients were excluded from the study: patients entitled to receive medical care under special schemes (Ministry of National Defence, Ministry of Internal Affairs and the Polish Railways), patients with bacteriologically confirmed pulmonary tuberculosis in a year preceding the years of interest in our study (i.e. in 1994 and 1999), patients living outside the territories of interest in our study (as the laboratories based in the three provinces we investigated also performed bacteriology testing for other provinces), patients who continued treatment outside the three provinces investigated following the initial phase of therapy and patients who had been registered at a healthcare facility (inpatient or outpatient) but whose medical records could not be found for various reason.

We then analysed inpatient and outpatient treatment records for patients diagnosed with pulmonary tuberculosis confirmed by bacteriology in 1995 and 2000 who did not meet the exclusion criteria.

A total of 708 patients were included in the study: 373 patients diagnosed with tuberculosis in 1995 and 333 diagnosed in 2000. We verified whether all the included patients had received antituberculosis treatment. Patients were considered untreated if:

— no records were found, despite every effort, to demonstrate that the patient had been registered at the healthcare facility from which the specimen for bacteriology was sent and the no

further bacteriology testing reports were available at the laboratory to show that the patient was being followed up;
— the medical records we found revealed no information about the commencement of antituberculosis treatment (for patients discharged home in whom no tuberculosis had been diagnosed we verified whether they were registered at their local pulmonary outpatient clinic or another outpatient clinic in the town they lived);
— they received antituberculosis drugs for less than a month (untreated patients according to the WHO definition) [1, 14].

We verified how many patients had started antituberculosis treatment, who were defined as patients who had received antituberculosis drugs for at least one day.

The selection of drugs and the duration of treatment were reviewed for compliance with the WHO guidelines [1, 14]. We considered the following combinations of drugs to be model treatment regimens:
— RMP+INH+PZA+EMB/SM for 2 months (initial phase) and RMP+INH for 4 months (continuation phase), or
— RMP+INH+PZA for 2 months (initial phase) and RMP+INH for 4 months (continuation phase);
— RMP+INH+EMB/SM for 3 months (initial phase) and RMP+IHN for 6 months (continuation phase).

If a patient had not received any of the model regimens, he/she was included in the group receiving another combination.

The durations of treatment with the individual antituberculosis drugs were calculated from the start and end of treatment dates. In the evaluation of the correctness of using individual combinations of drugs we accepted the possibility of extending or shortening of treatment phases by less than 10%. All the other cases were classified as "excessive" or "insufficient" duration of treatment.

If a patient had interrupted treatment and the interruptions were less than 2 months long and then continued treatment in accordance with the same regimen, then in line with the WHO guidelines [1] the treatment was considered as one course and the periods of drug intake were combined.

We also evaluated the percentage of patients with culture negativisation during the treatment period.

We evaluated the time to culture negativisation by counting the number of days between the start of treatment and the first negative sputum culture. It was impossible to evaluate the culture negativisation rate, as the cohort did not undergo regular bacteriology testing. Whether the treatment was systematic was evaluated on the basis of interruptions in drug intake. A "short interruption" was defined as an interruption in drug intake by the patient of less than 2 months. The cause of interruption was evaluated. The reasons for interrupting treatment were investigated, paying special attention to cases when the patient gave up treatment right after discharge from hospital.

Treatment outcomes were evaluated in accordance with the relevant WHO guidelines and patients were categorised as follows [1]:
— *Cure*: Patient who had completed full antituberculosis treatment and was culture negative at the end of the treatment.
— *Treatment completed*: Patient who had completed the assigned treatment but final sputum cultures were not obtained and the supervising doctor decided that the patient required no further treatment.
— *Default*: Patient who had taken antituberculosis drugs for one or more months and interrupted treatment for two or more months.
— *Treatment failure*: Patient in whom sputum culture remained or became positive at 5 months of antituberculosis treatment.
— *Death*: Patient who died for any reason during antituberculosis treatment.
— *Other*: Patient who does not meet the criteria to be classified as any of the above category. This group includes: patients who had not undergone antituberculosis treatment (i.e. patients who had not received any treatment at all and patients who had been treated for less than one month) and patients whom their doctor considered cured and terminated treatment but the duration of treatment was "insufficient".

