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Extrapulmonary Tuberculosis in Denmark From 2009 to 2014; Characteristics and Predictors for Treatment Outcome

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Background. Extrapulmonary tuberculosis (EPTB) represents an increasing percentage of tuberculosis (TB) cases in Europe. However, strategies on TB prevention and successful treatment outcomes primarily target pulmonary TB. In this nationwide study, we present characteristics of EPTB, treatment outcomes, and predictors for unfavorable treatment outcomes.

Methods. All patients diagnosed with EPTB from 2009 to 2014 were included. Logistic regression analyses were used to identify risk factors for unfavorable outcome. The following definitions were used: unfavorable outcome: the sum of treatment failed, lost to follow-up, and not evaluated; patient delay: time from TB-related symptom onset until first hospital contact related to TB; doctor delay: time from first TB-related contact in the health care system to start of TB treatment.

Results. A total of 450 EPTB cases were notified, which represented 21.1% of all TB cases in Denmark. Immigrants accounted for 82.9%. Lymph nodes were the most common site of EPTB (55.4%) followed by pleural TB (13.4%). Patient delay was significantly longer among immigrants than Danes (60 vs 30 days; $P < .01$), whereas doctor delay was significantly longer among Danes (38.5 vs 28 days; $P < .01$). Treatment completion rates were high and reached 90.9% in 2014. Male gender (odds ratio [OR], 5.18; 95% confidence interval [CI], 1.79–15.04) and age 0–24 years (OR, 16.39; 95% CI, 2.02–132.64) were significantly associated with unfavorable outcome.

Conclusions. EPTB represented a significant number of all TB cases and was predominantly seen among younger immigrants in Denmark. To maintain high treatment completion rates, increased focus on male gender and young age is needed.

Keywords. epidemiology; extrapulmonary tuberculosis; low incidence; surveillance; treatment outcome.

Extrapulmonary tuberculosis (EPTB) represents 20% of tuberculosis (TB) cases in the majority of countries in the European Union (EU) [1, 2], and even in resource-rich settings, the management of EPTB remains a challenge due to difficulties in diagnosis, delay in treatment and monitoring of treatment outcomes [3]. This is due to the varying localization, appearance, and pausibacillary nature and requirement of invasive sampling. Patients with extrapulmonary localization to the central nervous system, bone, or abdomen have a higher risk of sequela after completion of treatment, which may interfere with assessment of the outcome [4–8].

Overall, in the EU and the European Economic Area (EEA), TB notification rates have been decreasing since 2002 due to decreasing rates of pulmonary TB. Conversely, the rates for EPTB have remained stable, and consequently the proportion of EPTB has been increasing from 16.4% in 2002 to 22.8% in 2016 in the EU/EEA [1, 2]. Similar results have been reported in the United States [9].

Pulmonary TB, which is the main source of *Mycobacterium tuberculosis* (Mtb) transmission, still accounts for the majority of TB cases. However, EPTB contributes considerably to morbidity, lifelong sequelae, and mortality [4–8]. Routine contact tracing is generally only recommended in patients with smear-positive pulmonary TB [10, 11]. Yet, a recent study from the United Kingdom performed in a high–TB incidence setting found that EPTB cases were an indicator of household active and latent TB [12].

EPTB does not receive the same attention as pulmonary TB, and treatment outcomes for EPTB are often not referred to in TB control programs. Studies on treatment outcome in EPTB in low-incidence countries are scarce, and the treatment completion rates are reported with great discrepancies: from 56.9% to 89.2% [1, 8, 13–15]. The most recent Danish study from 1992

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reported a treatment completion rate for culture-positive EPTB of 67.6% [14]. Because reporting of TB treatment outcome is voluntary in Denmark, reports are often incomplete, and accurate information regarding treatment outcome in EPTB is missing. As a result, there is a need to address EPTB specifically, as this disease manifestation represents a significant burden of morbidity and mortality and has an impact on the health care system.

This study was conducted to elucidate EPTB treatment completion rates and to explore predictors for unfavorable treatment outcome in Denmark from 2009 to 2014.

