DURATION OF TREATMENT AND OTHER ASPECTS OF TUBERCULOSIS CONTROL

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DURATION OF TREATMENT AND OTHER ASPECTS OF TUBERCULOSIS CONTROL

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geboren op 2 augustus 1952
te Helmond

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Plinius

Satius est enim otiosum esse quam nihil agere.
(It is better to be free, than to be doing nothing
het is beter vrij te zijn dan niets te doen)
freely translated / vrij naar:
Plinius
Liber primus, epistulae 1,9:Plinius Minicio Fundano suo s.

Contents

Chapter 1

GENERAL INTRODUCTION AND AIMS OF THE STUDY: DURATION OF TUBERCULOSIS TREATMENT

Based on: *van Loenhout-Rooyackers JH, Lambregts-van Weezenbeek CSB, Veen J, onder medeverantwoordelijkheid van de redactiecommissie. De behandeling van tuberculose anno 1997. Geneesmiddelen bulletin 1997;31:75-81*

1.1 INCENTIVE

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*, for which long-term treatment is recommended. Treatment is considered to be successful when the patient is cured, is no longer infectious and does not suffer relapse. By combining the correct chemotherapeutic agents and monitoring treatment compliance, it should be possible to prevent resistant mutation. With the increasing availability of efficacious chemotherapeutic agents, the duration of treatment has gradually been shortened from 12-18 months to 6-9 months. Research has shown that the relapse rate after 4 months treatment was 12% [1]. It is possible for a patient to be complaint-free and no longer infectious before his chest X-ray has normalised. At this point, it cannot be established which patients will suffer relapse. Consequently, patients may have been receiving treatment for longer than is strictly necessary [1].

The direct incentive for writing this thesis was the difference in pulmonary tuberculosis treatment duration between the Netherlands and other countries, such as the United Kingdom and the United States. Since 1978, international studies have shown that a treatment duration of six months is sufficient for pulmonary tuberculosis caused by *M. tuberculosis* with normal sensitivity, provided that treatment compliance is high. This treatment regimen comprised an intensive phase with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) for two months, possibly with the addition of ethambutol (E) and/or streptomycin (S), followed by a secondary phase of four months with isoniazid and rifampicin.

In the late nineteen eighties, both the British Thoracic Society (BTS) and the American Thoracic Society (ATS) recommended a treatment duration of six months for patients with pulmonary tuberculosis based on these studies [2,3].

Far fewer studies have been performed on the effectiveness of chemotherapeutic treatment for extrapulmonary forms of tuberculosis. Probable reasons for this are that extrapulmonary forms of tuberculosis are less common than pulmonary tuberculosis and that extrapulmonary forms are not usually infectious, so they are of less importance to public health. Although both pulmonary and extrapulmonary forms of tuberculosis are caused by the same mycobacteria, it is more difficult to obtain bacteriological evidence and perform bacteriological treatment monitoring of the extrapulmonary forms. These two findings plus the fact that extrapulmonary forms are often recognised at a late stage, which means that irreversible organ damage can have occurred, have given rise to the theoretical discussion on whether chemotherapeutics adequately reach the source of infection. The ATS took into consideration that for extrapulmonary

forms of tuberculosis, such as tuberculous lymphadenitis and spinal tuberculosis, longer durations of treatment might be necessary. In contrast, the BTS recommended six months treatment, even for tuberculous lymphadenitis and spinal tuberculosis, but 12 months for tuberculous meningitis.
In view of the good treatment results in the Netherlands, the National Tuberculosis Policy Committee (CPT), part of the Royal Netherlands Tuberculosis Association (KNCV), were not prepared to adopt these recommendations without looking into the matter themselves first. Any missed doses of chemotherapeutics during the first six months of treatment would be compensated for by a longer treatment duration. Thus the number of patients who ultimately suffer relapse because of non-compliance will remain low. Therefore, an obvious course of action was to perform a thorough literature search on the treatment duration of pulmonary and extrapulmonary forms of tuberculosis, with *relapse rate* as the major parameter. On the basis of insights into the action of chemotherapeutic agents valid at that time and on the basis of experience with tuberculosis patients, it was decided that for the analysis, only studies would be considered that had a treatment duration of six months or longer and a treatment regimen that included isoniazid (H), rifampicin (R) and pyrazinamide (Z).

