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Mycobacterium genavense in the Netherlands: an opportunistic pathogen in HIV and non-HIV immunocompromised patients. An observational study in 14 cases

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Abstract

Mycobacterium genavense is an opportunistic non-tuberculous mycobacterium previously mostly associated with HIV-infected patients with CD4 counts below 100/μL. In this retrospective observational study of medical charts we studied all Dutch patients in whom *M. genavense* was detected between January 2002 and January 2010. Of the 14 patients identified, 13 (93%) showed clinically relevant *M. genavense* disease. All patients with *M. genavense* disease were severely immunocompromised, including HIV-infected patients, solid organ transplant recipients, those with chronic steroid use in combination with other immune modulating drugs, recipients of chemotherapy for non-Hodgkin lymphoma, and those with immunodeficiency syndromes. Two patients had non-disseminated pulmonary *M. genavense* disease. Of the 12 patients treated, eight (75%) showed a favourable outcome. Four patients died in this study, three despite treatment for *M. genavense* disease. We conclude that *M. genavense* is a clinically relevant pathogen in severely immunocompromised patients that causes predominantly disseminated disease with serious morbidity and mortality. *M. genavense* is increasingly seen among non-HIV immunocompromised patients.

Keywords: Clinical relevance, *Mycobacterium genavense*, non-tuberculous mycobacteria, opportunistic infections
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Introduction

Among the non-tuberculous mycobacteria (NTM), *Mycobacterium genavense* has been described as a pathogen causing disease with significant morbidity and mortality, especially in HIV-infected patients with CD4 counts below 100/μL [1,2]. It was first described by Böttger *et al.* in 1993 [3], and retrospectively first isolated in 1987 from an HIV patient with a disseminated infection [4].

In the period after the introduction of antiretroviral therapy (cART) in the late 1990s, the epidemiology of *M. genavense* changed. *M. genavense* was now acknowledged as an opportunistic pathogen in patients with non-HIV immunodeficiencies such as solid organ transplant recipients [5–7], patients with both innate and acquired impairment of cell-mediated immunity, as in some lymphoproliferative malignancies [8], in patients after allogeneic stem cell transplantation [9], and patients on immunosuppressive therapy [10–13]. The available literature focuses only on case reports. Little is known about clinical aspects, treatment and outcome in this category of patients.

M. genavense can be isolated from tap water, healthy birds and the gastrointestinal tract of healthy individuals. Hence, it is important to distinguish contamination and colonization from true infection if *M. genavense* is isolated from a

non-sterile source (e.g. the digestive or respiratory tract) [14,15]. The American Thoracic Society (ATS) has published guidelines to assist in this distinction [16]. The clinical relevance of an NTM species may be quantified by assessing the percentage of patients with positive cultures of the respective NTM who meet the ATS diagnostic criteria.

We studied the frequency and clinical relevance of *M. genavense* isolation in the Netherlands, using the ATS diagnostic criteria. We focus on clinical aspects, treatment and outcome of *M. genavense* disease.

Methods

The present study is a retrospective observational study of all patients in the Netherlands who had *M. genavense* detected in a clinical sample during the 2002–2010 period. Patients were identified by reviewing the database of the Dutch National Institute for Public Health and the Environment (RIVM) for clinical samples in which *M. genavense* was detected. The RIVM is the national mycobacteria reference laboratory that provides identification and drug susceptibility testing for all hospitals in the Netherlands. In addition, all hospitals that perform identification of NTM without referral to the RIVM were contacted to include their patients with clinical samples in which *M. genavense* was detected. We reviewed medical records of all identified patients in whom *M. genavense* was detected in the study period. We recorded demographic data, clinical data, treatment and outcome. The 2007 ATS diagnostic criteria were used to determine clinically relevant infections [16]; because *M. genavense* is extremely difficult to culture on routine media, we considered molecular detection of *M. genavense* to equal culture, as the ATS criteria are based on cultures. The ATS diagnostic criteria are designed specifically for pulmonary NTM disease. For non-pulmonary infections in this study, clinically relevant infection was defined by positive culture or molecular detection of *M. genavense* with clinical signs in accordance with the isolation site and, if applicable, fitting radiological findings.