Treatment success was defined as the sum of patients whose outcome was categorised as "cured" and "treatment completed".

If a patient interrupted treatment for more than two months and resumed treatment after the interruption, the outcome of retreatment was assessed. If multi-drug resistance to antituberculosis drugs was the cause of treatment failure, the group of these patients was excluded from further analysis.

Statistical analysis

The differences between related variables were analysed with the non-parametric Wilcoxon test. The test compares the sum of positive difference ranks with that of negative difference ranks. The differences in the frequencies of patients with the

trait of interest were analysed with the chi-square test (observed vs expected values). For binominal frequency tables (2 by 2) the chi-square test, v-square test, chi-square test with Yates correction or the Fisher test, as recommended by the relevant literature [15], were used. We assumed that the relationships or differences we were investigating would be statistically significant if the p value was less than 0.05.

Results

We evaluated medical records of 708 patients including 373 patients diagnosed in 1995 and 335 diagnosed in 2000. Positive smears were present in 157 (42.1%) and 119 (35.5%) patients, respectively. The proportion of smear-positive patients in 2000 was lower than that in 1995, although the difference was not statistically significant ($p < 0.0869$).

Management of patients in the study groups

In 1995 forty-three (11.5%) patients did not start treatment. Antituberculosis treatment was initiated in 330 (88.5%) patients but its duration was less than a month in 15 (4.5%) patients. In 2000 treatment was not initiated in 45 (13.4%) patients. The remaining 290 (86.6%) patients started treatment but in 8 (2.4%) patients its duration was less than a month (Fig. 1).

Sputum culture negativisation

In 1995 two hundred and seventy-nine (74.8%) patients achieved sputum culture negativisation, while 94 (25.2%) did not. The latter included 43 untreated patients, 25 defaults, 9 treatment failures and 13 patients who died in the course of treatment. In 2000 two hundred and sixty (77.6%) patients achieved sputum culture negativisation while, while 75 (22.4%) did not. The latter included 45 untreated patients, 11 defaults, 7 failures and 7 deaths.

Furthermore, 4 patients in 1995 and 2 in 2000 completed the correctly conducted therapy but because in the course of the treatment they had stopped expectorating, they could not undergo follow-up bacteriology and obtain a definite confirmation of sputum culture negativisation. Due to the lack of evidence for sputum culture negativisation these patients were included in this group. These patients had initially been sputum smear-negative.

No statistically significant difference was found between the years 1995 and 2000 in the number of patients achieving negativisation and the number of patients not achieving negativisation during the treatment ($p = 0.4877$).

