

## Defaulting from tuberculosis treatment in the Netherlands: rates, risk factors and trend in the period 1993–1997

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*Defaulting from tuberculosis treatment in the Netherlands: rates, risk factors and trend in the period 1993–1997. M.W. Borgdorff, J. Veen, N.A. Kalisvaart, J.F. Broekmans, N.J.D. Nagelkerke. ©ERS Journals Ltd 2000.*

**ABSTRACT:** The aim of this study was to assess the rate of defaulting from treatment among tuberculosis patients diagnosed in the Netherlands in the period 1993–1997, whether risk groups for defaulting can be identified at the start of treatment and the trend of defaulting over time.

The Netherlands Tuberculosis Register provided data on all patients diagnosed in the Netherlands during the period 1993–1997. Defaulting probabilities were determined using Kaplan-Meier survival analysis and risk factors were identified with Cox's proportional hazard analysis.

Of 7,529 patients with reported treatment outcome, 718 (10%) defaulted or left the country within 1 yr after starting treatment. Defaulting probabilities were 9% (95% confidence interval (CI) 8–10%) among 5,256 patients in low-risk groups, 17% (95% CI 14–19%) among 1,437 asylum seekers and 29% (95% CI 24–34%) among 836 patients in other high-risk groups (other recent immigrants, illegal immigrants, the homeless, prisoners and nationals from Eastern Europe). Defaulting probabilities decreased over time from 12% in 1993 to 7% in 1997.

Risk groups for defaulting can be recognized at the start of treatment. The decreasing defaulting probabilities were probably due in part to shortening treatment from 9 to 6 months and improved follow-up of asylum seekers. However, additional measures are needed to reduce defaulting among the homeless, recent immigrants, illegal immigrants and prisoners.

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In the Netherlands, the incidence of tuberculosis has decreased strongly during the course of the twentieth century among the native population, and is becoming concentrated in the elderly and in socially marginalized groups such as the homeless and alcohol or drug addicts [1, 2]. In recent years, the overall incidence of tuberculosis in the Netherlands has increased due to immigration from high-prevalence countries [2–4]. Ensuring completion of treatment in these risk groups, *i.e.* prevention of defaulting or loss to follow-up, is therefore a major task of tuberculosis control. This may require special measures. For instance, a high rate of defaulting was recognized among asylum seekers in 1994, leading to the appointment, in 1995, of a public health nurse to co-ordinate follow-up of tuberculosis patients in this group.

Since 1993, the treatment outcome of tuberculosis patients has been reported to the Netherlands Tuberculosis Register. Tuberculosis-associated mortality among tuberculosis patients diagnosed in the period 1993–1995 has been described in an earlier paper [5]. In the present paper, the risk of defaulting from treatment among patients diagnosed in the Netherlands in the period 1993–1997 was estimated and the relevant risk factors identified. One objective of the analysis was to determine whether

defaulting among asylum seekers has declined over time in response to improved procedures for the follow-up of these patients.

### Methods

The Netherlands Tuberculosis Register provided data on tuberculosis patients diagnosed in the period 1993–1997. Since 1993, patient data at diagnosis have been reported anonymously to the Netherlands Tuberculosis Register on a precoded report form. Reporting to the register is voluntary, but cross-matching with mandatory notifications to the Ministry of Health for all patients diagnosed with tuberculosis (with or without bacteriological confirmation) suggests >99% completeness. The register includes demographic data, localization of disease, previous treatment for tuberculosis, case-finding method, bacteriological data and risk groups. After completion of treatment, death or loss to follow-up, the outcome is reported to the Netherlands Tuberculosis Register on another precoded form.

The outcome of treatment is reported as follows: cured (with microbiological evidence of cure), completed treatment (and assumed cured), defaulted (*i.e.* lost to follow-up), died (cause of death tuberculosis), died (other cause of

death) and continuing treatment elsewhere (location unknown). The latter category includes mainly patients who have left the country, as patients transferred within the Netherlands should have their treatment outcome reported by the public health service in the new area of residence. In the analysis, two definitions of defaulting were applied. According to the restrictive definition, defaulting was restricted to those reported as defaulters. In the inclusive definition, used for the main analysis, patients reported as continuing treatment elsewhere (location unknown) were also considered defaulters. In the register, treatment failure is not recorded as an outcome; the final outcome is reported after completion of treatment (or death or loss to follow-up).

