

# Characteristics and Clinical Outcome of Bone and Joint Tuberculosis From 1994 to 2011: A Retrospective Register-based Study in Denmark

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**Background.** Most information on bone-joint (BJ)-tuberculosis is based on data from high-incidence areas. We conducted a nationwide register-based analysis of BJ-tuberculosis in Denmark from 1994 to 2011.

**Methods.** We linked data from the national tuberculosis surveillance system on BJ-tuberculosis, hospital records, the Danish Hospital and Civil Registration System.

**Results.** We identified 282 patients with BJ-tuberculosis, 3.6% of all tuberculosis cases ( $n = 7936$ ). Spinal tuberculosis was found in 153 of 282 patients (54.3%); 83.3% of all cases were immigrants. Danes were older and had higher Charlson comorbidity index scores than immigrants ( $P < .01$ ). C-reactive protein and erythrocyte sedimentation rates were elevated in most cases. Median time to diagnosis after first hospital contact was 19.5 days for spinal tuberculosis and 28 days for other forms of BJ-tuberculosis ( $P = .01$ ). Of patients with spinal tuberculosis, 54/133 (40.6%) had neurologic deficits at admission and 17.3% presented with cauda equina. Diagnosis was culture verified in 87%. (Resistance to any drug was found in 10.2%). Median time on antituberculous treatment for patients with spinal and other forms of BJ-tuberculosis was 9 months and 7 months, respectively ( $P < .01$ ). Surgery was required in 44.4% patients with spinal tuberculosis and in 32.6% patients with other forms of BJ-tuberculosis ( $P = .04$ ). Sequelae were reported in 57.5% of patients with spinal tuberculosis and 29.1% of patient with other forms of BJ-tuberculosis ( $P < .01$ ). One-year mortality was 25.5% among Danes compared with 1.3% among immigrants ( $P < .01$ ).

**Conclusions.** BJ-tuberculosis was rare and seen mainly in younger immigrants in Denmark. More than half of cases were spinal tuberculosis, presenting with more severe symptoms and worse outcome, compared with other forms of BJ-tuberculosis.

**Keywords.** spinal tuberculosis; Pott disease; tuberculous osteomyelitis; epidemiology.

Since the late 1980s, industrialized countries have experienced an increasing incidence of tuberculosis, mainly because of the increase in the number of immigrants to these countries. This has led to new public health challenges, in particular with respect to an increasing

number of extrapulmonary (EP) tuberculosis cases. Even though the notification rates of overall tuberculosis and pulmonary tuberculosis have been decreasing in the European Union and the European Economic Area since 2002, the proportion of EP tuberculosis has increased from 16.4% in 2002 to 22.4% in 2011 [1].

Bone and joint (BJ)-tuberculosis is a well-known infectious disease manifestation; in many reports, it is identified as the third most frequent localization of EP tuberculosis [1–4]. Most of the epidemiological characteristics, clinical features, and treatment trials of BJ-tuberculosis are based on data from areas where the prevalence of tuberculosis is high [5–8]. Even though spinal tuberculosis (Pott disease) is a severe manifestation of EP

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tuberculosis, the true worldwide incidence is unknown due to lack of notification data. Pott disease may lead to serious neurological sequelae and even death. Therefore, attention to this disease is important even in countries where the prevalence of tuberculosis is low.

Denmark has 5.6 million inhabitants of whom immigrants and their descendants constitute 567 932 (10.1%) persons. The overall tuberculosis incidence was 6.9/100 000 population in 2012 (388 notified cases). EP tuberculosis accounted for 26% of all cases. Immigrants or descendants made up 66% of all tuberculosis cases. The incidence was 2.6 and 44.0/100 000 population for Danes and immigrants, respectively [9].

We conducted a retrospective cohort analysis of BJ-tuberculosis that covered a 17-year period, with the aim of providing an overview of trends in notifications, clinical features, and treatment outcomes.