1.2 CURRENT TREATMENT AND LOGICAL BASIS FOR TREATMENT

General
The aim of the treatment is to cure that patient (of interest to the individual) and therefore limit the transmission of tubercle bacteria (of interest to public health). A patient is considered cured when no viable tubercle bacteria can be demonstrated and the risk of relapse is low. No absolute norm for a relapse rate has ever been established. The risk of relapse depends on the potency of the separate chemotherapeutic agents, on the combination administered and on the duration of treatment. In general, the treatment will be longer when the chemotherapeutics are less effective.

Action of chemotherapeutic agents
Tuberculosis patients are infected with bacteria that have varying levels of metabolic activity. Bacteria in oxygen-rich regions can divide rapidly. In poorly oxygenated and more acidic regions, such as caseous-filled caverns (i.e. cavities in which necrosis has occurred), division is much slower, whereas within a macrophage, cell division will almost be halted [4]. Bacteria that divide slowly

and/or are localised in inaccessible regions with poor blood circulation, are difficult to eliminate.

There is no single treatment that can eliminate all the bacteria simultaneously. An English physician, Mitchison, developed a theoretical model based on the localisation of the bacteria (intracellular or extracellular), the growth cycle (dividing, dormant or semidormant) and the activity of the various chemotherapeutics. In order to prevent resistance and because the modes of action of chemotherapeutics are different, treatment for active tuberculosis generally starts with three or four chemotherapeutics for a duration of two months (intensive phase) and is followed by treatment with two chemotherapeutics in the secondary phase.

Isoniazid (1952) is bactericidal and is active intracellularly in the macrophages and extracelluarly. Its mode of action is not fully understood, but it is known to inhibit the production of mycolic acid, which is an important component of the cell wall of bacteria [5]. The agent produces rapid reduction of large populations of continuously dividing tubercle bacteria, such as in those present in the cavern wall. Rifampicin and pyrazinamide have low activity at this site.

Rifampicin (1965) is bactericidal: it inhibits RNA polymerization, which arrests bacterial protein synthesis. It kills persistent semidormant bacteria during the short division phase. This chemotherapeutic agent is therefore essential for sterilising the disease process and preventing relapse. Sterilising action means the ability of the medication prescribed to render the disease process germfree.

Pyrazinamide (1950) in high dosages with an unacceptably large number of side-effects and since 1978 in therapeutically adequate dosages with an acceptable level of side-effects) is only active in an acidic environment. The chemotherapeutic agent is converted into pyrazine acid by the enzyme pyrazinamidase that comes from the tubercle bacteria. This lowers the pH value in the macrophages and kills any intracellular bacteria (inside the macrophages) and the bacteria in the acidic (caseous) inflammatory nidus [6]. Therefore, pyrazinamide is of particular importance in the intensive phase of treatment. It is only administered in the secondary phase in the case of multi-resistance.

The action of **aminoglycocides** (1941 **streptomycin** and **amikacine**) is based on blocking ribosomal RNA. These agents are bactericidal under aerobic conditions. The bactericidal action of streptomycin is limited to extracellular, actively dividing bacteria (e.g. in caverns).

Ethambutol (1961) influences the RNA synthesis of the bacteria and inhibits the incorporation of mycolic acid in the cell wall [7,8]. The agent is bacteriostatic at a dosage of 15 mg/kg body weight and bactericidal at a dosage of 25 mg/kg

body weight. At therapeutic dosages, it is far less effective than the above-described agents.

(Multi)resistance

Soon after the introduction of the first chemotherapeutic agents it became clear that monotherapy led to resistance formation. If streptomycin alone was administered, 80% of the cases developed resistance within three months. With isoniazid alone, 25% of the patients developed resistance after two weeks [9].
At the start of treatment, the bacteria population is large. To prevent resistance forming, it is necessary to administer a combination of chemotherapeutic agents in the intensive phase. In this way, one agent prevents the selection of mutations against the other agent. Isoniazid and rifampicin contribute more to the prevention of resistance formation than pyrazinamide and ethambutol. As the volume of the bacteria population decreases, the risk of resistance forming also decreases [10]. Multi-resistance develops through the step by step build-up of resistance as a result of inadequate treatment, or as a consequence of primary infection with a multi-resistant strain.

Treatment compliance

Insufficient treatment compliance leads to treatment failure and is partly responsible for resistance forming.