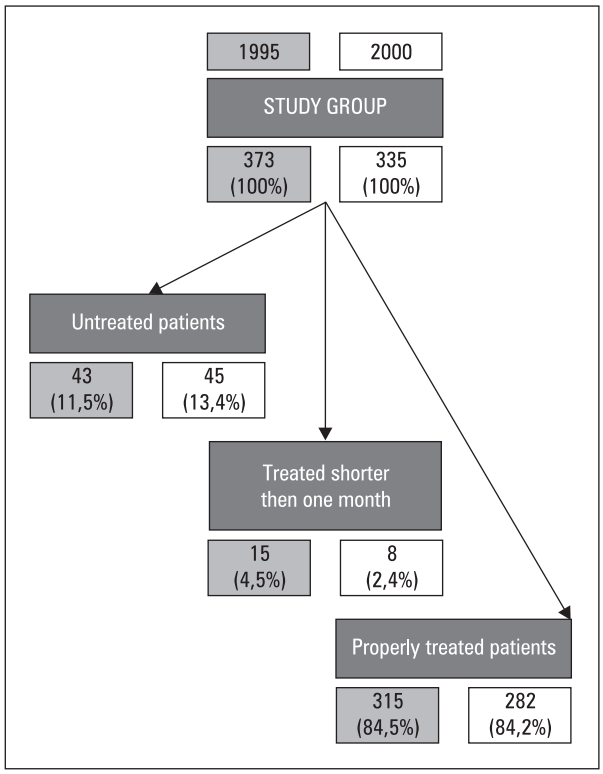

Figure 1. A history of patients in the study groups

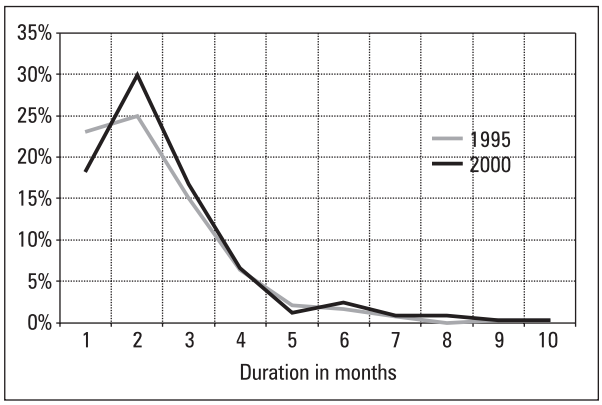

Figure 2. The time to conversion of positive sputum cultures in the study groups

By the end of 3 months of treatment negativisation was achieved in 235 (63%) patients in 1995 and in 217 (64.8%) in 2000. By the end of 5 months of treatment negative cultures were reported for further 32 (8.6%) and 26 (7.8%) patients, respectively.

Sputum culture negativisation was achieved in 12 (3.2%) patients in 1995 within 6–11 months and in 17 (5.1%) patients in 2000 within 6–24 months. This group included patients who had defaulted but subsequently resumed treatment to continue it and patients who did not undergo regular sputum bacteriology (Fig. 2).

Table 1. Reasons of the short interruptions of the treatment in the study groups

Reason for short interruption of treatment	1995		2000	
	Number of patients	Percent of patients	Number of patients	Percent of patients
Bad compliance	24	60,0	6	66,7
Side effects	16	40,0	3	33,3
Total	40	100,0	9	100,0

Regularity of treatment

Treatment was interrupted for less than 2 months by 40 out of 330 patients (12.1%) in 1995 and 9 out of 290 patients (3.1%) in 2000.

In 1995 brief interruptions of treatment were caused by adverse reactions in 16 patients and by incompliance in the remaining cases. The respective numbers in 2000 were 3 and 6 (Table 1). No statistically significant difference was found between the years 1995 and 2000 in the causes of brief interruptions of treatment ($p < 0.2059$, $p < 0.3137$).

Treatment outcomes

Cure, as defined by WHO [10], was achieved in 48.8% and 40.9% of the patients in 1995 and 2000, respectively. Treatment was completed by 11.0% and 13.1%, respectively. Treatment success was observed in 59.8% (223/373) and 54.0% (181/335) of the patients, respectively. In 1995 a total of 15.5% of the patients (58/373) defaulted: 54 due to incompliance and 4 due to poor treatment tolerability. At discharge from hospital 26 patients defaulted. After the treatment interruption 12 patients were re-treated, 5 of whom (41.6%) were cured and 7 defaulted again. In 2000 a total of 17.9% (60/335) of the patients defaulted: 53 due to incompliance and 7 due to poor treatment tolerability. At discharge from hospital 39 patients defaulted, 7 of whom were re-treated, 4 of whom (57.1%) were cured. Three patients defaulted again.

Treatment failure was observed in 2.4% (9/373) of the patients in 1995. Four patients were resistant to rifampin (RMP) and isoniazid (INH). Of the 5 patients with cultures positive for mycobacteria sensitive to the basic antituberculosis drug, sputum culture negativisation following re-treatment was achieved in 2 patients, who subsequently defaulted. Sputum culture negativisation could not be achieved in 3 patients.

In 2000, treatment failure was reported in 2.7% (9/335) of the patients. Six patients were found to be resistant to RMP and INH. Three drug sensitive patients were cured following re-treatment.

Four percent (15/373) and 3.3% (11/335) of the patients died in the course of treatment in 1995 and 2000, respectively, with tuberculosis being the cause of death in 3.2% (12/373) and 2.4% (8/335) of the cases, respectively.