METHODS

We conducted a nationwide retrospective cohort study in Denmark from January 1, 2009, to December 31, 2014.

Study Population

As part of a larger study, all TB cases notified were identified. All patients notified with EPTB were included in this study, whereas outcomes for patients with pulmonary TB are reported elsewhere. EPTB was defined according to the European Centre for Disease Prevention and Control (ECDC) classification: any bacteriologically confirmed or clinically diagnosed case of TB involving organs or anatomical sites other than the lungs, the tracheobronchial tree, or the larynx [16].

Patients were excluded if they were diagnosed with and treated for latent TB infection or infection with the *Bacillus Calmette-Guérin* (BCG) strain of *Mycobacterium bovis* due to intravesical BCG instillation only. If TB was diagnosed and treatment completed outside of Denmark, cases were excluded.

Patients were followed from time of first contact with the hospital due to EPTB until 1 year after TB treatment was completed.

Additional EPTB cases were included if a relapse/new episode of EPTB was identified in the patient record, and this case was not notified. A new episode/relapse was defined according to World Health Organization (WHO)/ECDC guidelines, and cases were only included once during a 12-month period [2, 17].

Data Source

Notification Data

TB notification has been mandatory in Denmark since 1905 and centralized since 1920 [18].

TB cases were diagnosed according to WHO definitions [17].

Microbiological Data

The International Reference Laboratory of Mycobacteriology at Statens Serum Institut performs mycobacteria diagnostics on all suspected TB cases in Denmark. This laboratory provided all bacteriological data.

Danish National Patient Registry

The Danish National Patient Registry (DNPR) contains data on all admissions to Danish public hospitals since 1977 and data on outpatient contacts since 1994 [19].

Data were obtained on all patients notified with TB in Denmark during the study period and on all patients who were assigned a TB diagnosis during the study period. Data from DNPR were used to calculate Charlson Comorbidity Index (CCI) scores [20] and to determine history of mental illness and previous TB diagnosis based on the patients' discharge diagnoses.

Data Linkage

To cross-link the registers, we used the unique Danish civil registration number (CRN), which is assigned to all residents of Denmark at birth or after residing legally in Denmark for 3 months. Patients who do not meet the criteria for obtaining a CRN are assigned a temporary CRN at first point of contact with the health care system. To accommodate for alterations in temporary CRNs, probabilistic linkage was done.

Hospital Records

For all patients identified by the notification system, medical records were reviewed for sociodemographics, clinical characteristics, and TB treatment. TB treatment outcome was obtained from hospital records, as reporting is voluntary and data from the Department of Infectious Disease Epidemiology & Prevention are incomplete [21]. TB treatment outcome was classified according to WHO definitions (Supplementary Table 1) [17].

Patient delay was calculated as time from TB-related symptom (constitutional symptoms: fever, weight loss, night sweats, and symptoms related to site of infection) onset until first hospital contact related to TB, whereas doctor delay was calculated as time from first TB-related contact with the health care system to start of TB treatment.

TB location was classified according to the origin of the sample submitted for culture and information from medical records. Cases that included >1 disease site were classified according to their major site. TB location was further divided into superficial and deep disease; skin and/or peripheral lymph node TB was considered superficial disease.

Alcohol abuse was quantified according to the Danish Health Authorities' recommendations (>14 units per week of alcohol for women and >21 units for men) [22].

Nonadherence was defined as 2 or more instances of nonattendance for clinical appointments and/or nonattendance described in the patient record.

Immigrant status was defined as patients born abroad or those born in Denmark for whom 1 or both parents had been born abroad, including in Greenland.

All hospital records were reviewed by I.K.H., and a preset format was used. In case of unclear interpretation, data were re-examined by a TB specialist: I.S.J.

Statistical Analysis

All EPTB cases were included in the data analysis describing patient characteristics. Categorical data were described by total numbers and percentages; the denominator for calculated percentages was the number of cases with known information. Data comparisons were made using the chi-square test or Fisher exact test if 20% of the expected cell values were ≤5. Continuous variables were described as medians and interquartile ranges and compared using the Wilcoxon rank-sum test. A P value of <.05 (5%) was considered statistically significant.