## MATERIAL AND METHODS

### *Tuberculosis Surveillance Data*

The Danish national tuberculosis surveillance system is hosted by the Department of Infectious Disease Epidemiology at Statens Serum Institut. We retrieved data on all notified BJ-tuberculosis cases as a primary or secondary localization from 1994 to 2011, including data on demographics, concomitant clinical manifestations, disease verification, and treatment outcomes reported. A standard form that was in accordance with World Health Organization definitions was used by the treating physicians since 2000 [10]. The treatment outcome results from the year 2000 were incomplete, and these data were excluded from analyses. The immigrant group included patients born abroad and their children as well as people from Greenland living in Denmark.

### *Principle of Data Linkage*

We cross-linked BJ-tuberculosis cases with administrative and medical registers using the unique Danish civil registration number, which is assigned to all residents of Denmark at birth or after residing legally in Denmark for 3 months [11].

### *Patient Records*

The available hospital records were reviewed for comorbidities, symptoms, duration of symptoms, and clinical and paraclinical findings, including mycobacteriological results, time from first hospital contact to diagnosis, and sequelae. However, some data from the beginning of the study period were missing due to routine destruction of paper-based medical records and late introduction of electronic medical records in some hospitals.

### *Danish Hospital Registry*

The Danish Hospital Registry was established in 1977 to collect information on all nonpsychiatric hospital admissions in

Denmark. Data from outpatient and emergency department visits have been included since 1994. For each contact, the registry records dates of admission and discharge, as well as discharge diagnoses assigned by the treating physicians and coded according to the *International Classification of Diseases, 10th revision*. We extracted data from this registry on patients' comorbidities, surgeries, and other invasive procedures related to a diagnosis of BJ-tuberculosis. The Charlson comorbidity index (CCI) was constructed based on discharge diagnoses before study inclusion, as described elsewhere [12].

### *Danish Civil Registration System*

The Danish Civil Registration System was established in 1968 and includes information on daily updated vital status and migration for all residents of Denmark.

### *Statistical Analysis*

We constructed contingency tables that display "characteristics of BJ-tuberculosis by immigrant status" and "clinical and paraclinical results by location (spinal/other BJ-tuberculosis)." Continuous variables were described as medians with interquartile ranges and compared using the Wilcoxon rank sum test. Categorical variables were described as proportions (percentages) and compared using the  $\chi^2$  test. All statistical tests were 2-tailed, and the significance level was  $P < .05$ . Stata, version 13 (Stata-Corp LP, College Station, Texas), and Microsoft Excel 2010 were used for data analysis.