As most patients completed treatment within 1 yr and because defaulting after having been treated for >1 yr is probably unimportant for tuberculosis transmission and treatment outcome, risk factors for defaulting were determined within 1 yr after starting treatment. Only risk factors known at the time of diagnosis were considered. In standard cohort analysis, tuberculosis programmes report the risk of defaulting, *i.e.* the proportion defaulting of those put on treatment [6]. A more precise and somewhat higher estimate of the rate of defaulting is provided by taking into account: 1) the time at which defaulting occurs; and 2) censoring of person/time of observation due to treatment completion or death. Therefore, the time of defaulting and final risk estimates were determined using Kaplan-Meier survival analysis. Adjustment for confounders was carried out using Cox's proportional hazards analysis. Variables for multivariate analysis were partly selected *a priori* (age, sex and being asylum seeker). Other variables were selected if they showed a univariate association with defaulting. They were included in the final model if this led to significant improvement ( $p < 0.05$ ).

## Results

In the period 1993–1997, of 8,130 registered tuberculosis patients, 7,935 (98%) were alive at the time of diagnosis. Treatment outcome and duration was reported for 7,529 (95%) of those alive at diagnosis. Reporting of treatment outcome was slightly more complete for females (96%) than males (94%) but was not associated with age of the patient. It was somewhat less complete for patients from Eastern Europe (85%) and Yugoslavia including former Yugoslavian territories (89%) than for other nationalities.

Of the 7,529 patients alive at the start of treatment and with reported treatment outcome, 839 (11%) were treated for >1 yr. In the latter group, 93% reportedly completed treatment, 2% died, 5% defaulted and 1% continued treatment at an unknown location. Of the 6,690 patients treated <1 yr, 5,521 (83%) reportedly completed treatment, 547 (8%) defaulted, 451 (7%) died and 171 (3%) continued treatment elsewhere. Thus, within the first year of treatment, of 7,529 patients, 718 (10%) defaulted (including those reportedly continuing treatment at an unknown location). Defaulting occurred regularly (evenly distributed throughout the treatment period) at a rate of 14.8 per 100 person-yrs (95% confidence interval (CI) 13.1–15.2). Defaulting probabilities decreased over the study period, from 12% in 1993 to 7% in 1997 (table 1).

Most risk factors for defaulting were similar when using the restrictive and the inclusive definition (table 1). Females defaulted less often than males. Defaulting did not depend strongly on age in univariate analysis, but increased with age when taking into account other risk factors. Non-Dutch patients, in particular those from Eastern Europe and Yugoslavia including former Yugoslavian territories, defaulted relatively often. Defaulting was more common in those who had been in the Netherlands for <1 yr. Asylum seekers and illegal immigrants showed high rates of defaulting, although asylum seekers had no increased risk of defaulting when taking other risk factors into account. Very high rates were observed among prisoners. Defaulting was less likely if the diagnosis was confirmed by bacteriology.

Homeless patients, sailors, and travellers from endemic areas had increased risks of defaulting according to the inclusive definition. However, when those reportedly continuing treatment elsewhere were excluded as defaulters, relative risks were not significantly increased: adjusted hazard ratios for the homeless were 1.5 (95% CI 0.8–2.8), for sailors 1.9 (95% CI 0.8–4.7) and for travellers from endemic areas 0.8 (95% CI 0.3–1.9). It is likely that many of these patients were transferred abroad (all six homeless and 24 sailors and 17 of 20 travellers from endemic countries who were reportedly continuing treatment elsewhere were of non-Dutch nationality). Patients detected through screening had an increased risk of defaulting, which was just significant according to the restrictive definition, but was not significant according to the inclusive definition (table 1).

When taking the above variables into account in the multivariate analysis, no significant association was found between defaulting and the following variables: urban residence, having defaulted from previous curative tuberculosis treatment, localization of tuberculosis, human immunodeficiency virus infection and addiction to alcohol or drugs.

In order to aid the prediction of defaulting (using the inclusive definition) at the start of treatment and to evaluate the possible impact of the increased attention, in recent years, to the follow-up of asylum seekers, a simple classification was used. Patients were categorized into three groups: 1) asylum seekers; 2) other high-risk groups (other recent immigrants, illegal immigrants, the homeless, prisoners and nationals from Eastern Europe including Yugoslavia and former Yugoslavian territories); and 3) all others. Of the 1,437 asylum seekers, 189 (13%) defaulted within 1 yr, giving a Kaplan-Meier probability of defaulting of 17% (95% CI 14–19%). Of the 836 patients in other high-risk groups, 186 (22%) defaulted, giving a Kaplan-Meier probability of defaulting of 29% (95% CI 24–34%). Of the 5,256 other patients, 343 (7%) defaulted, giving a Kaplan-Meier probability of defaulting of 9% (95% CI 8–10%). In all three risk groups, defaulting occurred regularly over the treatment period (fig. 1).

