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Clinical Characteristics and Diagnostic Delay in Spinal Tuberculosis Patients in The Netherlands

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Abstract

Introduction: With declining TB incidences diagnostic delays, especially in extra-pulmonary TB, may increase. We describe the patient and clinical characteristics of patients with spinal TB and assessed the course of diagnostic delays of spinal TB from 2000-2011 in The Netherlands.

Methods: Data from the Netherlands Tuberculosis Registry were studied, completed with basic demographic data and data considering patients-, doctors- and total diagnostic delay retrieved from the patient records at the public municipal health services.

Results: A total of 274 cases were studied. Median diagnostic delay was five months and stable during this period. Sex and age groups were associated with significant differences in diagnostic delay (male 4.5 *vs* female 5.5 months), and 4.5-5 months in the youngest age group and persons>65 years but 5.75 months in patients aged 35-64 years. No difference was observed between origin of patients, patients presenting with TB risk factors or with neurological symptoms. Typical TB symptoms at presentation lead, surprisingly, to significantly increased doctors' delay (typical symptoms 4.0 vs no typical symptoms 2.0 months, p=0.05).

Conclusion: Considering spinal TB diagnosis and act expeditious is necessary to limit the time to diagnosis in spinal TB. Refresher courses should be offered both to family physicians and clinical specialists in The Netherlands.

Keywords: Extrapulmonary tuberculosis; Diagnostics; Low-incidence countries

Introduction

Worldwide, tuberculosis (TB) remains a great healthcare problem. In 2013, 9 million TB cases were registered with 1.45 million deaths [1]. TB is the second leading cause of death from infectious diseases after HIV/AIDS [2]. Extra-pulmonary TB accounts for 1-5% of all TB cases. In turn, bone- and joint tuberculosis (BJTB) comprises 15-35% of all extra-pulmonary TB, of which 50 percent is localized in the spine [3-8]. Features associated with spinal TB include prolonged symptomatic course, absence of fever or chills, spinal angulation, neurological defects, and paraspinous masses. Night sweats and weight loss are constitutional symptoms of TB, although found less commonly in extra-pulmonary TB. Different regions of the spine are preferentially involved in different age groups and usually two vertebrae are involved, either contiguous or in a skip fashion. Classically, there is more extensive destruction of the ventral portion of the vertebrae, which results in anterior wedging as the bone collapses [9]. The distinction in imaging studies between TB and other diagnosis as malignancies of the spine can be difficult [10]. Diagnosis of spinal TB optimally entails recovery of the pathogen from the suspected site by (CT guided) needle biopsy showing caseating granulomas and yield *Mycobacterium tuberculosis* on culture.

Spinal TB was first described by Percivall Pott in 1779 (Pott's Disease) [11]. Treatment of spinal TB consists of chemotherapy for six months with at least isoniazid, rifampicin and pyrazinamide in case the infection is caused by normal susceptible *M. tuberculosis* complex. [12-15]. In selected cases chemotherapy should be combined with surgery [7,8,16,17].

In The Netherlands TB is a notifiable disease. For this purpose TB cases are registered in the Netherlands Tuberculosis Registry (NTR). Detailed information regarding presentation, diagnostics and treatment of individual TB cases is collected and registered on a voluntary basis by the Public Municipal Health Services (PMHS), and contains data of virtually all TB patients in The Netherlands.

TB incidence is declining in our country, with 1443 reported cases in 2000 and 1073 in 2010 [18]. As a consequence, patient- and clinical characteristics of (extra-pulmonary) TB become less well known. For this reason TB is no longer high in the list of differential diagnosis and this may lead to prolonged diagnostic delay.

Objective: In this study we aimed to describe the patient- and clinical characteristics of patients with spinal TB and to assess its course of diagnostic delay in The Netherlands from 2000-2011.

		Total
Sex	Male	163
	Female	111
Age	0-14	3
	15-24	52
	25-34	61
	35-44	60
	45-54	41
	55-64	19
	65-74	24
	>75	14
Origin	Dutch	41
	European	5
	African	155
	Asian	56
	South-American	17
Diagnosing physician	Pulmonologist	91
	Internal medicine	88
	Orthopedics	33
	Neurology	29
	Neurosurgery	10
	Surgery	4
	Other	19

Table 1: Patient characteristics.