### *Ethical Considerations*

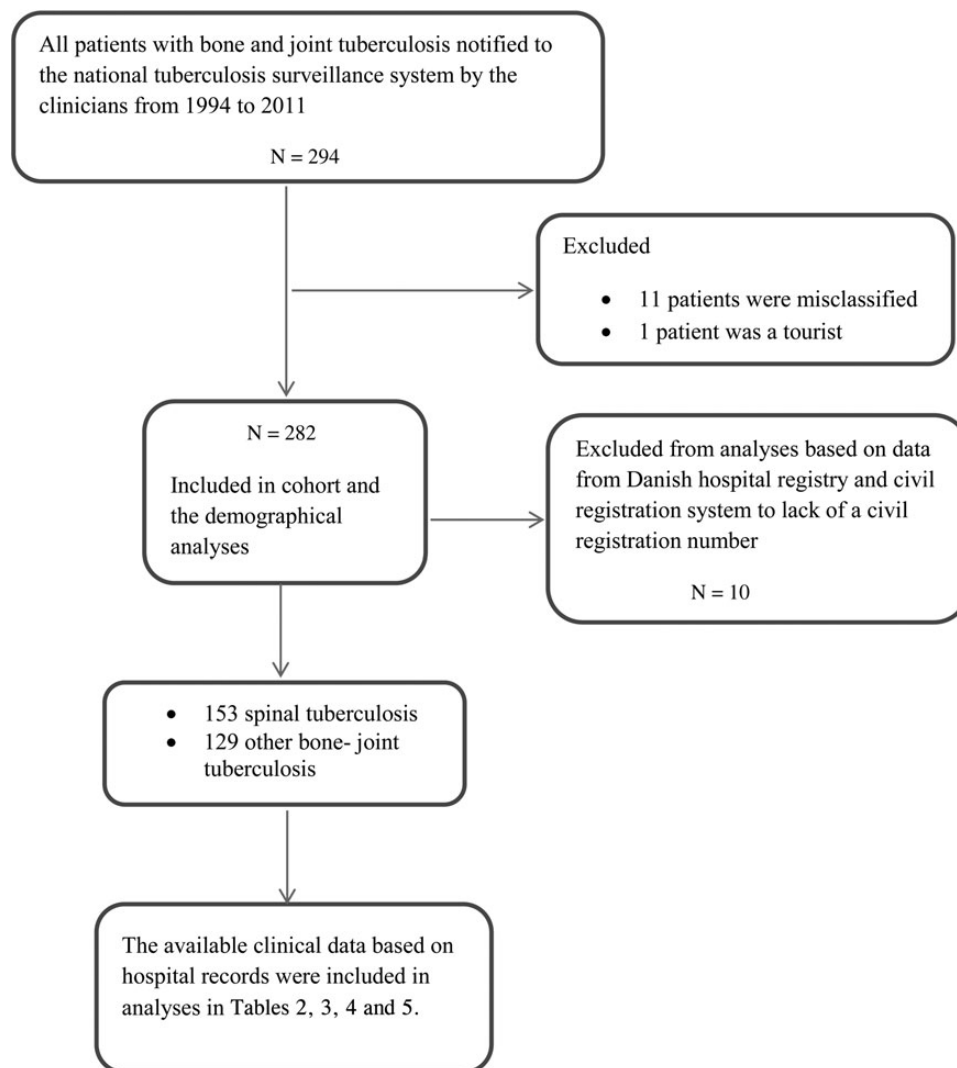
The Danish Data Protection Agency granted permission for the study (2012-41-0890), and the Danish Health and Medicines Authority (3-3013-294/1) gave approval to study patients' records.

## RESULTS

During the study period, we identified 294 patients with BJ-tuberculosis; 282 were included in the study (Figure 1). During this period, 7936 tuberculosis cases were reported and BJ-tuberculosis accounted for 3.6% (annual range, 0.2%–5.5%) of all tuberculosis cases. Trends in annual tuberculosis notification and BJ-tuberculosis are shown in Figure 2.

### *Demographic Characteristics*

In total, 47 (16.7%) patients were Danes and 235 (83.3%) were immigrants. Of immigrants, 63.8% ( $n = 150$ ) were of African origin and 133 (88.7%) of these were from Somalia. The second largest immigrant group was from Asia; there were 64 patients with the following distribution: Pakistan ( $n = 21$ ), Vietnam ( $n = 12$ ), India ( $n = 10$ ), and Sri Lanka ( $n = 8$ ). The 18 Europeans were from Balkan countries and Turkey. The remaining



**Figure 1.** Study enrollment flow chart.

patients were from Greenland ( $n = 2$ ), Iraq ( $n = 2$ ), Lebanon ( $n = 1$ ), and Peru ( $n = 1$ ).

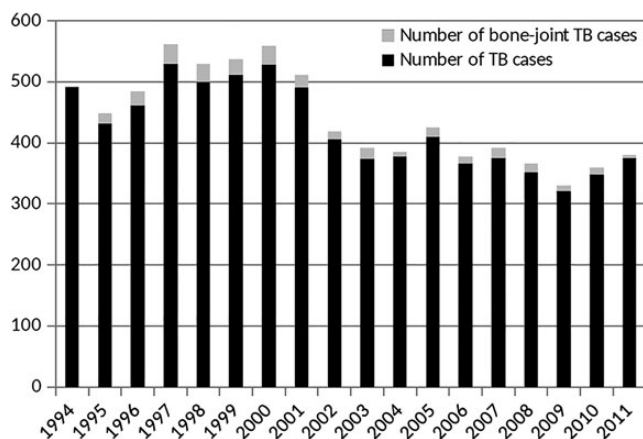
The general characteristics of the study population, stratified by immigrant status, are summarized in Table 1. The Danish cases were older and had more predisposing factors than those in the immigrant group. The CCI score was  $\geq 2$  in 28.3% of the Danish cases compared with 9.4% among immigrants ( $P < .01$ ). Only 20 (42.6%) of the Danish cases and 68 (28.9%) of immigrants were tested for human immunodeficiency virus (HIV); 2 tested positive. In total, 25.5% of the Danish cases died within 1 year after diagnosis compared with 1.3% of the immigrant cases ( $P < .01$ ).