To identify NTM, the RIVM used the INNO-LiPA Mycobacteria v2 (Innogenetics, Ghent, Belgium) reverse line blot assay, which has specific probes for *M. genavense*. Prior to 2004, 16S rDNA gene sequencing was performed by previously published methods [17], after ruling out membership of the *M. tuberculosis* or *M. avium* complex using the AccuProbe assays (GenProbe, San Diego, CA, USA). Similarly, 16S sequencing or INNO-LiPA assays were mostly used by the local hospitals. Drug susceptibility testing was not performed.

The local ethics committee approved the study.

Results

We identified 14 patients in whom *M. genavense* was detected in a clinical sample. Thirteen (93%) patients met the ATS diagnostic criteria. For 11 patients, *M. genavense* was detected by molecular methods only, in clinical specimens. In three, scanty growth was observed on Middlebrook 7H10 solid (n = 1) or 7H9 liquid medium (n = 2) supplemented with sheep blood and Mycobactin J and identified by the INNO-LiPA Mycobacteria v2 assay as *M. genavense*; no growth was observed upon subculture. Seven patients (54%) had *M. genavense* detected in pulmonary samples, of whom two had localized *M. genavense* disease (no other site from which *M. genavense* was detected)., In 11 patients (85%), extra-pulmonary samples including bone marrow (n = 6), blood (2), lymph node (4), liver (2) and stool (3) yielded *M. genavense*. The mean age of the patients at the time of isolation was 54.7 years (range 33–68 years). Of the patients with a clinically relevant *M. genavense* infection, four patients were HIV positive and nine patients were immunocompromised due to causes other than HIV infection.

HIV-infected patients

All four HIV-infected patients presented with disseminated *M. genavense* disease. The mean CD4 count at the time of *M. genavense* isolation was 35/μL (range 10–83). The patients mostly reported fever (n = 3), malaise (2) and gastrointestinal symptoms (2). In three patients enlarged abdominal lymph nodes were observed. A pulmonary localization of *M. genavense* was proven in one patient who presented with pleural fluid and multifocal nodular lesions on chest computed tomography (CT). Treatment was given in all cases and included ethambutol and clarithromycin in all patients. In one patient rifampicin was added to the regimen. Two patients were cured of *M. genavense* infection based on negative culture results and normalization of radiology results (Table 1). One patient died after 7 months treatment. Postmortem examination revealed the cause of death in this patient to be the combination of a disseminated *M. genavense* disease and a cerebral malignancy. One patient is currently still on treatment and showed complete resolution of *M. genavense*-related symptoms. As a result, a favourable response to treatment was observed in three HIV positive patients.

Non-HIV immunocompromised patients

M. genavense was detected in ten non-HIV patients. Nine patients had a clinically relevant *M. genavense* isolation, all of whom were diagnosed with an innate or acquired

TABLE 1. Individual clinical characteristics, treatment and outcome of the HIV-positive patients with *M. genavense* disease

Patient	Age/Sex	Year of diagnosis	CD4 count/μL	Detection site	Disseminated disease	Treatment	Outcome
1	33/M	2002	83	Abdominal lymph nodes.	Yes	E/Cla 7.5 years	Cured
2	53/M	2007	52	Liver	Yes	E/Cla	Chronic treated
3	49/M	2002	10	BM, faeces, pleural fluid, ascites, lung biopsy	Yes	R/E/Cla 26 months	Cured
4	64/M	2005	10	Faeces Post-mortem: AFB+ material in: BM, spleen, liver and lung	Yes	E/Cla several months	Died, cause of death: MG disseminated disease and intracerebral tumour

AFB, acid fast bacilli; BM, bone marrow; Cla, clarithromycin; E, ethambutol; Hb, haemoglobin; MG, *Mycobacterium genavense*; R, rifampicine.

immunodeficiency. Details of the non-HIV patients with a clinically relevant *M. genavense* isolation are summarized in Table 2.