Dosage

It is recommended to administer each chemotherapeutic agent once a day. The effectiveness of chemotherapeutic agents does not depend on continuous blood or tissue levels above the minimal bacterial growth inhibitory concentration (MIC). Owing to the fact that tubercle bacteria only have a short division phase, it is assumed that achieving a high serum concentration for a few hours is more important than maintaining a low serum concentration for 24 hours. This has actually been demonstrated for isoniazid [11]. High peak concentrations with a once daily dosage inhibit mutations with a low grade of resistance [12]. The risk is small that dividing bacteria are exposed to suboptimal chemotherapeutic levels with once daily dosages. Moreover, most bactericidal agents have an after-effect, or a postantibiotic effect: after the bacteria have been exposed to effective antibiotic concentrations, the bactericidal effect continues for some time. This also explains why intermittent treatment regimens, in which chemotherapeutics are administered two or three times per week, are also effective [13,14].

Treatment duration and effectiveness

In the nineteen sixties, a combination of isoniazid, streptomycin, ethambutol or para-aminosalicy acid (PAS, 1948) and a total treatment duration of 18-24 months led to relapse in 10% of the patients after the completion of treatment [15]. With the introduction of rifampicin in addition to isoniazid, it became possible to shorten the duration of treatment to nine months. In human pulmonary tuberculosis with normal sensitivity, nine months treatment with isoniazid and rifampicin, whether or not in combination with ethambutol or streptomycin, led to a relapse rate of 1% [16].

In the nineteen seventies, treatment with a (short) duration of six months that comprised isoniazid, rifampicin, pyrazinamide and streptomycin for the first two months and isoniazid and rifampicin for the following four months, proved to be very effective. Pyrazinamide played a crucial role. When pyrazinamide had been included in the treatment regimen, the relapse rates were 1.4% after two years and 3.4% after five years, compared to 7.8% and 20.3%, respectively, when it had been omitted [17]. At present, pyrazinamide is considered to be a chemotherapeutic agent of first choice.

If treatment fails in the case of good treatment compliance, there may have been insufficient biological availability of the chemotherapeutic agents. Pharmacokinetic tests are then indicated [18]. Determining serum chemotherapeutic levels is possible in the Netherlands. However, it is difficult to interpret the results, due to lack of experience. At this time, i.e. 2001, the pharmaceutical industry has little interest in research into the action of the above-described chemotherapeutic agents. These agents have proved to be effective and the incidence of tuberculosis in developed countries is low.

TABLE 1. Frequency of localisation of tuberculosis in Dutch and non-Dutch patients, average per year, absolute and %. Period 1993-1997, data from the Netherlands Tuberculosis Register (NTR) / Royal Dutch Tuberculosis Association (KNCV). Patients can have more than one localisation

	Dutch nationality		non-Dutch nationality	
Total No. of patients with tuberculosis average / year	743		893	
Primary tuberculosis	69	9.1%	42	4.7%
Pulmonary localisation	33	45.2%	445	49.8%
Other forms of tuberculosis of the respiratory tract	92	12.4%	114	12.8%
Oher organs,	60	8%	183	20.5%
incl. cervical lymph nodes	44	6%	149	17%
Meninges and central nervous system	11	1.5%	10	1.2%
Bones and joints	27	3.7%	41	4.6%
Genitourinary tract	27	3.6%	16	1.8%
Intestinal tract	11	1.5%	37	4.1%
Miliary tuberculosis	22	3%	15	1.7%
Unknown / not mentioned	119	16.1%	112	13.6%

1.3 AIMS OF THE STUDY

The aims of the study were to gain greater insight into the treatment of tuberculosis with a combination of isoniazid, rifampicin and pyrazinamide and particularly into treatment duration at a time when the circumstances surrounding tuberculosis are changing dramatically. These aims were addressed by conducting a number of systematic literature studies. As far as possible, the results of individual reports have been combined statistically. On the basis of the results of this literature review, recommendations are made about the treatment duration for tuberculosis. These recommendations can form the basis of treatment guidelines for tuberculosis physicians at Municpal Health Services (MHSs) and hospital clinicians. Below, a description is given of the tuberculosis situation in the Netherlands in the year 2000, with a low incidence, Dutch and non-Dutch patients, pulmonary localisations and extra-pulmonary localisations.