### Site of Infection and Clinical Findings

Spinal tuberculosis made up 54.3% of all BJ-tuberculosis cases. Concomitant pulmonary tuberculosis was seen in both groups,

and a few other EP localizations were seen among immigrant cases ( $P > .05$ ; Table 1). The BJ-tuberculosis diagnosis was verified by a positive culture in 245 (87%) patients, and there was no significant difference in diagnostic verification between the 2 groups (Table 1).

The presenting clinical features of spinal and other forms of BJ-tuberculosis are summarized in Table 2. Back pain or pain at the disease site were the dominating symptoms. Neurological symptoms were present in 40.6% of the patients with spinal tuberculosis compared with 3.6% of patients with other forms of BJ-tuberculosis ( $P < .01$ ). In total, 17.3% of spinal tuberculosis cases had cauda equina syndrome and 13.7% had paraplegia. Among the 23 patients with cauda equina, the median age was 33 years (range, 12–85) and all but 3 were immigrants.



**Figure 2.** Annually notified total and bone-joint cases of tuberculosis (TB) in Denmark from 1994 to 2011. The number of notified tuberculosis cases in 1994 was 495 and increased to 548 in the year 2000.

The median time to diagnosis after first hospital contact was 19.5 days for spinal tuberculosis and 28 days for other forms of BJ-tuberculosis ( $P = .01$ ; Table 2).

Low hemoglobin and normal white blood cell counts were seen in the majority of patients regardless of disease localization. C-reactive protein was elevated in more than 90% of patients. The erythrocyte sedimentation rate was elevated in 95% of patients with spinal tuberculosis and in 83.7% patients with other forms of BJ-tuberculosis (Table 2).

Standard plain radiograph was used more frequently in the diagnostic work-up of peripheral BJ-tuberculosis, whereas magnetic resonance imaging (MRI) was used more frequently in the diagnostic work-up of spinal tuberculosis ( $P < .01$ ; Table 2).

The disease sites of BJ-tuberculosis cases are listed in Tables 3 and 4. The thoracic and thoracolumbar spine combined was most commonly involved (44.8%) site, followed by the lumbar spine (29.4%; Table 3). In 5 patients with peripheral BJ-tuberculosis, paravertebral and psoas abscesses were also found. The locations of other forms of BJ-tuberculosis manifestations are listed in Table 4.

### Microbiological Results

The interferon gamma-release test (QuantiFERON-TB Gold) for *Mycobacterium tuberculosis* was performed in 32 patients; 23 (71.9%) had positive test results and 4 (12.5%) were indeterminate. Tuberculin skin test results were available for 69 cases; 62 (89.9%) were positive (Table 2).

Positive culture was obtained from BJ samples in 230 and non-BJ samples in 15 patients. Smear for acid-fast bacilli was positive in 114 (44.4%) patients. Nucleic acid amplification