Disseminated *M. genavense* disease

Seven of nine patients showed disseminated *M. genavense* disease. Two patients were solid organ transplant recipients, the other five patients were immunocompromised due to an immunological disorder, immunosuppressive drugs or a haematological malignancy (Table 2). Patient number 13, diagnosed with an idiopathic CD4+ T-cell lymphocytopenia, also had *Mycobacterium xenopi* and *Mycobacterium simiae* isolated from a bronchoalveolar lavage. Fever was the most common clinical sign (Table 3). Pancytopenia was seen at the time of *M. genavense* isolation in four cases, all of whom had *M. genavense* isolated from bone marrow. Enlarged para-aortic and mesenteric lymph nodes were the most common abnormalities on radiological examination ($n = 4$), followed by pulmonary dense airspace opacities (2). Six patients were treated for *M. genavense* disease, of whom two died; the other patients showed a good clinical response and are still, or chronically treated. One patient received a treatment for a presumed *M. tuberculosis* infection and died several weeks after the start of this treatment.

Pulmonary *M. genavense* disease

Two patients had *M. genavense* detected repeatedly, but in pulmonary samples only. They had no clinical suspicion of other organ involvement of *M. genavense* (patients 5 and 6 in Table 2). Patient 6 was free of any immune suppression at the time of first *M. genavense* detection. Fever was reported by both patients. Other complaints were dyspnoea, productive cough and chest pain. Radiological examination showed cavitations together with a reticulonodular pattern in both patients (Fig. 1). Treatment was initiated in both, one was cured and the other is still being treated.

Clinically irrelevant detection of *M. genavense* occured in bronchoalveolar lavage fluid obtained from a patient with a community-acquired pneumonia who improved on a course of amoxicillin and clavulanic acid. The patient was known to have type 2 diabetes; he had not been using immunosuppressive drugs before. No clinical signs or radiological abnormalities suggestive of mycobacterial disease were found during 2 years of follow-up.

Among the 12 patients treated for *M. genavense* disease (i.e. with regimens including a macrolide, ethambutol and often rifampicin) we recorded a favourable outcome in 75% (9/12) of patients (cured, 25% ($n = 3$); chronically treated but with resolution of *M. genavense*-related complaints, 50% ($n = 6$)); three died. Overall, four patients (4/13, 30%) died in this study because of (disseminated) mycobacterial disease: the three treated for *M. genavense* disease and one who received treatment for presumed *M. tuberculosis* infection (Tables 1 and 2).

Discussion

Mycobacterium genavense detection proved to be indicative of clinically relevant disease in 93% (13/14) of the patients in this study. Disseminated disease was seen in all HIV-positive patients and in 78% of the non-HIV immunosuppressed patients. To the best of our knowledge, we have reported the first two patients with a non-disseminated pulmonary *M. genavense* disease. One of these patients used prednisolone and azathioprine, a drug combination that was also used by one of the patients with disseminated disease. The other patient had been on systemic steroids and had a pre-existing pulmonary fibrosis with bullae, which probably predisposed to a pulmonary *M. genavense* infection. Although little is known about the pathogenesis of *M. genavense* infection, Ehlers and Richter [18] showed that immunocompetent mice cleared intravenous-injected *M. genavense*, in contrast to syngeneic gamma-interferon-gene-deficient mice. This observation is in agreement with our study, in which *M. genavense*-disseminated disease was only seen in severely immunocompromised patients, including HIV-infected patients, solid organ transplant recipients, those with chronic steroid use in combination with other immune modulating drugs, recipients of chemotherapy for non-Hodgkin lymphoma and those with immunodeficiency syndromes.