Treatment outcome was classified as "other" in 18.2% of the patients in 1995. The group comprised 49 untreated patients (including 6 patients who had received treatment for less than a month) and 19 patients who had been considered cured by their treating physicians and completed treatment as planned but the actual duration of treatment according to the regimen used was shorter than recommended.

In 2000 the "other" treatment outcome group comprised 22.1% of the patients, including 50 untreated patients (5 of whom had received treatment for less than a month) and 24 patients considered cured but whose duration of treatment was regarded as "insufficient". No statistically significant differences were observed in the treatment outcomes between the years 1995 and 2000 (Table 2).

In 1995 treatment success was reported in 52 patients (69.3%), default in 11 patients (14.7%), failure in 3 patients (4.0%) and death in 7 patients (9.3%) with all the fatal cases being due to tuberculosis. Two patients (2.7%) had not started antituberculosis treatment (with one patient dying before treatment was initiated).

In 2000 treatment success was observed in 69 patients (89.6%). There was one failure (1.3%) and no defaults or deaths in the course of treatment. Six patients considered cured by the doctor supervising the treatment had in fact been treated too briefly and one had not been treated at all (the patient had died from tuberculosis before treatment was initiated) (Table 3). The treatment success rate in 2000 was significantly higher than that in 1995 ($p = 0.0037$). The default and death rates in 2000 were significantly lower than those in 1995 ($p = 0.0005$ and $p = 0.0184$, respectively).

In 1995 the treatment success rate was 57.4%, default rate was 15.8%, failure rate was 2.0% and the death rate was 2.7%. Treatment outcomes were classified as "other" in 22.1% of the patients.

In 2000 the success rate was 43.4% and the default rate was 23.3%. The failure and death rates were 3.1% and 4.3%, respectively, and in 25.6% of the

Table 2. Treatment outcome in the study groups

Results	1995		2000		p-value
	Number of patients	Percent of patients	Number of patients	Percent of patients	
Cured	**182**	**48,8**	**137**	**40,9**	
					p = 0,1419
Treatment completed	**41**	**11**	**44**	**13,1**	
Defaulted	58	15,5	60	17,9	p = 0,4589
Treatment failure	9	2,4	9	2,7	p = 0,9935
Death	15	4,0	11	3,3	p = 0,7482
— death of tuberculosis	13	3,5	8	2,4	p = 0,5239
— other causes of death*	68	18,2	74	22,1	p = 0,2355
Total	373	100,0	335	100,0	

*1995 — 43 untreated patients + 6 patients treated shorter then one month + 19 patients treated too short
*2000 — 45 untreated patients + 5 patients treated shorter then one month + 24 patients treated too short

Table 3. Treatment outcome in 1995 and 2000 in Gdansk area

Results	1995		2000		p-value
	Number of patients	Percent of patients	Number of patients	Percent of patients	
Cured	**42**	**56,0**	**58**	**75,3**	
					p = 0,0037
Treatment completed	**10**	**13,3**	**11**	**14,3**	
Defaulted	11	14,7	0	0,0	p = 0,0005
Treatment failure	3	4,0	1	1,3	p = 0,5937
Death	7	9,3	0	0,0	p = 0,0184
— death of tuberculosis	7	9,3	0	0,0	p = 0,0184
— other causes of death*	2	2,7	7	9,1	p = 0,9589
Total	75	100,0	77	100,0	

*1995 — 2 untreated patients
*2000 — 1 untreated patient + 6 patients treated too short

patients treatment outcomes were categorised as "other" (Table 4). The treatment success rate in 2000 was significantly higher than that in 1995 (p = 0.005).

Long-term observations

Our review of the medical records demonstrated 2 relapses and 11 deaths in the 242 patients diagnosed in 1995 who completed treatment and were considered cured by their doctors. Both relapses occurred a year and a half after completion of treatment and all the deaths were unrelated to tuberculosis.

In the group of patients diagnosed in 2000 and considered cured following completion of treatment, there were 2 relapses (one year and a year and a half after completion of treatment) and 3 deaths (all unrelated to tuberculosis) (Table 5).