**Table 1. Characteristics of Bone-Joint Tuberculosis in Denmark From 1994 to 2011**

Characteristic	Danes		Immigrants		P Value
	n/N <sup>a</sup>	%	n/N <sup>a</sup>	%	
Patients (%)	47	16.7	235	83.3	
Sex					.59
Male	27	57.5	125	53.2	
Age, y					<.01
<15	0	0.0	14	6.0	
15–24	1	2.1	36	15.3	
25–44	9	19.2	133	56.6	
45–64	10	21.3	35	14.9	
≥65	27	57.5	17	7.2	
Predisposing factors					
Previous tuberculosis	12/38	31.6	18/136	9.7	<.01
Diabetes mellitus	3/39	7.7	13/188	6.9	.86
Biologic treatment	2/40	5.0	1/187	0.5	.03
Chronic renal failure	1/40	2.5	2/187	1.1	.47
Malignancy	7/40	17.5	1/187	0.5	<.01
Alcohol abuse	4/40	10.0	2/188	1.1	.01
Other immunosuppression	5/40	12.5	4/187	2.1	.02
Intravenous drug use	1/39	2.6	1/187	0.5	.22
Pregnancy	0/47	0.0	5/235	2.1	.31
HIV status					.44
HIV infected	0		2	2.94	
HIV uninfected	20	100.0	66	97.06	
Charlson comorbidity index					<.01
0	24	52.2	181	80.8	
1	9	19.6	22	9.8	
≥2	13	28.3	21	9.4	
Disease site					.29
Spine	22	46.8	131	55.7	
Nonspinal osteoarticular	25	53.2	104	44.3	
Concomitant site					.99
Pulmonary	7	14.9	37	15.7	
Pleural	0		2	0.9	
Lymphatic	0		9	3.1	
Other	0		3	1.3	
Disease verification					.32
Culture positive	40	85.1	205	87.2	
Smear positive	0	0.0	1	0.4	
Nucleic amplification positive	1	2.1	3	1.3	
Clinical symptoms	1	2.1	6	2.6	
Imaging	0		9	3.8	
Tuberculin skin test	1	2.1	4	1.7	
Interferon-γ release assay	1	2.1	4	1.7	
Histology	2	4.3	3	1.3	
Autopsy	1	2.1	0		
Dead within 1 year	12	25.5	3	1.3	<.01

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup> Information was not available on all included patients.

**Table 2. Presenting Clinical Features of Spinal and Other Bone-Joint Tuberculosis in Denmark**

Clinical Feature	Spinal Tuberculosis			Other Bone-Joint Tuberculosis			P Value
	n	N <sup>a</sup>	%	n	N <sup>a</sup>	%	
Fever	59	130	45.4	43	78	55.1	.17
Pain	124	136	91.2	60	86	69.8	.21
Night sweats	46	124	37.1	18	77	23.4	.04
Weight loss	61	127	48.0	25	77	32.5	.03
Cough	22	131	16.8	15	83	18.1	.81
Neurological deficit	54	133	40.6	3	82	3.7	<.01
Paraplegia	18	131	13.7	0	82	0	<.01
Cauda equina syndrome	23	133	17.3	0	82	0	<.01
Interferon- $\gamma$ release assay	18	21	85.7	5	7	71.4	.07
Tuberculin skin test	38	43	88.4	24	26	92.3	.85
Diagnostic biopsy	15	153	9.8	7	129	5.4	.17
Symptom duration (median, days)	120	(60–180)		90	(30–300)		.69
Time to diagnosis (median, days)	19.5	(7.5–31)		28	(13–90)		.01
Hemoglobin (mmol/mL)							.97
Normal (8–10.5)	25	97	25.8	14	55	25.5	
Low (<8)	72	97	74.2	41	55	74.5	
White blood cell count (million/L)							.91
Normal (3.5–9)	73	93	78.5	39	49	79.6	
High (>9)	20	93	21.5	10	49	20.4	
C-reactive protein (mg/L)							.47
Normal (<20)	7	102	6.9	4	55	7.3	
Moderate–elevated (20–100)	62	102	60.8	28	55	50.9	
High (>100)	33	102	32.4	23	55	41.8	
Erythrocyte sedimentation rate (mm/h)							.04
Normal (<20)	4	80	5	7	43	16.3	
Elevated (>20)	76	80	95	36	43	83.7	
Imaging method performed							
Standard radiograph	84	130	64.6	67	84	79.8	.02
Bone scintigraphy	17	136	12.5	15	79	19.0	.2
Computed tomography	52	137	38.0	21	81	25.9	.07
Magnetic resonance imaging	121	140	86.4	24	81	29.6	<.01
Positron emission tomography–computed tomography	3	137	2.2	0	81	0	.18

<sup>a</sup> Information was not available on all included patients.

analysis for *M. tuberculosis* was positive in 94 (66.6%) cases (BJ samples in 93 and lymph node biopsy in 1); the test was not performed in 83 patients.