TABLE 2. Individual clinical characteristics, treatment and outcome of the non-HIV immunosuppressed patients who presented with *M. genavense* disease

Patient	Age/Sex	Underlying condition	Immune suppression	Detection site	Disseminated disease	Treatment	Outcome
5	55/M	Possible RA	Prednisone, azathioprine, leflunomide	Sputum, lung biopsy	No	R/E/Cla 18 months	Cured
6	57/M	Sarcoidosis, diagnosed 10 years before first isolation	Several years prednisone; stopped several months before first isolation.	Sputum	No	R/Cla/Moxifloxacine	Resolution of complaints. AFB negative. Still on treatment
7	63/M	NHL	Chemotherapy (including retuximab) 3 months before first isolation	BM	Yes	R/E/Cla	Resolution of pancytopenia after 3 weeks treatment. Chronic treated
8	72/ M	Sarcoidosis	Prednisone, azathioprine,	BM	Yes	(R)/E/Cla/Ciprofloxacin R stopped after 1 month treatment because of hepatoxicity	Died, within 8 weeks after MG isolation because of multi-organ failure
9	73/F	Renal transplantation 18 years before first isolation	Prednisone, mycophebolate mofetil	Abdominal LN	Yes	R/E/H/Z	Died, within 4 weeks after MG isolation
10	54/F	Liver transplantation 19 years before first MG isolation	Prednisone, azathioprine	Blood, faeces, BM	Yes	R/E/Cla 12 months	Resolution of pancytopenia after 2 weeks treatment Chronic treated R /Cla
11	43/M	Innate IL-12 receptor deficiency	IL-12 receptor deficiency	Sputum, cervical LN, BM	Yes	R/E/Cla	Chronic treated
12	57/M	Interstitial nephritis with granuloma	Prednisone, cyclophosphamide	Sputum	Yes	R/E/Cla 14 months	Died
13	42/M	Idiopatic CD4+ lymphocytopenia	Idiopatic CD4+ lymphocytopenia	BM	Yes	R/E/Cla.	Chronic treated

AFB, acid fast bacilli; BM, bone marrow; Cla, clarithromycin; E, ethambutol; F, female; H, isoniazide; LN, lymph node; M, male; MG, *Mycobacterium genavense*; NHL, non-Hodgkin lymphoma; R, rifampicine; Z, pyrazinamide.

Prior to the cART era, *M. genavense* disease was predominantly seen among HIV-infected patients. Tortoli *et al.* retrospectively reviewed all patients in Italy with *M. genavense* isolation between 1992 and 1996. All 24 patients appeared to be HIV positive with a mean CD4 count of 23/μL [1]. The epidemiology seems to have changed since the introduction of cART; 71% of the patients in this study were HIV negative. This finding is in line with the replacement of HIV-related *M. genavense* case reports by non-HIV-related *M. genavense* case reports identified in the literature since the publication of Tortoli [5–13]. In the Netherlands this epidemiological shift has also been observed since the last literature report of HIV-related *M. genavense* infection was published in this country in 1998 [19]. This epidemiological transition probably reflects the rising number of indications for the use of immunosuppressive drugs, and increasing number of solid-organ transplant recipients, together with a better life expectancy of this group of patients. Anti-TNF therapy is increasingly seen as one of the important immunosuppressive drugs that giving a higher risk of mycobacterial disease [20,21]. However, we have not found any patient using anti-TNF therapy. No case reports have been described in the literature either regarding *M. genavense* disease related to anti-TNF therapy. TNF inhibition alone might not be enough for *M. genavense* to become pathogenic in humans.

Whether the number of HIV patients presenting with an *M. genavense* infection is decreasing cannot be concluded from our data. However, because *M. genavense* infection is especially observed at CD4 counts below 100/μL, the early initiation of cART in the disease course of an HIV patient has certainly influenced its epidemiology; a similar phenomenon has been noted for *M. avium* infections in this group [22].