Defaulting probabilities decreased over time from 12% in 1993 to 7% in 1997 (table 1). The proportion of patients defaulting decreased over the study period in all three groups (fig. 2). A major change occurring during the study period has been the introduction of shorter regimens. Until 1996, the national guidelines recommended 9 months' treatment; since 1996 the recommended duration has been 6 months [7]. The median duration of

Table 1. – Risk factors for defaulting within 12 months after diagnosis among 7,529 tuberculosis patients alive at diagnosis

	Subjects n	Restrictive definition*			Inclusive definition <sup>+</sup>		
		Default %	Adjusted <sup>#</sup> hazard ratio	95% CI	Default %	Adjusted <sup>#</sup> hazard ratio	95% CI
Year of diagnosis							
1993	1437	10	1		12	1.0	
1994	1687	9	0.9	0.7–1.1	11	1.0	0.8–1.2
1995	1464	7	0.7	0.6–0.9	9	0.8	0.6–1.0
1996	1569	5	0.7	0.5–0.9	7	0.8	0.6–1.0
1997	1372	6	0.7	0.5–0.9	7	0.7	0.5–0.9
Sex							
Male	4505	8	1		11	1.0	
Female	3024	6	0.7	0.6–0.9	8	0.8	0.7–0.9
Age group yrs							
<25	1796	7	1.0		9	1.0	
25–34	2099	8	1.0	0.8–1.3	11	1.1	0.9–1.4
35–44	1170	8	1.4	1.0–1.8	12	1.3	1.1–1.7
45–54	701	6	1.3	0.9–1.8	9	1.3	1.0–1.8
55–64	518	6	1.4	0.9–2.0	8	1.3	0.9–1.9
65–74	565	6	1.4	0.9–2.1	7	1.6	1.1–2.4
75	680	6	2.1	1.4–3.1	7	2.1	1.5–3.0
Nationality							
Dutch	3354	5	1		6	1.0	
Moroccan	800	6	1.0	0.7–1.4	7	1.2	0.9–1.7
Somalian	886	10	2.0	1.4–2.9	11	2.2	1.6–3.1
Surinamese	170	6	1.3	0.7–2.3	7	1.3	0.7–2.4
Turkish	415	9	1.7	1.2–2.4	12	2.2	1.5–3.0
(ex-) Yugoslavian	163	14	2.1	1.3–3.6	18	2.8	1.8–4.3
Other African	544	11	2.0	1.4–2.8	15	2.3	1.7–3.1
Other Asian	780	8	1.5	1.0–2.1	13	2.2	1.7–2.9
Eastern European	77	22	4.0	2.3–7.0	35	5.9	3.8–9.3
Latin American	81	9	2.0	0.9–4.4	19	3.2	1.8–5.6
Other/missing	259	8	1.7	1.1–2.7	22	3.6	2.6–4.9
Urban							
Yes	2569	7	-	-	10	-	-
No	4960	7	-	-	9	-	-
Time in the Netherlands							
<1 yr	1196	12	1.2	0.9–1.5	20	1.7	1.4–2.1
Other	6333	6	1		8	1.0	
Previous default from curative TB treatment							
Yes	159	13	-	-	18	-	-
No/unknown	7370	7	-	-	9	-	-
Detection							
Screening	1088	13	1.3	1.0–1.7	18	-	-
Other	6441	6	1		8	-	-
Risk group <sup>§</sup>							
Asylum seekers	1437	11	1.1	0.8–1.4	13	0.9	0.7–1.1
Illegal immigrants	201	15	1.8	1.2–2.8	24	1.5	1.1–2.1
Homeless persons	96	10	-	-	17	1.9	1.1–3.1
Alcohol addicts	80	10	-	-	10	-	-
Drug addicts	236	10	-	-	12	-	-
Prisoners	123	21	2.9	1.8–4.5	33	3.9	2.8–5.5
Health workers	144	3	-	-	6	-	-
Sailors	49	10	-	-	59	7.9	5.3–11.9
Travellers to endemic areas	126	4	-	-	19	2.7	1.8–4.2
Localization							
Pulmonary	4643	7	-	-	10	-	-
Extrapulmonary	2315	7	-	-	9	-	-
Pulmonary and extrapulmonary	571	6	-	-	8	-	-
Bacteriological confirmation							
Yes	5570	6	0.5	0.4–0.6	8	0.6	0.5–0.7
No	1959	10	1		13	1.0	
HIV infection							
Yes	307	7	-	-	11	-	-
No	7222	7	-	-	13	10	-