### Drug Resistance

Drug susceptibility test results were available for the 245 culture-verified cases. Resistance to any drug was found in 25 (10.2%) patients. Monodrug resistance to isoniazid was found in strains from 11 cases. Ethambutol monoresistance was found in 1 strain, pyrazinamide monoresistance was found in 6 *Mycobacterium bovis* isolates and 2 *M. tuberculosis* isolates, whereas resistance to isoniazid and pyrazinamide was found

in 1 isolate. Resistance to rifampicin, isoniazid, and ethambutol (multidrug resistance) was found in 1 strain.

### Treatment

Information on the duration of antituberculous treatment was available for 139 patients with spinal tuberculosis and for 86 patients with other BJ-tuberculosis localizations. There was a significant difference in median time on antituberculous treatment between patients with spinal and other forms of BJ-tuberculosis (9 month vs 7 months;  $P < .01$ ; Table 5). One patient with multidrug-resistant tuberculosis in the spine was treated with amikacin, ofloxacin, cycloserine, and ethambutol

**Table 3. Site of Spinal Tuberculosis in Denmark**

Site	Patients	
	n/143	%
Cervical	9	6.3
Thoracic	50	35.0
Thoracolumbar	14	9.8
Lumbar	42	29.4
Lumbosacral	8	5.6
Sacral	9	6.3
Multiple spinal level	11	7.7
Paravertebral abscess	61	42.7
Epidural abscess	36	25.2
Psoas abscess	46	32.2
Number of vertebrae involved		
1–2	97	67.8
3–4	34	23.8
5 or more	12	8.4

for 24 months. In cases of monoresistance or drug intolerance, either ofloxacin (before 2007) or moxifloxacin (after 2008) was included in the treatment regimen. Rifabutin was replaced with rifampicin in 1 HIV-positive patient because a protease inhibitor was part of the antiretroviral treatment. Surgery was required in 68 (44.4%) patients with spinal tuberculosis and 42 (32.6%) patients with other forms of BJ-tuberculosis ( $P = .04$ ; Table 5).

### Recurrence

Three cases were registered with a recurrence during the study period. All were immigrants, aged 25–44 years. A woman with a

**Table 4. Site of Other Bone-Joint Tuberculosis**

Site	Patients	
	n/N	%
	107/129	82.9
Sternoclavicular	2	1.9
Rib	3	2.8
Sternum	7	6.5
Shoulder	5	4.7
Elbow-arm	6	5.6
Wrist-hand	6	5.6
Sacroiliac	8	7.5
Hip	14	13.1
Femur	6	5.6
Knee	14	13.1
Tibia	3	2.8
Ankle joint	11	10.3
Foot	14	13.1
Other	8	7.5

**Table 5. Treatment Duration, Surgery, and Sequelae of Bone-Joint Tuberculosis by Site in Denmark**

Duration (mo)	Spinal Tuberculosis		Other Bone-Joint Tuberculosis		<i>P</i> Value
	n = 139	%	N = 86	%	
<6 <sup>a</sup>	6	4.3	9	10.5	
6	56	40.3	43	50.0	
9	36	25.9	19	22.1	
≥12	41	29.5	15	17.4	
Median time on treatment	9 (IQR 6–12 mo)		7 (IQR 6–9 mo)		<.01
Surgical treatment	68/153	44.4	42/129	32.6	.04
Sequelae	66/139	47.5	25/86	29.1	<.01

Abbreviation: IQR, interquartile range.

<sup>a</sup> Death (n = 10) or lost to follow-up (n = 5).

previous history of tuberculosis relapsed twice. She was initially treated for culture-negative cervical tuberculosis for 9 months. She was then treated twice for culture-positive lumbar tuberculosis 2 years later. The isolate was drug susceptible in both episodes, and she was treated for 12 months. The second patient was initially treated for culture-positive lumbar tuberculosis with a psoas abscess for 6 months and 2 years later was retreated for culture-negative thoracic tuberculosis for 6 months. The third patient was treated for culture-positive drug-susceptible tuberculosis in the sternum and retreated 4 years later for culture-negative pulmonary and thoracic spinal tuberculosis for 10 months.