The exact environmental source of *M. genavense* remains unknown. *M. genavense* has been found in hospital tap water [23], and has been isolated with high bacterial load from the intestines of apparently healthy birds [24]. Furthermore, Dumonceau *et al.* [14] reported DNA isolation of *M. genavense* from macroscopically healthy intestinal biopsy samples in five out of nine HIV-negative patients. All these patients were free of any clinical sign of infection. This finding supports the hypothesis that *M. genavense* may colonize the gut and disseminate from it when patients become immunocompromised [25]. If colonization can be found in a high number of healthy individuals, as suggested by Dumonceau, then the risk of dissemination from the gut is low because the frequency of *M. genavense* isolation in the Netherlands (2–4/year) is only a small part of the total number of NTM isolated (800/year) [26]. Considering the difficulty in culturing

TABLE 3. Frequency (%) of symptoms and signs in non-HIV immune-suppressed Dutch and previously published cases presenting with disseminated *M. genavense* disease [5–13]

Symptom or sign	Dutch patients (*n* = 7)	Literature (*n* = 9)
Fever	86	67
Weight loss	57	22
Malaise/Fatigue	57	22
Productive cough	43	22
Night sweats	29	11
Diarrhoea	29	44
Dyspnoea	29	0
Abdominal pain	14	44
Vomiting	14	0

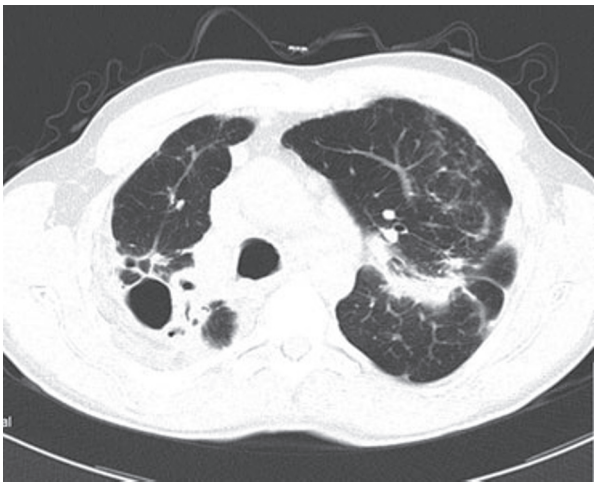

FIG. 1. Computed tomography of patient 6. Cavitations are seen in the right upper lobe together with a reticulonodular pattern, especially seen in the left lung.

M. genavense, underestimation of *M. genavense* disease incidence is likely. Further study is warranted to explore the frequency of *M. genavense* presence in intestines in healthy individuals and factors associated with dissemination. Probably, HIV infection with low CD4 counts is an important risk factor for dissemination from a colonized gut because the Swiss HIV cohort study found *M. genavense* in 12.8% of the disseminated NTM infections diagnosed between 1990 and 1992 [2].

Diagnosis of *M. genavense* infection remains a challenge for clinicians because of the absence of specific symptoms and the difficulties with culturing the organism using standard mycobacterial culture methods. In an immunocompromised host, especially with signs of disseminated disease (pancytopenia, abdominal lymph nodes), mycobacterial disease including *M. genavense* dissemination has to be considered. Nucleic acid amplification techniques are useful to establish a fast and reliable diagnosis. Attempts to culture *M. genavense* are probably best carried out on solid media (Middlebrook 7H11) supplemented with blood and charcoal and acidified to pH 6.2 ± 0.2 [27].