\*: excluding those reportedly continuing treatment elsewhere (location unknown); <sup>+</sup>: including those reportedly continuing treatment elsewhere (location unknown); <sup>#</sup>: for the variables; <sup>§</sup>: the reference category for the hazard ratios are those not in the risk group concerned. CI: confidence interval; TB: tuberculosis; HIV: human immunodeficiency virus.

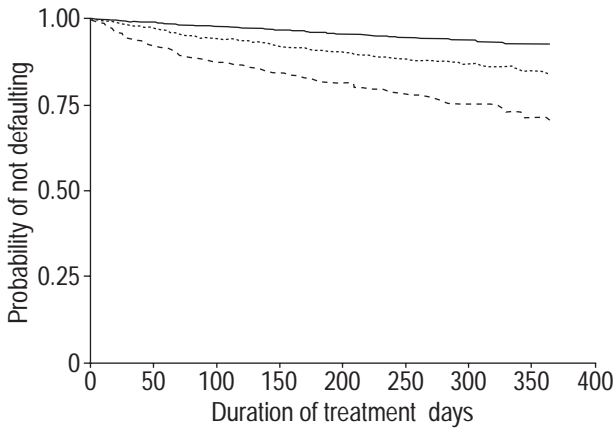


Fig. 1. – Probability of outcome other than defaulting in three risk groups among tuberculosis patients diagnosed in 1993–1997 in the Netherlands. - - - : asylum seekers; . . . : other high-risk groups including other recent immigrants, illegal immigrants, the homeless, prisoners and nationals from Eastern Europe; —: all others.

treatment decreased from 40 weeks in 1993 to 29 weeks in 1997 (fig. 2). If the trend of defaulting before 6 months is examined over time, the risk of defaulting declined from 6–3% for the low-risk group ( $p < 0.001$ ) and from 12–7% for asylum seekers ( $p < 0.01$ ), but was stable at 15% for the other high-risk groups (fig. 3).

**Discussion**

This study has shown that the risk of defaulting from tuberculosis treatment in the Netherlands was  $\sim 10\% \cdot \text{yr}^{-1}$ , risk groups for defaulting can be identified at the start of treatment and defaulting has decreased over the past few years.

National rates of defaulting from tuberculosis treatment are not widely reported in Europe. The published rates of defaulting are usually in the range 5–15% [8–10], and are thus similar to those observed in the present study. A limitation in comparing the results of these studies is that

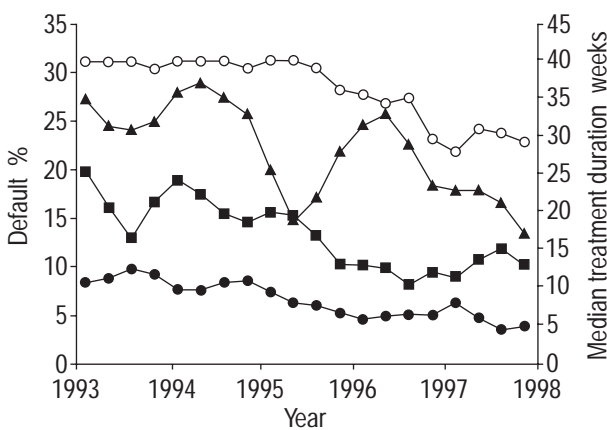


Fig. 2. – Proportion of tuberculosis cases in the Netherlands defaulting within 12 months in three risk groups by enrolment period in 1993–1997. ● : low-risk group (n=5,256); ■ : asylum seekers (n=1,437); ▲ : other high-risk groups including other recent immigrants, illegal immigrants, the homeless, prisoners and nationals from Eastern Europe (n=836). ○ : median duration of treatment.