In the data analysis describing predictors for unfavorable treatment outcome, multidrug-resistant (MDR; n = 4), isoniazid-resistant EPTB treated with second-line drugs (n = 10) and patients who died (n = 15) or transferred out (n = 24) were excluded. Finally, 1 case was excluded due to missing medical record. Cases were excluded if the patient died or was transferred outside of Denmark during the observation period to ensure that all patients in the study population had a chance to complete treatment successfully. Treatment outcome was categorized into 2 groups: treatment completed or unfavorable outcome (the sum of treatment failed, treatment interrupted, and not evaluated). Characteristics of cases with unfavorable outcomes were compared with cases with treatment completion using univariable logistic regression. Variables for multivariable analysis were selected if they showed a univariable association with the unfavorable outcome ($P < .05$).

Incidence rates were calculated using the midyear estimates from Statistics Denmark [23]. The population was defined as contributing to 1 person-year per resident per year in the incidence rate analyses. The crude annual incidence rates were calculated as the number of incident cases per 100 000 person-years. Incidence rate ratios were assessed using Poisson regression.

Data from hospital records were entered into a Microsoft Excel 2010 version 16.29.1 (Microsoft, Redmond, Washington, USA) workbook. All statistical analysis was performed using Stata, version 15.2 (StataCorp Inc., College Station, TX, USA).

Ethics

The study was approved by the Danish Data Protection Agency (Jnr. 15/34961) and the Danish Health Authority (Jnr 3-3013-1213/1).

RESULTS

Population

Between January 1, 2009, and December 31, 2014, a total of 2150 TB cases were notified, 36 cases were excluded (latent TB [n = 6], infection with BCG strain of *Mycobacterium bovis* due to intravesical BCG instillation [n = 4], double registration [n = 12], diagnosed and treated before 2009 or after 2015 [n = 6], misdiagnosed and TB treatment terminated [n = 7], diagnosed and treated outside of Denmark [n = 1]), and an additional 17 cases were included due to relapse of TB that was not reported; this resulted in a total of 2131 cases. EPTB accounted for 450 (21.1%) cases, who were all included in this study. The distribution between PTB and EPTB did not change significantly from 2009 to 2014 (20.7%–20.8%), nor did the incidence rate of EPTB (1.23–1.17 per 100 000). When the study population was divided into immigrants (10.27–9.42 per 100 000) and Danes (0.28–0.14 per 100 000), there was still no significant change in incidence rates of EPTB during the study period (Figure 1).

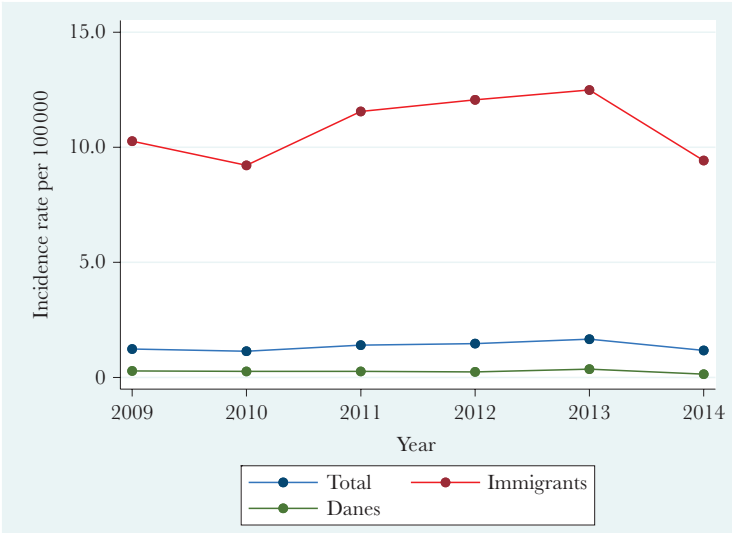

Figure 1. Extrapulmonary tuberculosis incidence rate in Denmark, 2009–2014.

Sociodemographic and Clinical Characteristics

The general characteristics of the population are summarized in Table 1.