Before cART became available, survival from disseminated *M. genavense* infection was poor and comparable with disseminated *Mycobacterium avium* complex (MAC) disease with a mean survival time of 8.5 months [1,2,22,28]. After cART was introduced, no studies were published concerning treatment outcome and survival for *M. genavense*-infected HIV patients. In our study, one patient died and one patient is still being treated. Probably, as also observed in MAC disease, survival for *M. genavense* improved dramatically because of the combination of cART and anti-mycobacterial drugs. However, this has to be confirmed in future (international) studies. Little is known about factors associated with mortality in the *M. genavense*-infected non-HIV population. Delay in diagnosis and thus treatment, ongoing immune suppression and treatment duration are factors to be considered [8,13]. The optimal treatment regimen for *M. genavense* disease remains unclear. *In vitro* susceptibility data are limited because of the fastidiousness of the organism. Previous studies, reviewed in the ATS Statement, have recorded *in vitro* susceptibility to rifamycins, streptomycin, macrolides, fluoroquinolones and amikacin [16]. In our study, all initiated treatments for *M. genavense* consisted of clarithromycin. Ethambutol was added in nine patients, rifampicin in eight and moxifloxacin in one patient. Current ATS guidelines only state that macrolide-based regimens are preferable over other regimens; the rifampicin, ethambutol and macrolide regimen advised for *M. avium* complex disease is likely to be preferable for *M. genavense* disease too. Life-long treatment was given in a high percentage of patients and may be indicated when the immunosuppressive condition persists; otherwise, therapy may be continued until the patient has been culture-negative for 12 consecutive months [16].

In conclusion, *M. genavense* is an opportunistic pathogen in HIV and non-HIV immunocompromised patients, causing mostly disseminated disease with serious morbidity and mortality. After the introduction of cART, the epidemiology has changed, with a switch to non-HIV immunocompromised patients. The optimal treatment regimen and duration is unclear. Because the organism can colonize the gut of healthy individuals, more research is needed to determine factors associated with dissemination and disease.

Transparency Declaration

All authors have no conflict of interests to be declared.