Tuberculosis incidence indicates the number of persons that are tuberculosis-free at the beginning of a calendar year but develop tuberculosis in the course of that year. The incidence of tuberculosis in the Netherlands is extremely low: 8.9/100,000 (data from the Netherlands Tuberculosis Register (NTR) 2000). Among non-Dutch nationality subjects, the incidence of tuberculosis is 136.2/100,000. Among subjects with the Dutch nationality, the incidence is 3.4/100,000, comparable to Scandinavia. In the majority of West-European countries, the incidence is three or four times higher, while in East-European countries, it is 10 to 20 times higher. In the mid nineteen eighties, the number of patients with tuberculosis stopped decreasing and started to increase. The highest incidence was found among AIDS patients in regions with high endemic tuberculosis. The incidence is especially high in sub-Sahara Africa and South-East Asia: more than 100/100,000 per year (data from the World Health Organisation). The number of patients with tuberculosis in the Netherlands is directly related to the influx of migrants and asylum seekers, many of whom are from regions with high endemic tuberculosis. The risk is even higher in the case of comorbid HIV infection.

Other persons with an increased risk of tuberculosis are (a) persons returning from a trip to countries where tuberculosis is common; (b) persons who may have been exposed to infection and are therefore invited for source and contact tracing; (c) persons addicted to drugs or alcohol; (d) elderly tuberculosis patients who have never been treated or have not received adequate treatment; (e) the homeless; (f) prison detainees; (g) health care workers; (h) seamen. The Netherlands Tuberculosis Register shows that the annual number of patients with tuberculosis varied from 1192 in 1987 to 1811 in 1994. In the period 1993-1997, an average of 743 Dutch persons per year had active tuberculosis, compared to 893 non-Dutch persons (55%) (Table 1).

About 70% of the patients with intact immunity and active tuberculosis had pulmonary tuberculosis, while 30% had an extra-pulmonary form of tuberculosis. The frequency of extra-pulmonary tuberculosis and the frequency per organ localisation differ between population groups. Cervical tuberculous lymphadenitis is the most common extra-pulmonary localisation. In immune-compromised patients, such as HIV positive persons, tuberculous lymphadenitis more commonly accompanies active tuberculosis in other organs [19]. It is also important to take atypical mycobacteria into consideration, as these are more common in AIDS patients [20].

If patients are from countries that do not have good tuberculosis programmes, there is a risk of importing primary resistant tubercle strains. In addition, there is a risk of inducing secondary resistance in the Netherlands, for example,

through treatment errors. The risk of treatment errors is larger when there is no uniform treatment policy and when there is no supervision of treatment.
Migrants and asylum seekers who enter the Netherlands are directly screened for tuberculosis. Treatment is started by the MHSs and asylum seekers are often transferred many times between shelters. Furthermore, the diagnosis of tuberculosis can be made in patients with complaints. In this way, general practitioners and hospital clinicians encounter tuberculosis. The absolute numbers of tuberculosis patients that are treated by a general practitioner or hospital clinician are small, which means that individual physicians can never gain sufficient clinical experience with tuberculosis. The risk of treatment errors is greater when the treating physicians do not have a uniform treatment policy and the duration of treatment increases. Therefore, there is a clear need for uniform policies and guidelines.

1.4 STRUCTURE OF THE THESIS

After the above description of the aims of the study, Chapter 2 gives an overview of the literature studies on the treatment of pulmonary tuberculosis caused by human tubercle bacteria with normal sensitivity; diagnoses and relapses were bacteriologically proven. The question was: Can treatment for pulmonary tuberculosis be shortened from 9 to 6 months?
In contrast with pulmonary tuberculosis, it is far more difficult to obtain bacteriological proof of the diagnosis of extrapulmonary forms of tuberculosis and to make a bacteriological evaluation of the course of treatment. Chapter 3A therefore addresses the diagnosis of cervical tuberculous lymphadenitis. The question is: Can a diagnostic decision tree be developed for the Dutch situation and what is the value of simple basic testing compared to advanced modern techniques?
In Chapter 3B an overview is given of literature studies on the treatment of cervical tuberculous lymphadenitis. The question is: Can the duration of treatment be shortened to 6 months?
Chapter 4 gives an overview of the literature studies on the treatment of tuberculous meningitis. The question is: Is 6 months treatment equally as effective as longer treatment? An important point is whether during treatment, the chemotherapeutics are able to adequately reach the focus of infection. In patients with tuberculous meningitis, the diagnosis is often made after irreversible organ damage has occurred and the physician is confronted with a dramatic disease course. In children, chemotherapeutics, including isoniazid, are

often administered in high dosages (10-20 mg/kg body weight per day). Very few patient studies mention pharmacokinetic data on chemotherapeutics in general, or on the central nervous system in particular. In the Netherlands, in contrast with the American guidelines, it is recommended to administer isoniazid in a dosage of 4-8 mg/kg body weight/day, instead of 10-20 mg/kg body weight/day. However, it is questionable whether in children with an active form of tuberculosis, an isoniazid dosage of 5 mg/kg body weight is effective. Therefore Chapter 5 discusses the treatment results for all forms of tuberculosis in children in the Netherlands.