### Treatment Outcome

Sequelae were reported in 66 of 139 (47.5%) patients with spinal tuberculosis and in 25 of 86 (29.1%) patients with other forms of BJ-tuberculosis ( $P < .01$ ; Table 5). Of 23 patients with cauda equina, 2 (8.6%) died, 1 (4.3%) had tetraplegia, 5 (21.7%) had impaired movement, and 3 (13%) had back pain as sequelae. There was no significant difference in sequelae among patients with spinal tuberculosis in relation to surgical treatment. Sequelae were reported in 31 (47%) patients who underwent surgery and in 35 (53%) who did not. Of the patients who died, 2 (40%) underwent surgery and 3 (60%) did not ( $P = .86$ ). For patients with other forms of BJ-tuberculosis localization, there were also no differences in outcome with regard to surgery. The majority of patients had pain as sequelae, but impaired physical ability and deformities were also reported.

The treatment outcomes for 130 patients were reported from 2001 to 2011. Treatment success was achieved in 108 (83%) of the cases. Six (5%) patients died, 5 (4%) were lost to follow-up, 3 were transferred, and the outcome was unknown for 8 (6%).



## Mortality

Twelve Danes (25.5%) and 3 (1.3%) immigrants died within 1 year from the time of diagnosis. However, reliable survival data were only available for 225 immigrants because civil registration numbers were missing for 10 patients. Tuberculosis was the cause of death in 7 Danes and 1 immigrant. Sudden death after completion of tuberculosis treatment was registered for 1 Dane and 1 immigrant. Two Danes died from pancytopenia/bleeding during antituberculous treatment and pulmonary cancer, respectively. No medical records were available for the remaining 3 patients.

## DISCUSSION

The principal finding of the present study is that even in a low-incidence, high-resource setting with free and equal access to healthcare, spinal tuberculosis has a poor prognosis with debilitating sequelae and high mortality. The second major finding is that the proportion of immigrants with BJ-tuberculosis was significantly higher than that of Danes with BJ-tuberculosis in Denmark. Demographic characteristics of the study populations were significantly different. The typical Danish patient was aged >65 years whereas the typical immigrant patient was aged 25–44 years. Finally, the overall 1-year mortality was higher among Danes compared with immigrants.

The present study provides data from a period of time when the number of immigrants to Europe from high-incidence tuberculosis areas increased substantially. We found a 10% increase in the number of notified tuberculosis cases from 1994 to 2000 (Figure 2); this increase was mainly due to immigration from Somalia [13]. However, due to restriction in immigration policy in the year 2000, the number of cases dropped from 2000 to 2002 and has remained almost steady with only a weak decline from 2002 to 2011. The relative high percentage of BJ-tuberculosis in the early years of the study period can probably be explained by the large number of Somali patients with tuberculosis in general. During the study period, 83% of all BJ-tuberculosis cases were immigrants. This was quite a remarkable change from the previous decade when immigrants only made up 18% of all BJ-tuberculosis cases [14]. Furthermore, immigrants accounted for 85.6% of all spinal tuberculosis cases, a figure that is, in general, in line with the reported 92% in the United Kingdom [15], 68% in France [16], and 65.9% in the Netherlands [17]. However, a lower proportion of immigrants has been reported in other studies [18, 19].

The bimodal age distribution found in this study has also been seen in other areas where the incidence of tuberculosis is low [15, 18, 19]. Comorbidities apparently increased the risk of BJ-tuberculosis among the aging Danish population with latent tuberculosis. The high CCI scores among Danes also underline the existence of a bimodal age distribution related to ethnicity.

The global HIV epidemic did not contribute to the increased incidence of tuberculosis or BJ-tuberculosis in Denmark [20], and only 2 of the immigrant patients with BJ-tuberculosis had HIV coinfection, even though only one third of cases were tested.