The population consisted of 373 (82.9%) immigrants and 77 (17.1%) Danes (Table 1). Among immigrants, 353 (78.4%) were foreign born; of these, 99 (28.1%) patients were diagnosed with EPTB within 2 years of arrival. The majority of immigrants originated from Asia (n = 220; 59.0%); of these, Southeast Asia accounted for 44.1% (n = 97). Cases from Africa represented 27.3% (n = 102), and 55.9% (n = 57) originated from Somalia. Europeans (n = 35; 9.4%) and Greenlanders (n = 16; 4.3%) comprised the remaining cases.

The median age of the study population (interquartile range [IQR]) was 35 (27–48) years. Danes were significantly older than immigrants (47 vs 33 years; $P < .01$). Significantly more men were homeless, smokers, and had abused alcohol when compared with women ($P < .01$). The Danish cases were older and had higher CCI scores, and abuse of alcohol and tobacco was significantly more frequent among Danes when compared with immigrants ($P < .01$).

A total of 348 (75.3%) cases had an HIV test performed at any time during TB treatment. Nine tested positive for HIV. During the study period, the number of cases tested for HIV increased significantly, from 52.9% in 2009 to 95.5% in 2014.

The most common symptom at first contact was pain at the TB site and anemia. Patient delay was significantly longer among immigrants, whereas doctor delay was significantly longer among Danes (Table 1).

Site and Microbiological Characteristics of EPTB

The most common site of EPTB infection was lymph node (n = 246; 55.4%), followed by pleural TB (n = 62; 13.4%); this

Table 1. Characteristics of Patients With Extrapulmonary Tuberculosis in Denmark, 2009–2014

	Danes			Immigrants			
Characteristics	n	N[a]	%	n	N[a]	%	*P*
Patients		77	17.1		373	82.9	
Sex							
Male	46	77	59.7	183	373	49.1	.09
Age, y							
Median (IQR)	47	77	(32–62)	33	373	(26–44)	<.01
0–24	12	77	15.6	70	373	18.8	<.01
25–44	26	77	33.8	210	373	56.3	
45–64	22	77	28.5	82	373	22.0	
≥65	17	77	22.1	11	373	2.9	
Predisposing factors							
Alcohol	17	76	22.4	16	341	4.7	<.01
Tobacco	34	76	44.7	84	336	25.0	<.01
Cannabis	4	75	5.3	9	2.7	337	.23
History of illegal drug use	3	77	3.9	7	368	1.9	.28
Homelessness	2	77	2.6	9	371	2.4	.93
History of incarceration	0	77	0	3	368	0.8	.43
Previous TB	8	69	10.4	31	357	8.7	.64
Charlson comorbidity score							<.01
0	37	77	48.0	288	356	80.9	
1	18	77	23.4	39	356	11.0	
≥2	22	77	28.6	29	356	8.1	
Identification by contact tracing	9	77	11.7	6	368	1.6	<.01
Delay							
Patient delay, median (IQR), d	30	61	(9–120)	60	336	(26–120)	<.01
Doctors' delay, median (IQR), d	38.5	70	(14–82)	28	358	(12–63)	<.01
Total delay, median (IQR), d	90	58	(53–180)	98	328	(46–184)	<.01
Symptoms at first contact							
Weight loss	27	76	35.5	139	365	38.1	.68
Night sweat	23	72	31.9	115	349	33.0	.87
Fever	24	76	31.6	141	366	38.5	.26
Pain TB site	25	76	32.9	164	367	44.7	.06
Anemia[b]	23	40	57.5	72	167	43.1	.10

Abbreviations: IQR, interquartile range; TB, tuberculosis.

[a]Information was not available on all included patients.

[b]Women: Hgb < 7.5 mmol/L. Men: Hgb < 8.0 mmol/L.