In Chapters 6 and 7, overviews are given of the chemotherapeutic treatment of spinal and renal tuberculosis. The question is: Can treatment be shortened to 6 months?

It is necessary to prolong the duration of treatment if intake is inadequate. Supervision of treatment compliance and source and contact tracing are carried out by the MHS after the patient has been reported by the laboratory or treating physician. In order to establish whether tuberculosis is under-reported, Chapter 8 evaluates whether the amount of pyrazinamide dispensed by chemists agreed with the number of days of pyrazinamide use noted per patient by the Netherlands Tuberculosis Register.

Chapter 9A describes contact tracing around an asylum seeker, the source, as performed by the MHS. Chapter 9B answers the question of whether after contact tracing was closed, other patients were reported whose infection could probably be attributed to the same source.

In the Netherlands, tuberculosis is fairly uncommon and the treating physicians belong to various organisations. Chapter 10 evaluates which factors may have played a role in the implementation of treatment advice that originated from structured overviews and meta-analyses of the treatment of tuberculosis.

On the basis of all the above-mentioned studies, recommendations are made about the duration of treatment with isoniazid, rifampicin and pyrazinamide in patients with tuberculosis.

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Chapter 2

TREATMENT DURATION FOR PATIENTS WITH PULMONARY TUBERCULOSIS CAN BE SHORTENED FROM 9 TO 6 MONTHS ON THE BASIS OF LITERATURE DATA

van Loenhout-Rooyackers JH, Veen J, Verbeek ALM

Verkorting van de therapieduur bij patiënten met longtuberculose van 9 naar 6 maanden verdedigbaar op grond van gepubliceerde gegevens
Ned Tijdschr Geneeskd 1996;140:2181-7

2.1 ABSTRACT

Aim: to determine whether in the Netherlands, as in other countries, the duration of treatment for pulmonary tuberculosis with normal bacterial sensitivity can be shortened from 9 to 6 months.
Design: literature study.
Setting: Municipal Health Service Nijmegen, the Netherlands.
Method: relevant literature was analysed, in which the relapse rate was used as criterion. Analysis was restricted to patients with bacteriologically confirmed pulmonary tuberculosis, in whom human tubercle bacteria with normal sensitivity had been isolated. Treatment had to include isoniazid, rifampicin and pyrazinamide. There were no reports on a treatment duration of 9 months. Predetermined criteria were used in Medline to select studies with a treatment duration of 6 months, published between 1980 and 1991.
Results: 25 publications containing 44 treatment regimens of 6 months duration were suitable for analysis. Six months treatment resulted in a relapse rate of 2.4% (95% CI 2.0-2.8) over a period of 12 to 94 months follow-up after the completion of treatment. These results were not affected by additional streptomycin or ethambutol during the intensive phase, self-medication or treatment under close supervision, daily or intermittent treatment. It was not possible to make comparisons with the relapse rate of 1% reported in the literature after 9 months of treatment without pyrazinamide (1%, 0.2-2.9). Recent calculation of the number of persons in the Netherlands with tuberculosis relapse resulted in a relapse rate of 2.5% (1.8-3.2). The American Thoracic Society reported a relapse rate of <5%, which was adopted as a guideline.
Conclusion: On the basis of relapse rates reported in the literature, it would be justified to shorten the duration of treatment from 9 to 6 months in the Netherlands.

2.2 INTRODUCTION

From time immemorial, chemotherapeutics have been distinguished according to their so-called bactericidal and sterilant action. Swift bactericidal activity rapidly interrupts the transmission of infection, while the sterilant action destroys the total bacterial population and prevents the development of resistant strains. Pyrazinamide is a chemotherapeutic with a strong sterilant effect. In the Netherlands, it has been recommended to administer pyrazinamide in the so-called intensive phase of tuberculosis treatment since 1978. The duration

of treatment for an infection with a non-resistant human tubercle bacillus in the Netherlands is 9 months; during the first 2 months (the intensive phase) isoniazid, rifampicin and pyrazinamide are administered daily. In the 7-month continuation phase, the daily administration of isoniazid and rifampicin is considered to be sufficient. This treatment regimen can be summarized as: 2HRZ/7HR (H = isoniazid; R = rifampicin; Z = pyrazinamide). No studies have been performed on the relapse rate with this treatment regimen. The 9-month treatment regimens that included isoniazid and rifampicin gave a relapse rate of 1% (95% CI: 0.2-2.9) [1].