Discussion

Successful antituberculosis treatment and the continuous reduction in the incidence of tuberculosis are determined by the percentage of patients completing therapy and achieving treatment success, which should not be lower than 85%, according to the WHO guidelines [1, 14]. This group of patients comprises cured patients with negative sputum culture at the end of treatment and patients who have completed treatment as planned but have not undergone sputum bacteriology at the end of treatment for various reasons. Therefore, the percentage of defaults, deaths and treatment failures cannot exceed 15% in total [1, 16].

We demonstrated that the success rate in 1995 and 2000 (the combined rate of cured and treatment completed) was much higher than that recommended by WHO (Table 2).

During treatment sputum culture negativisation was achieved in 74.8% and 77.69% of the patients in 1995 and 2000, respectively (Fig. 2). The main reason for the disproportions between the percentage of patients with negative sputum cul-

Table 4. Treatment outcome in 1995 and 2000 in Warsaw and Siedlce area

Results	1995		2000		p-value
	Number of patients	Percent of patients	Number of patients	Percent of patients	
Cured	**140**	**47,0**	**79**	**30,6**	
					p = 0,0050
Treatment completed	**31**	**10,4**	**33**	**12,8**	
Defaulted	47	15,8	60	23,3	p = 0,2054
Treatment failure	6	2,0	8	3,1	p = 0,5930
Death	8	2,7	11	4,3	p = 0,4561
— death of tuberculosis	6	2,0	8	3,1	p = 0,5930
— other causes of death*	66	22,1	67	25,6	p = 0,9021
Total	298	100,0	258	100,0	

*__1995__ — 41 untreated patients + 6 patients treated shorter then one month + 19 patients treated too short
*__2000__ — 44 untreated patients + 5 patients treated shorter then one month + 18 patients treated too short

Table 5. A three-year follow up history of the patients who had a positive treatment outcome in years 1995 and 2000

Follow up history	1995		2000	
	Number of patients	Percent of patients	Number of patients	Percent of patients
Relapse of tuberculosis	2	0,8	2	1,0
Death	11	2,9	3	0,9
Total	242	100,0	205	100,0

ture in the course of treatment and the percentage of patients achieving permanent sputum culture negativity was the high percentage of patients defaulting after initial negativisation of sputum cultures. Sputum culture negativisation in the initial phase of treatment, when the patient is usually hospitalised and is taking medication under supervision, does not mean cure. Only a correct course of therapy without treatment interruptions guarantees treatment success and minimises the risk of relapse [1].

Our study revealed that 11.5% and 13.4% in 1995 and 2000, respectively, did not start antituberculosis treatment in spite of the bacteriological confirmation of tuberculosis (Fig. 1). These comprised patients unregistered at pulmonary clinics in whom no evidence of receiving antituberculosis treatment was found or who died before treatment was initiated [17].

The management of tuberculosis is a long-term process which requires concurrent administration of multiple drugs, which may cause many side effects. Tuberculosis management is therefore not only a pharmacological issue but also a psychological and social problem. It is difficult to persuade a patient who is not experiencing any symptoms into taking antituberculosis drugs. Good patient-doctor rapport, persuading the patient to undergo treatment and motivating him/her to continue treatment may contribute to improved outcomes [18–20].

The default rates in 1995 and 2000 were similar (15.5% vs 17.9%) (Table 2). Nearly 50% of the patients who defaulted in 1995 did so at discharge. In 2000 the percentage of these patients was even higher and equalled 65%. According to literature, patients most commonly interrupt treatment after being discharged from hospital [21].

In Poland, in line with the applicable legal regulations adopted years ago (Act of 22 April 1959 on tuberculosis control and, more recently, Act of 6 September 2001 on infectious diseases and infections), there is an obligation of registering tuberculosis cases [22, 23]. Any doctor, irrespective of specialty, who makes a diagnosis of tuberculosis is obliged to report the case in line with the applicable procedure. Our study has shown that this obligation is not always complied with. If a patient starts antituberculosis treatment in a hospital and is subsequently discharged for further treatment in the outpatient setting, the discharging doctor should sent the current treatment documentation to the outpatient clinic in which the patient intends to continue treatment. If the clinic is notified of the case of tuberculosis, it is possible for it to undertake actions to persuade the patient who

fails to show up into continuing therapy. Efficient flow of information between hospitals and outpatient clinics would make it possible to reduce the number of patients who default after completion of hospitalisation.