Table 2. Disease Site and Microbiological Characteristics of Patients With Extrapulmonary Tuberculosis in Denmark, 2009–2014

	Danes			Immigrants			
Characteristics	n	N[a]	%	n	N[a]	%	*P*
Site of disease							<.01
Pleural	23	77	29.9	39	373	10.5	
Lymphatic	30	77	39.0	216	373	57.9	
Spondylodiscitis	2	77	2.6	32	373	8.6	
Abdominal	3	77	3.9	25	373	6.7	
Genitourinary	3	77	3.9	12	373	3.2	
Meningitis	3	77	3.9	12	373	3.2	
Skin	4	77	5.2	8	373	2.4	
Bone and joint	3	77	3.9	10	373	2.7	
Intracerebral	0	77	0	2	373	0.5	
Ocular	4	77	5.2	9	373	2.4	
Other[b]	0	77	0	5	373	1.3	
Superficial disease[c]	34	77	44.2	220	373	59.0	.02
Deep tissue disease	43	77	55.8	153	373	41.0	
Concomitant site							
Any	0	77	0	18	373	4.8	.05
>1	0	77	0	1	373	0.3	.65
Diagnosed supported by							
Culture positive	46	66	69.7	282	341	82.7	.02
Smear positive	11	66	16.7	79	340	23.2	.24
Nucleic amplification							
Positive	33	53	62.3	181	299	60.5	.81
Tuberculin skin test	7	9	77.8	19	23	82.6	.75
IGRA	30	44	68.2	180	216	83.3	<.01
Drug resistance							
INH mono-resistance	1	37	2.7	21	254	8.3	.23
MDR (INH and RIF resistance)	0	37	0	4	254	1.6	.44
XDR TB	0	37	0	0	254	0	0

Abbreviations: IGRA, interferon gamma release assay; INH, isoniazid; MDR, multidrug-resistant; RIF, rifampicin; TB, tuberculosis; XDR, extensively drug-resistant TB resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.

[a]Information was not available on all included patients.

[b]Genitourinary tract, cerebral other than meningitis, pericarditis, abscess.

[c]Superficial site of disease: lymph node or/and skin.

was applicable among all age groups and across immigration status (Table 2). There was a significant disparity in the distribution of EPTB within age groups. TB meningitis was most frequent among the 0–24-year age group (odds ratio [OR], 6.27; $P < .05$), whereas lymph node TB was more common in the age group 24–44 years (OR, 2.55; $P < .05$). Pleural TB was most frequent among those age 45–64 years (OR, 1.96; $P < .05$). Finally, urogenital TB was most common in the age group >64 years (OR, 4.39; $P = .05$).

Only 18 (3.5%) cases had a concomitant site of infection and fulfilled the criteria for disseminated TB; 1 of these was co-infected with HIV, and all cases were immigrants.

In total, 55 (12.2%) patients with EPTB were previously treated. Among these, 5 patients relapsed within 12 months. Two patients were diagnosed and initiated TB treatment outside of Denmark. In 406 cases, a clinical specimen was sampled for microbiologic diagnostics: 90 (20.1%) cases were smear positive, 328 (73.2%) cases were *Mycobacterium tuberculosis* culture positive, and 87 (26.6%) cases were smear and culture positive. In 291 (88.7%) cases, drug susceptibility testing was done (Table 2). Isoniazid monoresistance was identified in 22 (4.9%) cases, MDR-TB in 4 (0.9%) cases, and none of the cases had XDR-TB (Table 2). A nucleic amplification test was performed in 352 cases, of which 214 (60.6%) were positive. A total of 103 (22.9%) cases were diagnosed on clinical criteria only.

Treatment

A total of 444 cases started TB treatment. The remaining 6 patients (1.3%) died before treatment was initiated. The median treatment duration (IQR) was 6 (6–7) months. Among the drug-susceptible EPTB cases, 216 (51.1%) received the standard treatment of 2 (3 months) (the national guideline was modified in 2010; the intensive phase was decreased from 3 to 2 months) months of intensive-phase treatment including 4 drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) and 4 months of