The clinical characteristics and laboratory findings presented here were similar to those described previously [15–17, 19]. Constitutional symptoms were present in up to 50% of cases, but pain was the dominant symptom, especially for patients with spinal tuberculosis. In studies from the European region, neurological deficits varied from 24% to 50% [15, 16, 18]. In the present study, 40.6% of patients had neurological symptoms upon admission and 17% had cauda equina. Of note, the typical patient with cauda equina in our study was an immigrant aged <50 years, and half of these patients experienced severe sequelae. Concomitant pulmonary tuberculosis was less frequent in this study compared with other European studies [15, 19] in which the proportion varied from 22.9% to 35%. This may be explained by the very high percentage of young immigrants in whom EP tuberculosis is seen more frequently [3].

Biochemical tests are known to add little to the final diagnosis of BJ-tuberculosis. Nevertheless, the majority of patients had low hemoglobin and elevated C-reactive protein and sedimentation rates, which are typical signs of chronic infection. These features have also been described previously [16]. Of note, 95% of the patients with spinal tuberculosis had an elevated sedimentation rate.

Imaging methods have an important role in diagnosing BJ-tuberculosis, and MRI remains the method of choice, especially in spinal tuberculosis [21]. The majority of patients with spinal tuberculosis had an MRI performed.

Culture verification of EP tuberculosis has, in general, been reported to be low due to difficulties in sampling and the paucibacillarity of tuberculosis. In the European region, it was reported that only 33.7% of EP tuberculosis cases were culture verified [1], and culture confirmation varied from 10% to 80% [22]. We found a high culture verification rate of 87%, which is higher than those previously reported of 50% to 76% [15, 16, 19]. The key to successful management of BJ-tuberculosis is early diagnosis and treatment. Also, culture verification has a pivotal role, especially in areas where the incidence of tuberculosis is low, where pyogenic BJ-tuberculosis infections are increasing among the elderly [23].

Standard treatment regimens were used at all centers, but the total length of treatment varied from 6 months to 12 months and longer. National guidelines suggest treatment duration of 6 months, except in severe cases, where treatment regimens can be prolonged to 9–12 months. This is also recommended by international guidelines [6, 10, 24, 25], although the duration of treatment is still being discussed [26]. The patients in our study with spinal tuberculosis were treated significantly longer than patients with other forms of BJ-tuberculosis. One

explanation could be that spinal tuberculosis is perceived as a more severe disease. In our study, there were few recurrences without correlation with treatment duration.

The role of surgery in the treatment of spinal tuberculosis has been evaluated in several trials conducted by the Medical Research Council Working Party. The combination of surgery and chemotherapy was found to improve both short- and long-term outcomes [27]. The indications for surgery are still being discussed and not clearly described in the Danish guidelines. In total, 44% of patients in our study underwent surgery. The role of surgery in peripheral BJ-tuberculosis is limited and has not been studied as extensively as in spinal tuberculosis [28, 29]. Additional surgical treatment was performed in significantly fewer cases with peripheral BJ-tuberculosis in our study.

The overall treatment success was 83% and higher than the 79% level of success for newly diagnosed culture-positive pulmonary tuberculosis patients [30]. Good treatment outcome has generally been reported in other European studies [16, 18]. The overall 1-year mortality was 5.5% in our study but with a significantly higher mortality among Danes. Long-term sequelae were reported in 47.5% of patients, which is comparable to 38.5% in a Spanish study [18].

The major strengths of our study are the population-based design and linkage of nationwide registries using the unique Danish civil registration number, thus resulting in limited loss to follow-up. Although most cases were culture positive and laboratory notified, possible underreporting of culture-negative BJ-tuberculosis is a limitation. Finally, we were unable to retrieve all hospital records and had incomplete laboratory data on a significant number of patients from the early period of the study.

## CONCLUSION

BJ-tuberculosis is a rare disease in Denmark and affects mainly young immigrants. Spinal tuberculosis has a poor prognosis and should be a differential diagnosis in young immigrants with back pain, elevated C-reactive protein, and elevated erythrocyte sedimentation rate.

## Notes

**Author contributions.** Conception and design: I. S. J., S. B., and Å. B. A. Acquisition of data: I. S. J., S. L. N., M. H., M. K., S. S., A. V. T. W., P. H. A., S. B., C. W., and Å. B. A. Analysis and interpretation of data: I. S. J., S. L. N., and C. W. Drafting of the article: I. S. J. All authors contributed with critical comments and accepted the final version of the manuscript.

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