Many authors confirm that treatment success may only be ensured by observed therapy [6, 7, 24––27]. Directly observed treatment cannot be limited to the mere observation of patients while they are swallowing their medication. The DOTS emphasises the important role of patient-doctor cooperation viewing it as a partner relation in which the doctor is responsible for persuading the patient to undergo treatment, dispelling any concerns and drawing the patient's attention to the risks associated with interruption of therapy [18].

According to Salomon et al. [28], implementation of an antituberculosis treatment programme based on DOT as early as during hospitalisation with concurrent training on the justifiability of treatment, health benefits and risks resulting from giving up the treatment made patients accept the necessity to undergo observed treatment after discharge from hospital and continue treatment in the outpatient setting, thanks to which most of these patients completed therapy as planned.

Tsuchida et al. [25] demonstrated that following the principles of observed treatment by community nurses increased treatment success rates compared to patients who were taking their medication unsupervised (68.3% vs 87.2%).

We found that both in 1995 and 2000, when patients defaulted in the continuation phase, already on the outpatient setting, records of several patients only demonstrated entries confirming attempts to make contact with the patients to remind them of the necessity to continue treatment. Most commonly, however, as indicated by the medical records, no actions were undertaken to persuade patients into continuing treatment.

Twelve patients in 1995 and 7 in 2000 were re-treated, but treatment success was noted only in half of these patients. The remaining patients subsequently defaulted again. According to a study conducted in Istanbul, Turkey, treatment success was achieved in 85% of patients who had been re-treated [29].

For public health, treatment default is more dangerous than tuberculosis-related deaths because incomplete treatment, while protecting the patient from death, leads to increased number of individuals who are sources of infection. Patients whose treatment is erratic are infectious for longer periods and more frequently develop resistance to basic antituberculosis drugs, which requires using second-line drugs and prolonged treatment [4].

Poor tolerability of antituberculosis drugs may be another reason for treatment default [30]. In our study, however, this was the case in isolated patients. The number of defaults due to adverse reactions was 16 in 1995 and 3 in 2000 (Table 1). Medical records did not allow us to establish the causes of early discontinuation of drugs. The majority of patients had experienced unspecified side effects without objective confirmation in laboratory tests, which might suggest too hasty decisions to discontinue essential antituberculous drugs.

The treatment failure rate was 2.4% in 1995 and 2.7% in 2000 (Table 2). Treatment failures comprised patients with multi-drug resistance and patients taking their medication irregularly.

Tuberculosis-related deaths occurred in patients who had not started treatment and in patients undergoing treatment. Tuberculosis-related deaths in patients undergoing treatment were more frequent in the first days of therapy, which means that their condition on admission had been very grave and they received treatment too late.

The "other" treatment outcome category included patients who did not fit any other outcome category defined by WHO. These were untreated patients and patients who had received treatment for insufficient time from their doctors [31]. The rates of "other" outcome were 18.2% and 22.1% in 1995 and 2000, respectively (Table 2). Similar rates have been reported by Sevim et al. [32] and Lillebaek et al. [33].

According to observations made in many countries, only directly observed therapy is capable of improving treatment outcomes [7, 11, 13, 27].

The effectiveness of the DOTS strategy is also confirmed by our own studies. When we compared treatment outcomes in the former Gdansk Province, where DOT was followed in 2000, we found a significant improvement compared to the year 1995, when DOT had not yet been implemented in the outpatient setting. Of note is the fact that in 2000 none of the patients defaulted compared with the default rate of 15% in 1995 (Table 3).

When we compared the treatment outcomes in 1995 and 2000 in Warsaw and Siedlce Provinces, where DOTS was not followed, we found a significant reduction in the success rate in 2000 versus 1995 and no significant differences between 1995 and 2000 in the treatment failure rate or the default rate (Table 4).