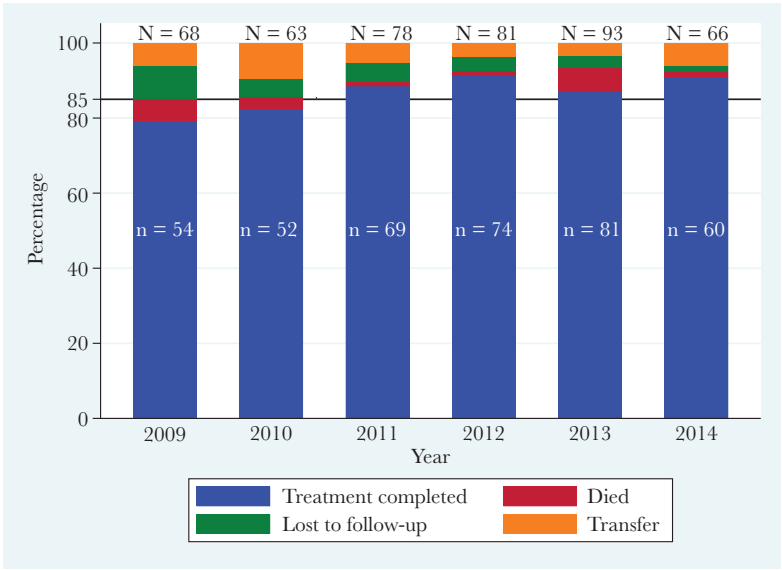

Figure 2. Extrapulmonary tuberculosis treatment outcome in Denmark, 2009–2014.[a] [a]None of the patients had the following outcome: treatment failed, not evaluated, or still on treatment.

continuation-phase treatment including 2 drugs (rifampicin, isoniazid).

TB Treatment Outcome

Treatment completion increased from 79.4% to 90.9% during the study period (Figure 2).

The highest risk for unfavorable treatment outcome was in the age group 0–24 years, and all patients were between 15 and 24 years old. Among these, the majority were male (66.7%), and 88.9% were immigrants. None of these patients smoked or abused cannabis, alcohol, or narcotics or were homeless. All were lost to follow-up and did not complete TB treatment. The median time of treatment (IQR) was 2 (1.6–3.5) months. One of the patients returned to the hospital 1.5 years later with pulmonary TB and completed TB treatment.

In total, 15 patients died. These patients were significantly older (mean age, 58 vs 37 years) and had higher CCI scores (median CCI, 0 vs 3) when compared with the remaining cases. Of those who died, Danes represented 60% of the patients. Nine patients initiated treatment. The median treatment duration (IQR) was 1.1 (1–3.5) months. The majority of the patients who died had pleural TB (40%). Two patients were diagnosed with TB meningitis, and another 2 patients had lymphatic TB. None of the patients had a concomitant site of infection.

Table 3 shows the final multivariable model fitted on 395 cases. A significantly increased risk of an unfavorable outcome was found among males and among patients <25 years of age.

DISCUSSION

In this nationwide study, we found that EPTB mainly affects young healthy immigrants from high-incidence countries. Lymph node TB was the most frequent site of EPTB. In spite of significant patient delay, the overall treatment completion rate was high and increased during the study period (P = .06). Unfavorable outcome was significantly associated with male gender and age 0–24 years.

In Denmark, the incidence of TB increased marginally from 2009 to 2012 (6.0–6.9 per 100 000) and declined thereafter [24]. The increase in TB was caused by an increased incidence in TB among immigrants [25]. The overall incidence of EPTB peaked in 2013 and decreased thereafter; however, this was not significant. The proportion of EPTB followed the same trend. Hence, we did not find a significant change in incidence or proportion of EPTB in Denmark during our study period. The proportion of PTB was persistently high, and the smear positivity among PTB cases was high at 54.6% during the study period, which is a predictor for insufficient TB control in Denmark [21].

The localization of EPTB has been related to age, gender, and ethnicity. We found that lymph node TB was the most common site of EPTB, followed by pleural TB. In addition, certain types of EPTB were associated with specific age groups. This is in line with earlier studies from low-incidence countries [7, 15, 26–31]. Earlier studies from high-incidence countries have indicated that EPTB is associated with female sex [32, 33]. We were not able to demonstrate this, as 50.9% were males. However, this is in accordance with studies from other low-incidence countries [8, 34, 35].