Study population and Methods

A retrospective, descriptive study was conducted based on the NTR data in the period 2000-2011. Patients registered with BJTB were selected and all spinal TB cases were evaluated. To study the individual case records, prior permission was needed from the physicians of the PMHS. Basic demographic data, clinical presentation, localization in the spine, TB risk factors, diagnostic methods, and therapy were recorded. As to diagnostic methods, spinal TB was considered and confirmed in patients who were diagnosed by culture or by positive ZN as well as PCR results, according to the European Centre for Disease Prevention and Control (ECDC) criteria [19]. Patients' delay was defined as the time from initial onset of symptoms to the first consultation to a physician [20,21]. Doctors' delay was defined as the time from the first consultation to the time of diagnosis. Diagnostic delay was defined as the time from the moment symptoms developed to the time diagnosis was established [20]. Time to diagnosis is strictly not always delay; we have used this definition to be consistent with the use in the general literature [22].

		Treatment			Total
		Conservative (%)	Surgery (%)	Unknown	
Involved spinal sites	One	124 (65)	64 (34)	2	190
	More	34 (64)	19 (36)	0	53
	Unknown	19 (61)	6 (19)	6	31
Localization in the spine*	Cervical	32 (65)	17 (35)	0	49
	Thoracic	78 (58)	54 (40)	2	134
	Lumbar	83 (69)	36 (30)	1	120
	Sacral	24 (86)	4 (14)	0	28

Table 2: Spinal localizations and treatment. *Total>274 as 53 patients have more than one affected site.

Statistical analysis was performed in SPSS, version 18.0. Basic demographic data, clinical presentation, localization in the spine, TB risk factors, diagnostic methods, and therapeutic interventions were presented descriptively. Patients', doctors' and diagnostic delay were also described using appropriate measures of central tendency and spread considering the non-normal distribution of these delays. Delays subdivided according to patient characteristics or possible other determinants were described as we were primarily interested in clinically relevant (long) differences in delay. They were also tested using the Wilcoxon rank sum test, Kruskall Wallis one-way ANOVA or correlation analysis (Spearman correlation coefficient) dependent on the determinant. Correction for multiple testing was not done.

Ethics

As this was a chart review, ethics approval was not required under Dutch law (WMO).

Results

From 2000-2011, a total of 14,382 TB patients were registered in the NTR. Seven hundred and thirty five had BJTB (735/14,382 (5%)). Fifty percent of these (366) were spinal TB. Three PMHS did not give permission to study the patient records for various reasons, 15 patient records could not be studied due to logistic reasons, and 42 patient records were missing. Five patients were wrongly registered in the NTR. A total of two hundred and seventy-four patients were evaluated in this study (Figure 1).

Patient's characteristics are summarized in Table 1. Fifty nine percent (163/274) were males. Eighty Five percent was foreign-born (233/274).

Symptoms most frequently presented were backache (96.7%), weight loss (54.2%), night sweats (39.9%). In total, 80 patients (29%) presented with this trias of symptoms. In addition, patients presented with fever (31.9%), generalized limb weakness and -numbness (15.8%), isolated limb weakness (11%) or isolated limb numbness (5.5%). Seven patients (2.6%) had paraplegia, three patients (1.1%) had tetraplegia. Affected spinal sites are summarized in Table 2. Nineteen

percent of the patients had more than one affected site (53/274). The thoracic spine was affected most (49%), followed by lumbar (44%), cervical (18%) and sacral sites (10%).

TB risk factors

Seventy-five patients (27%) had risk factors for TB and some had more than one. Type 2 diabetes mellitus (n=23), known TB contacts (21), pregnancy (14), malignancy (11), intravenous drug abuse (n=5), HIV-infection (n=4), BCG-treatment for bladder cancer (2), renal failure (2), surgery (2) and alcohol abuse (1) were risk factors found in the studied group.

Diagnostics and treatment

157 patients initially visited a general physician. From 104 patients this information could not be retrieved from the patient record. Diagnosis was made by specialists in respiratory disease (33.2%), internal medicine (32.1%) and others specialists like neurology and orthopedic-/neuro-surgery (34%). All patients met the clinical criteria of TB, defined as signs, symptoms and/or radiological findings consistent with active TB. In addition, some had positive acid-fast bacilli detected, had detection of *Mycobacterium tuberculosis* (MTB) in nucleic acid, or showed granulomas. Diagnosis was confirmed by a positive culture in 196 patients (72%). Sixty-two patients (23%) were treated based on clinical and radiological symptoms. Sixteen had positive PCR results (5.8%) or histological evidence for TB (4.0%). 171 cases had normal susceptibility for all first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). 19 cases (6.93%) had mono-resistant TB, 6 (2.19%) had multidrug resistant (MDR) TB. In 78 cases drug susceptibility could not be determined due to negative cultures or to the fact that no culture was performed.