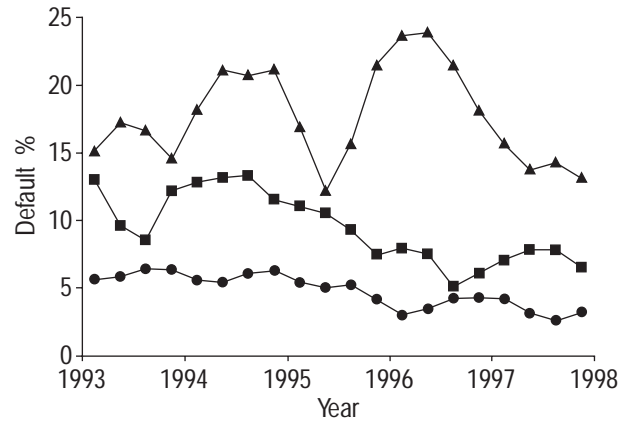


Fig. 3. – Proportion of tuberculosis cases in the Netherlands defaulting within 6 months in three risk groups by enrolment period in 1993–1997. ● : low-risk group (n=5,256); ■ : asylum seekers (n=1,437); ▲ : other high-risk groups including other recent immigrants, illegal immigrants, the homeless, prisoners and nationals from Eastern Europe (n=836).

the selection of patients and duration of follow-up varies between them. The recent introduction of standard definitions and methods in European tuberculosis surveillance should facilitate more direct comparisons between countries in the near future [6].

Noncompliance with therapy is associated with poor treatment outcome, acquired drug resistance and an increased risk of relapse [11–17]. Directly observed therapy has been an important strategy in improving compliance and treatment outcome, in particular in the USA [12, 15, 18, 19]. In the Netherlands, directly observed therapy was not used widely during the study period. In the period 1994–1996, it was given to  $\sim 5\%$  of patients (personal communication, M. Verhagen, Netherlands School of Public Health, Utrecht). It appears that, for most tuberculosis patients in the Netherlands, adequate treatment results can be obtained without generally applying directly observed therapy. However, results in high-risk groups are not excellent and show no sign of improvement. Measures to improve treatment outcome in these high-risk groups are being considered, and will include a wider application of directly observed therapy.

In the present study alcohol and drug addicts showed no increased rates of default, contrary to reports from other countries [13, 14]. The reason for the relatively low rate of default in these groups in the Netherlands may be that they have been recognized as high-risk groups for some time and are followed-up much more closely than the average patient. As present results appear adequate in this group, they may not be a priority group for expansion of directly observed therapy.

For patients who wish to be transferred abroad, including sailors and travellers from endemic countries, incomplete information on the outcome of treatment may not be completely avoidable and, in the analysis, these have not been included in the "other high-risk groups" for defaulting. However, recent immigrants, illegal immigrants, the homeless and prisoners all showed high rates of defaulting, and an expansion of measures to reduce defaulting rates appears indicated for these groups. In addition to directly observed therapy, improved co-ordination between municipal health services and prison authorities

(on continuation of treatment after discharge of prisoners) and immigration authorities (on completion of treatment of recent immigrants and illegal immigrants) needs to be considered.

The reduction in defaulting over the study period from 12–7% is probably partly attributable to shortening the recommended duration of treatment from 9–6 months. However, among asylum seekers and low-risk groups, an additional reduction in defaulting was observed within the first 6 months of treatment. The risk of defaulting among other high-risk groups, although somewhat declining overall, did not decrease over the first 6 months of treatment. Defaulting was recognized as a problem among asylum seekers in 1994 and was attributed, in part, to frequent transfers with loss of information between health authorities of different regions. Improved co-ordination of the follow-up of asylum seekers with tuberculosis, facilitated by the recruitment of a public health nurse at national level in 1995, may have contributed to decreased defaulting in this group.

The study aimed to include all patients who started tuberculosis treatment in the Netherlands in the period 1993–1997. As cross-matching with mandatory notifications suggest >99% completeness, initial reporting is unlikely to contain strong biases. However, information on completion of treatment (or death, default or transfer out) was available only for 95% of patients. As completeness of reporting was somewhat lower for groups in which defaulting was more common (such as patients from Eastern Europe), defaulting rates overall, and, in particular in the high-risk groups, may have been somewhat underestimated.

Most of the present analyses included patients who continued treatment elsewhere (location unknown) in the group of defaulters. Although not all of the patients reported as having moved away may have defaulted, the risk of defaulting is likely to be high in this group [20]. Although the level of defaulting may have been somewhat overestimated by this approach, the inclusion or exclusion of this group made little difference in the analysis of most risk factors.

It is concluded that the risk of defaulting was ~10% and risk groups for defaulting can be recognized at the start of treatment. Defaulting decreased over time, probably, in part, due to shortening treatment from 9–6 months and improved follow-up of asylum seekers. However, additional measures are needed to reduce defaulting among the homeless, recent immigrants, illegal immigrants and prisoners.

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