It was expected that the strong sterilant action of pyrazinamide would make it possible to shorten the duration of treatment. Owing to the fact that the effectiveness of a treatment regimen is not only determined by the nature of the medication, but also by the duration of administration, several international studies have been performed since 1978 on the effectiveness of a treatment duration of 6 months or even shorter for pulmonary tuberculosis. These studies have chiefly been performed in countries with a high tuberculosis prevalence. The American Thoracic Society put forward a relapse rate of <5% as a criterion for the effectiveness of a treatment regimen [2]. A shorter duration of treatment is known to increase treatment compliance, reduce the risk of side-effects and decrease the financial cost.

The question arises as to whether it is justified to shorten the continuation phase by 3 months in patients with pulmonary tuberculosis (*M.tuberculosis*, normal sensitivity) in the Netherlands. To answer this question, a literature study was performed to determine the bacteriologically confirmed relapse rate after treatment with isoniazid, rifampicin and pyrazinamide.

2.3 METHODS AND DEFINITIONS

Relevant literature published in the period 1980 to 1991 was collected using Medline. A total of 53 papers were analysed. The 6-month treatment regimens which included isoniazid, rifampicin and pyrazinamide were selected on the basis of the following inclusion criteria:

The treatment regimen must be clearly described and the medication dose must be adequate, i.e. isoniazid 300 mg/day or 15 mg/kg body weight 3 times per week; rifampicin 600 mg/day (body weight $\geq$ 50 kg), 450 mg/day (body weight < 50 kg) or 3 times per week; pyrazinamide 1.5 or 2 g/day or 2-2.5 g intermittently (i.e. several times per week).

Two additional chemotherapeutics were permitted: streptomycin (S) 1 g i.m. or ethambutol (E) 25 mg/kg daily for the first 2 months, 15 mg/kg in the continuation phase or 30 mg/kg intermittently.

The chemotherapeutics must be taken daily or intermittently for a period of 6 months. Mention must be made of whether or not administration took place under close monitoring. Studies with combination tablets were not taken into consideration, unless the biological activity was documented [8,11].

Patients must not have received chemotherapeutics in the past, unless the patient had been treated for less than 2 weeks in the past year, or prior to that, for no longer than 4 months in total. Patients who had received the treatment regimen 2HRZ/4HR for less than 30 days in the past half year were included in the study [10]. Previous isoniazid prophylaxis was also permitted.

Patients had to be older than 14 years, without compromised resistance. Only patients with a diagnosis of "pulmonary tuberculosis and/or pleuritis", without any extrapulmonary localisations, were included in the study.

Radiological abnormalities must be described and the diagnosis confirmed bacteriologically. Ziehl-Neelsen staining could be negative, but the Löwenstein culture had to be positive for *Mycobacterium tuberculosis* with normal sensitivity to the usual chemotherapeutics. A growth of $\geq$ 20 colonies in at least one culture was taken as the criterion for antibiotic resistance to the following or higher antibiotic concentrations: isoniazid 0.2 mg/l; rifampicin 32 mg/l; pyrazinamide 50 mg/l (at the correct pH level); streptomycin $\geq$ 32 mg/l.

After the start of treatment, (provoked) sputum must be tested at least once a month. The date on which the first negative culture of two consecutive sputa occurred was taken as the moment of so-called sputum conversion, provided that the sputum remained negative during the subsequent 16 weeks of treatment.

If after 12 weeks of treatment, 2 or more positive cultures were found within an interval of at least 1 month, then the treatment was considered to have failed. Treatment was considered successful when sputum conversion occurred during the first 16 weeks of treatment, provided that the sputum remained negative. Treatment must not be interrupted for longer than 14 consecutive days. Moreover, at least 80% of the chemotherapeutics must have been taken by the patient. After the completion of successful treatment, the patient must be followed-up for at least 1 year and the sputum tested once or twice a month. Subsequently, sputum must be tested once every 3 to 6 months. "Bacteriologically confirmed recurrence" was defined in the same way as that employed by the author.