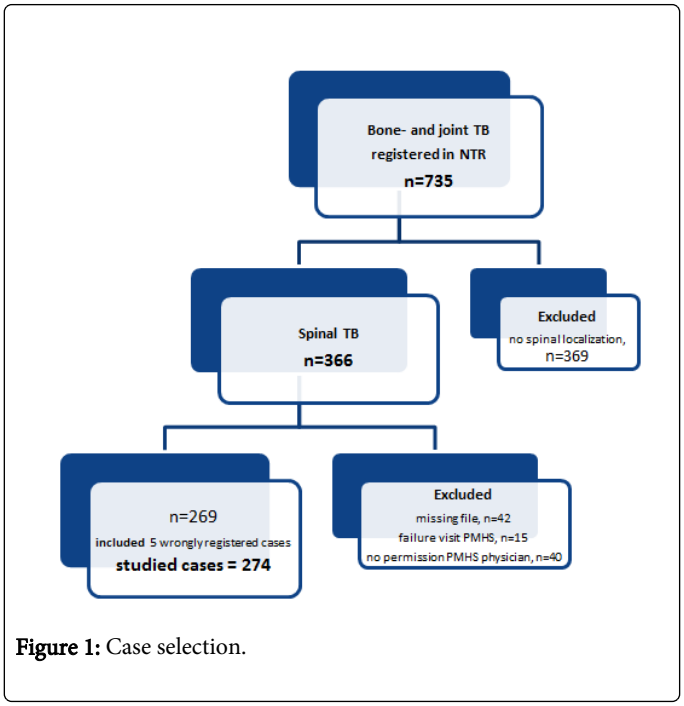

Figure 1: Case selection.

Determinant	value	Patients' delay Median in months (min-max)		Doctors' delay Median in months (min-max)		Diagnostic delay Median in months (min-max)	
Sex*	M	0.75 (0-37.5)		2.25 (0-24)		4.5 (0.25-38.5)	
	F	1.00 (0-72)	P=0.139	4.00 (0-52)	P=0.052	5.5 (0-76)	P=0.004
Age#	0-34 ys	0.75 (0-9)		2.00 (0-52)		4.5 (0.25-52)	
	35-64 ys	1.00 (0-72)	P=0.235	4.00 (0.25-27)	P=0.022	5.75 (0.75-76)	P=0.006
	>65 ys	1.50 (0-18)		3.25 (0-24)		5.00 (0-25)	
Origin*	NL	1.5 (0-12)		2.5 (0-24)		5.0 (0-30)	
	Fb¶	1.0 (0-72)	P=0.883	3.0 (0-52)	P=0.370	5.0 (0.25-76)	P=0.665
Risk factors*	Yes	1.0 (0-72)		3.0 (0-12.5)		5.0 0.75-46)	
	No	1.0 (0-37.5)	P=0.967	3.0 (0-52)	P=0.581	5.25 (0-52)	P=0.889
Trias of symptoms*	Yes	0.5 (0-35)		4.0 (0-27)		5.50 (0.5-46)	
	No	1.0 (0-72)	P=0.483	2.0 (0-24)	P=0.050	5.0 (0-76)	P=0.582
Neurol sympt*	Yes	0.88 (0-18)		3.75 (0.25-24)		4.25 (0.25-24)	
	No	1.0 (0-72)	P=0.049	2.25 (0-13)	P=0.403	5.5 (0-76)	P=0.070

Table 3: Determinants of delay. *Mann-Whitney test, #Kruskal Wallis test, ¶Fb: Foreign Born, Trias of symptoms: night sweats, weight loss and back pain, Neurol sympt: Neurological Symptoms at presentation.

Treatment

All patients were treated by a physician with a full (at least 6 months) course of anti-TB therapy. 264 patients (96%) completed treatment. 6 patients died before finishing treatment, none directly related to TB. 4 patients were lost to follow-up. Patients with cervical lesions underwent surgery in 35%, with thoracic lesions in 40%, with lumbar lesions in 30% and with sacral lesions in 14% of the cases. A total of 83 patients (30%) underwent surgery, of whom 64/190 (34%) presented with spinal lesions localized in one site, and 19/53 (36%) had multiple spinal lesions.