A smoothly functioning healthcare system supported by appropriate funding results in measureable effects, as evidenced by treatment outcomes achieved in New York, where the budget for tuberculosis control increased from 4 to 40 million

dollars between 1988 and 1994 and DOTS was implemented on a large scale. By the end of 1994 such treatment had been received by 1200 patients compared to the mere 50 patients in 1983. In order to make sure that patients were taking their medication as prescribed, social workers visited them at home and at work, and visited shelters, deserted houses, parks and underground stations in search for homeless people. In 1991 the Department of Health recommended using regimens of at least four antituberculosis drugs (INH, RMP, pyrazinamide [PZA] and ethambutol [EMB]) in all the patients, which, on the one hand, enabled a more rapid negativisation paralleled by a shortened duration of treatment and, on the other, minimised the risk of treatment failure when drug resistance developed [2]. Already in the first two years a 21-percent reduction in new cases of tuberculosis was observed, and the treatment success rate rose from less than 50% in 1985 to more than 90% in 1994 [34].

Experience from Baltimore, USA, shows that DOT provided to all patients is superior to DOT provided to risk groups only [6].

In China and Cuba, treatment success rates of 90% were achieved following the implementation of DOTS [7].

If the combat against tuberculosis is to be effective, tuberculosis control programmes must be in place [35, 36]. If the system is not efficient, even rich countries do not meet the treatment targets required by WHO [37]. In Poland, according to the Central Tuberculosis Register, relapses have accounted for about 10% of tuberculosis cases for many years now [38]. According to the literature, tuberculosis most commonly relapses in the first two years after completion of treatment [33].

In the group of patients with pulmonary tuberculosis diagnosed in 1995 who achieved treatment success the disease relapsed in 2 cases within 3 years of treatment completion. Both patients relapsed 1.5 years after treatment completion. In the group of patients with pulmonary tuberculosis diagnosed in 2000 who completed treatment as planned, 4 patients were re-treated. Only 2 cases were relapses confirmed by bacteriology, and thus met the WHO criteria for relapse [1, 14]. One relapse was detected after a year and the other after 1.5 years after completion of treatment (Table 5).

The data presented demonstrate that the relapse rate among patients completing the prescribed therapy was low and equalled 0.8% and 1.0% (Table 5). Similar outcomes in compliant patients are also achieved in other countries [33, 37, 39]. Relapse rates in incompliant patients are higher [39]. In Switzerland, in the group of incompliant patients, the relapse rate at 3 years after treatment completion was 21% [37].

The number of deaths among treatment completers diagnosed in 1995 and 2000 was 11 (2.9%) and 3 (0.9%), respectively, but none of the deaths was related to tuberculosis (Table 5).

We demonstrated that the treatment outcomes in the investigated Polish provinces were worse than those reported to the Central Tuberculosis Register at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland [40]. The percentages of patients with treatment success in 1995 and 2000 alike were lower than those recommended by WHO, which largely results from the large number of untreated patients and defaults. In most cases, patients defaulted right after being discharged from hospital and being referred to outpatient clinics for further treatment.

The directly observed treatment recommended by WHO, used in outpatients, is aimed to prevent treatment defaults and to improve treatment efficacy. In 1995 directly observed treatment was being provided only to inpatients. During the data collection outside the investigated regions (Podlaskie and Gdansk Provinces) DOT was not generally being used in outpatients. The improved efficacy of treatment thanks to the implementation of DOTS is evidenced by the 2000 year outcomes in the former Gdansk Province, which were significantly better than those in 1995, before the implementation of this strategy.

Conclusions

1. The percentage of patients with permanently negative sputum culture in the cohort in whom treatment success was achieved (cured and treatment completed) was 58.8% and 54.0% in 1995 and 2000, respectively, and was lower than the percentage recommended by WHO (at least 85%).
2. The treatment outcomes in the Mazowieckie and Siedleckie Provinces in 2000 were significantly worse than those in 1995 and the outcomes achieved in the former Gdansk Province in 2000, after the DOTS strategy had been implemented, were significantly better than those in 1995, which supports the effectiveness of the strategy.

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