Overall, TB treatment completion rates were high and did increase during the study period, reaching 90.9% in 2014. We recently found an overall treatment completion rate of 86.6% in 2014 in pulmonary TB [21]. This difference could be explained by higher adherence and less substance abuse

Table 3. Odds Ratio for Unfavorable Outcome vs Treatment Completion Among EPTB Patients in Denmark, 2009–2014

Characteristics at Time of EPTB Diagnosis	No. of Cases (%)		Factors Associated With Unfavorable Treatment Outcome, Univariate Logistic Regression		Factors Associated With Unfavorable Treatment Outcome, Multivariate Logistic Regression	
	Unfavorable Outcome	Treatment Completion	OR	95% CI	OR	95% CI
Total	20 (5.1)	376 (94.9)				
Sex						
Female	4 (2.0)	195 (98.0)	RF			
Male	16 (8.2)	181 (91.8)	4.33	1.42–13.23	5.18	1.79–15.04
Age, y						
0–24	9 (12.3)	64 (87.7)	13.36	1.65–108.32	16.39	2.02–132.64
25–44	9 (4.4)	195 (95.6)	4.41	0.55–35.39	4.44	0.55–35.64
45–64	1 (1.0)	95 (99.0)	RF		RF	
≥65	1 (4.4)	22 (95.6)	4.32	0.26–72.01	5.73	0.33–100.3
Country of origin						
Denmark	3 (4.5)	64 (95.5)	RF			
Other	17 (5.2)	313 (94.8)	1.17	0.33–4.11		
Predisposing factors						
Alcohol	2 (7.4)	25 (92.6)	1.87	0.40–8.73		
Tobacco	7 (6.7)	98 (93.3)	1.98	0.72–5.49		
Cannabis	2 (16.7)	10 (83.3)	4.83	0.96–24.4		
History of illegal drug use	1 (12.5)	7 (87.5)	2.75	0.32–23.58		
Homelessness	2 (20.0)	8 (80.0)	5.08	1.00–25.74		
History of incarceration	0 (0.0)	1 (100.0)	NA			
Previously TB	3 (8.6)	32 (91.4)	2.09	0.57–7.70		
History of mental illness	2 (11.8)	15 (88.2)	2.67	0.57–12.58		
Charlson comorbidity score						
0	17 (5.8)	275 (94.2)				
1	0 (0.0)	52 (100.0)				
≥2	1 (2.4)	40 (97.6)	0.05–3.12	0.38		
Concomitant site						
Any	0 (0.0)	14 (100.0)	NA			
Superficial site of disease[c]	11 (4.8)	218 (95.2)	RF			
Deep site of disease	9 (5.4)	158 (94.6)	1.12	0.45–2.78		
Diagnosis supported by:						
Culture positive	16 (5.0)	307 (95.0)	0.90	0.29–2.79		
Identification by contact tracing	0 (0.0)	13 (100.0)	NA			
Clinical symptoms						
Symptom duration >30 d	11 (5.1)	205 (94.9)	1.18	0.42–3.27		
Time to diagnosis >30 d	8 (4.2)	181 (95.8)	0.81	0.31–2.10		
Weight loss	8 (5.6)	136 (94.4)	1.14	0.45–2.87		
Fever	10 (7.1)	131 (92.9)	1.85	0.75–4.56		
Night sweet	9 (7.3)	114 (92.3)	1.70	0.68–4.23		
Adherence[b]	3 (0.8)	357 (99.2)				
Nonadherence	16 (48.5)	17 (51.5)	112	29.7–422.38		

Abbreviations: CI, confidence interval; EPTB, extrapulmonary tuberculosis; OR, odds ratio; RF, reference; TB, tuberculosis.

[a]A total of 395 cases were included in the multivariable analysis.

[b]Nonadherence: if described in patient records and/or ≥2 episodes of nonattendance for clinical appointments.

[c]Superficial site of disease: lymph node or/and skin.

and homelessness in the EPTB group. A Finnish study found a treatment completion rate of 56.9% in patients with EPTB; however, these patients were older (median age, 70.1 years) and had more comorbidities, and immigrants only represented 10.9% [8]. A study from Texas reported an EPTB treatment completion rate of 82.5%. The study population differed in terms of higher prevalence of HIV and drug use. Location of EPTB close to the central nervous system and peritoneum was more frequent [5]. This emphasizes that even between low-incidence countries, TB treatment outcomes can be challenging to compare without knowledge regarding risk factors and comorbidity.