References

1. Tortoli E, Brunello F, Cagni EA *et al. Mycobacterium genavense* in AIDS patients, report of 24 cases in Italy and review of the literature. *Eur J Epidemiol* 1998; 14: 219–224.
2. Pechère M, Opravil M, Wald A *et al.* Clinical and epidemiologic features of infection with *Mycobacterium genavense*. Swiss HIV Cohort Study. *Arch Intern Med* 1995; 155: 400–404.
3. Böttger EC, Hirschel B, Coyle MB. *Mycobacterium genavense* sp. nov. *Int J Syst Bacteriol* 1993; 43: 841–843.
4. Böttger EC. *Mycobacterium genavense*: an emerging pathogen. *Eur J Clin Microbiol Infect Dis* 1994; 13: 932–936.
5. de Lastours V, Guillemain R, Mainardi JL *et al.* Early diagnosis of *Mycobacterium genavense* infection. *Emerg Infect Dis* 2008; 14: 346–347.
6. Doggett JS, Strasfeld L. Disseminated *Mycobacterium genavense* with pulmonary nodules in a kidney transplant recipient: case report and review of the literature. *Transpl Infect Dis* 2011; 13: 38–43.
7. Nurmohamed S, Weenink A, Moeniralam H, Visser C, Bemelman F. Hyperammonemia in generalized *Mycobacterium genavense* infection after renal transplantation. *Am J Transplant* 2007; 7: 722–723.
8. Krebs T, Zimmerli S, Bodmer T, Lämmle B. *Mycobacterium genavense* infection in a patient with longstanding chronic lymphocytic leukaemia. *J Intern Med* 2000; 248: 343–348.
9. Lu KJ, Grigg A, Leslie D, Finlay M, Sasudeusz J. *Mycobacterium genavense* duodenitis following allogeneic peripheral blood stem cell transplantation. *Transpl Infect Dis* 2009; 11: 534–536.
10. Lorenzen J, Meyer-Olson D, Haubitz M *et al.* Infection with *Mycobacterium genavense* in a patient with systemic lupus erythematosus. *Clin Rheumatol* 2009; 28 (suppl 1): S39–S41.
11. Léautez S, Boutoille D, Bemer-Melchior P, Ponge T, Raffi F. Localized *Mycobacterium genavense* soft tissue infection in an immunodeficient HIV-negative patient. *Eur J Clin Microbiol Infect Dis* 2000; 19: 51–52.
12. Sharifian A, Humphris J, Leong RWL, Jones DB. Gastrointestinal: *mycobacterium genavense* enteritis in an immunocompromised patient. *J Gastroenterol Hepatol* 2009; 24: 1474.
13. Bodgan C, Kern P, Richter E *et al.* Systemic infection with *Mycobacterium genavense* following immunosuppresive therapy in a patient who was seronegative for human immunodeficiency virus. *Clin Infect Dis* 1997; 24: 1245–1247.
14. Dumonceau JM, Fonteyne PA, Realini L, van Gossum A, van Vooren JP, Portaels F. Species-specific *Mycobacterium genavense* DNA in intestinal tissues of individuals not infected with human immunodeficiency virus. *J Clin Microbiol* 1995; 33: 2514–2515.
15. Dumonceau JM, Van Gossum A, Adler M *et al.* Detection of fastidious mycobacteria in human intestines by the polymerase chain reaction. *Eur J Clin Microbiol Infect Dis* 1997; 16: 358–363.
16. Griffith DE, Aksamit T, Brown-Elliot BA *et al.* An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367–416.
17. Kirschner P, Springer B, Vogel U *et al.* Genotypic identification of mycobacteria by nucleic acid sequence determination: report of a 2-year experience in a clinical laboratory. *J Clin Microbiol* 1993; 31: 2882–2889.
18. Ehlers S, Richter E. Gamma interferon is essential for clearing *Mycobacterium genavense* infection. *Infect Immun* 2000; 68: 3720–3723.
19. Kuijper EJ, de Witte M, Verhagen DW, Kolk AH, van der Meer JT, Dankert J. *Mycobacterium genavense* infection in 2 HIV seropositive patients in Amsterdam. *Ned Tijdschr Geneeskd* 1998; 142: 970–972.
20. Van Ingen J, Boeree MJ, Dekhuijzen PN, van Soolingen D. Mycobacterial disease in patients with rheumatic disease. *Nat Clin Pract Rheumatol* 2008; 4: 649–656.
21. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-α therapy. *Emerg Infect Dis* 2009; 15: 1556–1561.
22. Karakousis PC, Moore RD, Chaisson RE. Mycobacterium avium complex in patients with HIV infection in the era of highly active antiretroviral therapy. *Lancet Infect Dis* 2004; 4: 557–565.
23. Hillebrand-Haverkort ME, Kolk AHJ, Kox LFF, Ten Velden JJAM, ten Veen JH. Generalized *Mycobacterium genavense* infection in HIV-infected patients: detection of the mycobacterium in hospital tap water. *Scand J Infect Dis* 1999; 31: 63–68.
24. Hoop R, Böttger EC, Ossent P, Salfinger M. Mycobacteriosis due to *Mycobacterium genavense* in six pet birds. *J Clin Microbiol* 1993; 31: 930–933.
25. Böttger EC, Teske A, Kirschner P *et al.* Disseminated *Mycobacterium genavense* infection in patients with AIDS. *Lancet* 1992; 340: 76–80.
26. van Ingen J, Hoefsloot W, Dekhuijzen PN, Boeree MJ, van Soolingen D. The changing pattern of clinical *Mycobacterium avium* isolation in the Netherlands. *Int J Tuberc Lung Dis* 2010; 14: 1176–1180.
27. Realini L, de Ridder K, Hirschel B, Portaels F. Blood and charcoal added to acidified agar media promote the growth of *Mycobacterium genavense*. *Diagn Microbiol Infect Dis* 1999; 34: 45–50.
28. Thomson VO, Dragsted UB, Bauer J, Fuursted K, Lundgren J. Disseminated infection with *Mycobacterium genavense*: a challenge to physicians and mycobacteriologists. *J Clin Microbiol* 1999; 37: 3901–3905.