Patients' delay, doctors' delay, diagnostic delay and its determinants. Patients delay could be extracted from the patient record in 142 out of 274 cases (52%). Median patient delay was 1.0 month (range 0-72). Patients' delay showed a slight decrease during our study period (Figure 2). In 164 out of 274 cases (60%) we were able to define doctors' delay from the patient records. Median doctors' delay was 3.0 months (range 0-52). Finally, from 197 out of 274 patient records (72%) we were able to determine diagnostic delay. Median delay was 5.0 months (range 0-76). Twenty nine patients (11%) had a diagnostic delay longer than 12 months. Diagnostic delay appeared to be constant over the years, possibly showing a slight decrease in recent years (Figure 2). Patient characteristics and determinants and their association with patients' delay, doctors' delay and diagnostic delay are shown in Table 3.

Focusing on doctors' delay, we learn from this table that female sex is associated with a clinically relevant longer doctors' and diagnostic delays (resp. median 2.25 *vs* 4.0 months and 4.5 *vs* 5.5 months). Another feature is that middle-aged patients (35-64 years) appear to show more doctors' and diagnostic delay than younger patients. Of note, we did not observe an association between the occurrence of risk factors for TB, including origin of the patient, neurological symptoms at presentation and doctors' delay. The most common 'trias of symptoms' for spinal TB (night sweats, weight loss and backache) was even associated with longer doctors' delay.

Discussion

In this study we described patient and clinical characteristics of patients with spinal TB in The Netherlands and we assessed patients', doctors' and diagnostic delay from 2000-2011. We found a median diagnostic delay in spinal TB of five months which remained constant during the studied period. Sex and age groups were associated with significant differences in doctors' and diagnostic delay. No difference in delay was observed between foreign born patients and patients originated from The Netherlands; patients with TB risk factors did not have shorter doctors' or diagnostic delay; and presentation with neurological symptoms did also not lead to shorter doctors' delay. More surprisingly, a combination of typical TB symptoms (back pain, night sweats and weight loss) at presentation even leads to significantly increased doctors' delay.

Diagnostic delay may increase morbidity, such as kyphotic deformities of the spine, eventually resulting in cosmetic problems, ventilatory compromise and paralysis as shown in previous studies [3,23,24]. Only few studies regarding diagnostic delay of spinal TB have been performed in low incidence countries [5,25-27]. Jutte et al. found a mean diagnostic delay of 203 days during 1993-2000 [27]. In our study, we found a median diagnostic delay of five months, which is hard to compare as we used the more appropriate measure of central tendency. Our mean diagnostic delay was 7.9 months, showing a diagnostic delay roughly similar to the previous period in The Netherlands. Patients' delay seemed to decline during 2000 to 2011 (Figure 2). We were unable to determine whether this is by chance or a true drop. Whether this decline could be explained by improved accessibility to health care of risk groups as immigrants, illegal or substance abusers could not be defined.

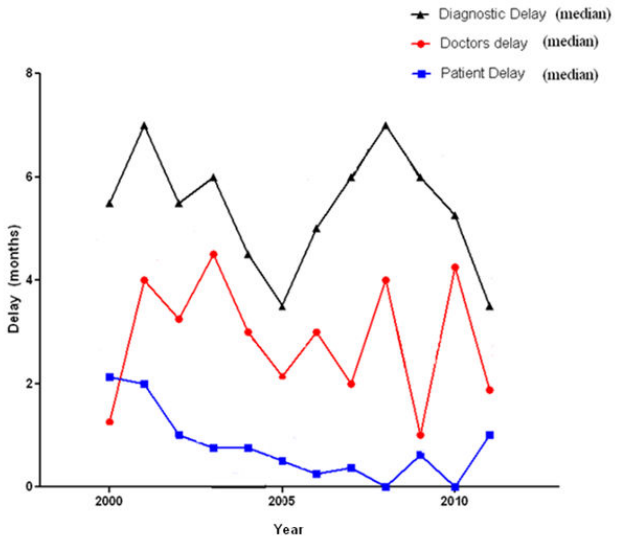

Figure 2: Course of the patients delay, doctor's delay and diagnostic delay through the years.