TABLE 1. Distribution of treatment regimens (n=44) used to treat patients with tuberculosis in 25 selected publications (3-27)

Group	Treatment
I	2HRZ/4HR
II	2HRZS/4HR
III	2HRZE/4HR
IV	$2HRZ/4H_3R_3$
V	$2HRZ/4H_2R_2$
VI	$2HRZS/4H_3R_3$
VII	$2HRZS/4H_2R_2$
VIII	$2H_3R_3Z_3S_3/2H_3R_3S_3/2H_3R_3$ $4H_3R_3Z_3S_3/2H_3R_3$
IX	Z for 6 months, monophasic regimen
X	Z for 6 months, biphasic regimen

H = isoniazid R = rifampicin Z = pyrazinamide S = streptomycin E =ethambutol

The number in front of the letters is the number of months that the chemotherapeutics with those letters were administered. The chemotherapeutics were taken daily. If the chemotherapeutics were taken intermittently (a number of times per week), this is depicted by a number in subscript after the letter of the chemotherapeutic. Example: $4H_3R_3$ means 4 months of isoniazid and rifampicin 3 times per week

Selected papers

Based on the above-described criteria, 25 papers were selected with a total of 44 treatment regimens [3-26]. In each paper, several combinations of chemotherapeutics were compared. The selection procedure made it possible to draw conclusions, as though all the studies formed part of a larger study [27-30].

Relapse rates were classified according to (a) follow-up duration after the completion of treatment, (b) chemotherapeutic intake: self-medication or medication taken under close supervision; distinction was also between daily and intermittent intake, (c) different treatment groups. Although all the treatment regimens included isoniazid, rifampicin and pyrazinamide, there were differences between studies (Table 1).

Data analysis

The relapse rate reported for each treatment regimen or calculated from absolute numbers was noted; 95% confidence intervals were taken from the papers or calculated [31].

2.4 RESULTS

A total of 25 papers with 44 6-month treatment regimens were analysed (Table 2) [3-26]; we accepted that a number of papers did not fully comply with the criteria described above. For example, it was not always reported whether the sensitivity pattern had been determined [4-6,21]; and/or sputum had not been tested once a month in the first year of follow-up, but every 3 months instead [4,6,9,21]. One study had been conducted under primitive circumstances, which meant that follow-up in the second year after the completion of treatment did not take place every 3 to 6 months [7]. In 4 papers, the procedure was not described [4,5,11,24].

The 44 treatment regimens were divided into 10 treatment groups (see Table 1) and according to the duration of follow-up after the completion of treatment (see Table 2). The 95% confidence intervals of the relapse rates of the 44 treatment regimens overlapped (Fig. 1). The risk of relapse appeared to increase as the duration of follow-up increased. Fifty per cent of the relapses occurred in the first 6 months; the 75th percentile fell within 1 year after the completion of treatment in the 4 studies with follow-up periods of 18, 24, 30 and 36 months, respectively (Table 3).

After 6-months of treatment, relapse occurred in 116 out of the 4833 patients, 2.4% (2.0-2.8). Relapse rates after regimens conducted under close supervision did not differ from those conducted under self-medication. The total number of bacteriologically confirmed relapses after the completion of treatment in the 15 treatment regimens in which the medication had been taken daily was 28/1515 (1.8%; 1.1-5.5). The relapse rate of the 6 treatment regimens in which the medication had been taken daily under close supervision was 15/650 (2.3%; 1.3-3.7). The relapse rate in the 23 regimens in which the medication had been taken intermittently under close supervision was 71/2565 (2.8%; 2.2-3.5). There was only one study of intermittent self-medication. These patients were followed-up for 48 months after the completion of treatment. The recurrence rate was 2/103 (2%; 0.2-7.0).

2.5 DISCUSSION

Since the introduction of pyrazinamide in 1978, no studies have been published on the effectiveness of the treatment regimen 2HRZ/7HR. Therefore it was not possible to compare 2HRZ/4HR to 2HRZ/7HR (a commonly used regimen in the Netherlands) on the basis of a literature analysis. However, studies have

TABLE 2. Treatment for tuberculosis in the literature: treatment regimens including isoniazid (H), rifampicin (R) and pyrazinamide (Z)