All patients classified as having an unfavorable outcome were lost to follow-up. In line with an earlier study, men were identified to be at significantly higher risk for unfavorable treatment outcomes [8]. This could be partly explained by a significantly higher frequency of use of cannabis, alcohol abuse, and being homeless, all factors that contribute to poor adherence among men with EPTB. The risk of an unfavorable outcome was significantly associated with the age group 0–24 years. All these patients were lost to follow-up. We did not find any known risk factors for being lost to follow-up: for example, abuse of alcohol or drugs or homelessness. However, these patients were predominantly immigrants and might have experienced language difficulties that led to misunderstandings regarding treatment and follow-up.

Treatment outcome was evaluated at the time of treatment completion and categorized as successful if there were no signs of failure according to the current definition by the WHO [17]. Signs of failure were typically assessed by clinical appearance, advanced imaging techniques, inflammation markers, and Hgb. New tissue samples were often not collected, as this would involve an invasive procedure; consequently, these patients could not be classified as having experienced treatment failure. In line with earlier studies, we suggest that treatment outcomes should be assessed 12 months after treatment completion, and in case of relapse, the treatment outcome should be categorized as treatment failure [36, 37].

Immigrants had a significantly longer patient delay than Danes. The Danish health care system provides free and equal health care to all legal residents in Denmark; hence the patient delay among immigrants cannot be explained by inequality in access to health care. However, immigrants might experience language barriers that result in misunderstandings and misinterpretations when approaching the health care system. This emphasizes the need for professional translators. In addition, cultural differences can cause delay in seeking professional care, as TB still is stigmatizing in many high-incidence countries [38, 39]. Doctor delay was significantly higher among Danes when compared with immigrants. This might be explained by less suspicion of EPTB among Danes because of a low incidence of EPTB in this group. The fact that Danes were older and had coexisting illness could have made the EPTB diagnosis difficult and contributed to delay. In a recent study, we found that doctor delay in pulmonary TB was much lower for both Danes and immigrants (9 and 5 days, respectively) [21]. EPTB can be challenging to diagnose, as the disease can affect virtually all organs and the clinical presentation can be nonspecific. As a result, these patients can present to doctors with minimal experience with TB. In addition, the EPTB site can be relatively inaccessible, causing sampling of a specimen to be challenging.

This is the first study to provide a complete review of EPTB treatment outcomes during a 6-year period in Denmark. Additionally, this study provides clinical data as well as comprehensive outcome information on a large group of Danish EPTB patients. However, the study has limitations: The population was identified by notification data; hence patients who were not notified were not included. This could have introduced selection bias. Yet, a recent study from Denmark has assessed the underreporting of TB to 7.5% in the same period. The non-notified cases were all culture-negative and did not differ significantly in treatment outcomes and risk factors from the notified cases [40]. All clinical information was from hospital records; hence there was no direct patient contact. The quantity and quality of information solely depended on the hospital records. Treatment was prolonged in patients who did not respond satisfactorily, and new samples were not collected because of the risk associated with an invasive procedure. This has potentially led to an underestimation of treatment failure. Patients who were lost to follow-up may still have completed treatment. However, this concern is limited, as the CRN allowed us to trace patients who appeared at another hospital or emigrated during the study period. CCI could not be assessed for patients with temporary CRNs, because they were not registered in the DNPR. These patients accounted for 3.8% (n = 17) of the entire population. Finally, the number of patients with an unfavorable outcome was relatively small, thereby decreasing the power of the study and potentially preventing us from identifying predictors associated with an unfavorable outcome.

CONCLUSIONS

EPTB represents a significant number of TB cases in Denmark. Doctor delay was significantly longer among Danish patients, which emphasizes that EPTB should be considered a differential diagnosis in Danish patients, especially in the older age group. Even with a treatment completion rate as high as 90.9% in 2014, a continuous effort is needed to prevent unfavorable outcomes and mortality, especially among males and those aged <25 years, which as male sex and age <25 years were identified as risk factors for an unfavorable outcome.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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