Night sweats and weight loss are symptoms considered classical constitutional symptoms for TB but are frequently lacking in patients with (extra-pulmonary) spinal TB. In a patient presenting with constitutional symptoms a physician should consider TB as a diagnosis. In our study, we found that patients presenting with night sweats, weight loss and back pain had clinically relevant longer doctors' delay than patients not presenting with this 'trias'. To the best of our knowledge, no studies detected this phenomenon before.

Of our study population, 6/274 (2.19%) had Multi Drug Resistant (MDR) TB. Compared to the MDR TB cases in the total TB population in this period (140/14382, 0.97%) [28], this showed a difference of 1.22%. This indicates that obtaining material for culture and Drug Susceptibility Testing (DST) is very important in spinal TB.

Sex and age groups were associated with significant differences in delay. As to the effect of age, 30-40% of the Dutch population, between the ages of 45-63 years, visit their family physician with complaints of backache [29]. Their pain is mostly attributed to other causes than TB and this may explain why patients in our study, aged 45-55 years, had significantly longer diagnostic delays.

The clinically relevant difference of doctors' and diagnostic delay between men and women is striking to occur in a developed country, but a known phenomenon in developing countries with a high incidence of TB. Lower access to diagnosis and treatment, biological difference in incidence, and lower sputum smear sensitivity for women compared to men have been reported as possible explanations in developing countries for the difference in diagnostic delay in TB [30-32]. In general, sex differences are widely observed in medicine

and are increasingly recognized as important interventional targets to further improve quality of healthcare [33].

Foreign born origin and the presence of TB risk factors were not associated with shorter delays. This is undesirable and more attention to continuous education should be paid to prevent late diagnoses and unnecessary morbidity among patients having typical clinical features and characteristics associated with (spinal) TB. Excellent initiatives to increase the awareness of family physicians to immigrant diseases in The Netherlands already exist and should be promoted continuously [34].

This study has limitations. Patients'-and doctors' delay was registered in the NTR until 2005. Consequently, the PMHS probably did collect less data on the issue resulting in less accurate findings from this year. Besides this data collection issue, the reported duration of symptoms is always based on patients' recall and interpretation. Recall bias is thus a threat to the estimates of patients' delay. Second, due to the retrospective nature of our study, there was many missing data.

Conclusion and recommendations

Considering spinal TB diagnosis is necessary to limit the time to diagnosis in spinal TB, especially in age groups frequently presenting with backache in general and in women. Refresher courses should be offered both to family physicians and clinical specialists in the era of declining TB incidence in order to raise the awareness and knowledge of TB. Hospital TB coordinators may play a crucial role in education to maintain TB expertise among specialists in their hospitals and participate in clinical decision making in difficult diagnostic cases.

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Author contributions

All authors contributed to the design of the study. Dirk Ijdema and Cecile Magis-Escurra were responsible for the data collection and first draft of the manuscript. Statistical analyses were performed by Dirk Ijdema, Cecile Magis-Escurra and Rob Aarnoutse and checked by a statistician. The final manuscript was drafted by Dirk Ijdema and Cecile Magis-Escurra and finalized with the input of all authors.

References

1. World Health Organisation. Tuberculosis Fact sheet N°104. March 2012.
2. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C (2003) Tuberculosis. Lancet 362: 887-899.
3. Kamara E, Mehta S, Brust JC, Jain AK (2012) Effect of delayed diagnosis on severity of Pott's disease. Int Orthop 36: 245-254.
4. Le Page L, Feydy A, Rillardon L, Dufour V, Le Hénanff A, et al. (2006) Spinal tuberculosis: a longitudinal study with clinical, laboratory, and imaging outcomes. Semin Arthritis Rheum 36: 124-129.
5. Mulleman D, Mammou S, Griffoul I, Avimadje A, Goupille P, et al. (2006) Characteristics of patients with spinal tuberculosis in a French teaching hospital. Joint Bone Spine 73: 424-427.
6. Su SH, Tsai WC, Lin CY, Lin WR, Chen TC, et al. (2010) Clinical features and outcomes of spinal tuberculosis in southern Taiwan. J Microbiol Immunol Infect 43: 291-300.
7. Zhang Z (2012) Late onset Pott's paraplegia in patients with upper thoracic sharp kyphosis. Int Orthop 36: 381-385.
8. Jutte PC, Van Loenhout-Rooyackers JH (2006) Routine surgery in addition to chemotherapy for treating spinal tuberculosis. Cochrane database of systematic reviews. 2006: CD004532.
9. Iseman MD (2000) A clinician's guide to tuberculosis. Lippincott Williams & Wilkins.
10. Jutte PC, van Altena R, Pras E, Thijn CJ (2005) Causes of misdiagnosis and mistreatment of spinal tuberculosis with radiotherapy in nonendemic areas: a pitfall in diagnosis and treatment: hazards of radiotherapy on the tuberculous lesion. Spine (Phila Pa 1976) 30: E300-304.
11. Tuli SM (2007) Tuberculosis of the spine: a historical review. Clin Orthop Relat Res 460: 29-38.
12. American Thoracic Society; CDC; Infectious Diseases Society of America (2003) Treatment of tuberculosis. MMWR Recomm Rep 52: 1-77.
13. van Loenhout-Rooyackers JH, Verbeek AL, Jutte PC (2002) Chemotherapeutic treatment for spinal tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 6: 259-265.
14. Dutch Association of Physicians for Lung Disease and Tuberculosis (NVALT) (2005) Richtlijn Medicamenteuze behandeling van tuberculose. NVALT Guidelines.
15. (1998) Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax 53: 536-548.
16. Moon MS, Moon JL, Kim SS, Moon YW (2007) Treatment of tuberculosis of the cervical spine: operative versus nonoperative. Clin Orthop Relat Res 460: 67-77.
17. Rajasekaran S (2012) Kyphotic deformity in spinal tuberculosis and its management. Int Orthop 36: 359-365.
18. Slump E, CGME JFvR, Schimmel HJ, Šebek MMGG, van Soolingen D (2010) Tuberculose in Nederland. Recommendations of the Royal Dutch Tuberculosis Foundation (KNCV) Working Group.
19. Commission EU. 2008/426/EC: Commission decision of 28 April 2008 amending decision 2002/253/EC laying down case definitions for reporting communicable diseases to the community network under decision No 2119/98/EC of the European Parliament and of the Council. 2008.
20. Sherman LF, Fujiwara PI, Cook SV, Bazerman LB, Frieden TR (1999) Patient and health care system delays in the diagnosis and treatment of tuberculosis. Int J Tuberc Lung Dis 3: 1088-1095.
21. Almeida CP, Skupien EC, Silva DR (2015) Health care seeking behavior and patient delay in tuberculosis diagnosis. Cad Saude Publica 31: 321-330.
22. Storla DG, Yimer S, Bjune GA (2008) A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 8: 15.
23. Jutte P, Wuite S, The B, van Altena R, Veldhuizen A (2007) Prediction of deformity in spinal tuberculosis. Clin Orthop Relat Res 455: 196-201.
24. Storla DG, Yimer S, Bjune GA (2008) A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 8: 15.
25. Pertuiset E, Beaudreuil J, Lioté F, Horusitzky A, Kemiche F, et al. (1999) Spinal tuberculosis in adults. A study of 103 cases in a developed country, 1980-1994. Medicine (Baltimore) 78: 309-320.
26. Kenyon PC, Chapman AL (2009) Tuberculous vertebral osteomyelitis: findings of a 10-year review of experience in a UK centre. J Infect 59: 372-373.
27. Jutte PC, van Loenhout-Rooyackers JH, Borgdorff MW, van Horn JR (2004) Increase of bone and joint tuberculosis in The Netherlands. J Bone Joint Surg Br 86: 901-904.
28. KNCV.

29. Picavet HS, Schouten JS (2003) Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain 102: 167-178.
30. Huong NT, Vree M, Duong BD, Khanh VT, Loan VT, et al. (2007) Delays in the diagnosis and treatment of tuberculosis patients in Vietnam: a cross-sectional study. BMC Public Health 7: 110.
31. Karim F, Islam MA, Chowdhury AM, Johansson E, Diwan VK (2007) Gender differences in delays in diagnosis and treatment of tuberculosis. Health Policy Plan 22: 329-334.
32. Gosoniu GD, Ganapathy S, Kemp J, Auer C, Somma D, et al. (2008) Gender and socio-cultural determinants of delay to diagnosis of TB in Bangladesh, India and Malawi. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 12: 848-855.
33. Doyal L (2001) Sex, gender, and health: the need for a new approach. BMJ 323: 1061-1063.
34. Pharos LHVeNHG (2012) Huisarts-migrant. 2012; Maria van den Muijsenbergh, huisarts (chief editor).