1 st author	treatment regimen*	follow-up in months after completing treatment regimen whether or not under close supervision (+/-)	relapse rate in patients after successfully completing treatment (%; 95%CI)
Hong Kong Chest Service [3]	6HRZE	12 +	1/161 (1; 0.02- 3.46)
	$6H_3R_3Z_3S_3E_3$	12	1/150 (1; 0.02- 3.71)
	$6H_3R_3Z_3E_3$	12	4/164 (2; 0.66- 6.25)
	$6H_3R_3Z_3S_3$	12	2/150 (1; 0.16- 4.82)
Onadeko [4]	2HRZS/4HR	12 -	0/ 23 (0; 0.00-14.82)
	2HRZS/4HRZ	12	0/ 20 (0; 0.00-16.84)
	2HRZS/4HZ	12	0/ 22 (0; 0.00-15.44)
Fujiware †	2HRZ/4HR	12 -	1/ 95 (1; 0.03- 5.73)
	2HRZE/4HR	12	1/ 95 (1; 0.03- 5.73)
Angel [5]	2HRZS/4HR 2HRZE/4HR	12 -	4/287 (1.4; 0.38- 3.57)
Miles [6]	2HRZS/4HR	12 +	1/ 35 (3; 0.07-14.92)
Algerian Working Group [7]	2HRZE/4HR	18 -	4/131 (3; 0.83- 7.82)
Singapore Tuberculosis Service [8]	$2HRZ/4H_3R_3$	18 +	1/ 44 (2; 0.06-12.02)
	$1HRZS/5H_3R_3$	18	1/ 46 (2; 0.06-11.53)
	$2HRZS/4H_3R_3$	18	0/ 47 (0; 0.00- 7.55)
Combs [9]	2HRZ/4HR	24 -	6/267 (2.6; 0.87- 5.18)
Brändli [10]	2HRZ/4HR	24 -	0/ 27 (0; 0.00-12.77)
Ormerod [11]	2HRZ/4HR	6-24 -	2/110 (2; 0.22- 6.57)
East and Central African/British Medical Research Council. [12]	2HRZS/4HR	24 +	4/166 (2.4; 0.66- 6.17)
East and Central African/British Medical Research Council. [13]	2HRZS/4HR		
Snider [14]	$2HRZ/4H_2R_2$ ‡	24 +	4/110 (3.6; 0.99-9.31)
	$2HRZS/4H_2R_2$$	24 +	1/ 52 (1,9; 0.05-10.26)
Snider [15]	$2HRZS/4H_2R_2$$	24 +	1/ 56 (2; 0.05-9.55)
	$2HRZ/4H_2R_2$‡	24 +	4/116 (3; 0.94-8.83)
	$2HRZS/4H_2R_2$	30 +	0/ 85 (0; 0.00- 4.25)
Hong Kong Chest Service [16]	$4H_3R_3Z_3S_3$-$2H_3R_3$	30	8/133 (6; 2.60-11.85)
	$4H_3R_3Z_3S_3$-$2H_3R_3Z_3$	30 +	2/142 (1; 0.17-5.09)
	$2H_3R_3Z_3S_3$-$2H_3R_3S_3$-$2H_3R_3$	30	4/149 (3; 0.73-6.87)
	$6H_3R_3Z_3$	30 +	6/135 (4;1.63-9.67)
British Thoracic Society [17]	2HRZE/4HR	36 -	4/127 (3.1; 0.86-8.06)
	2HRZS/4HR	36	2/119 (1.7; 0.20-6.07)
British Thoracic Association [18]			
Cohn [19]	2 weeks HRZS 6 weeks $H_2R_2Z_2S_2$ 18 weeks H_2R_2	36 +	2/ 88 (1.6; 0.28-7.97)
Eule [20]	$6H_2R_2Z_2S_2$	48 -	2/103 (2; 0.20- 7.0)
Hong Kong Chest Service [21]	6HRZE	54 +	6/150 (3.8; 1.47-8.71)
	$6H_3R_3Z_3S_3E_3$	54	6/147 (4; 1.50-8.88)
	$6H_3R_3Z_3E_3$	54	7/149 (4.4; 1.89-9.68)
	$6H_3R_3Z_3S_3$	54	2/139 (1.3; 0.17-5.20)
Singapore Tuberculosis Service [22]	$2HRZ/4H_3R_3$	54 +	3/105 (3; 0.59-8.35)
	$2HRZS/4H_3R_3$	54	2/ 96 (2; 0.25- 7.32)
	$1HRZS/5H_3R_3$	54	2/ 96 (2; 0.25- 7.32)
Baba [23]	2HRZS/4HRZ	60 -	3/108 (3; 0.57-8.12)
	2HRZE/4HRZ	60-	1/ 84 (1; 0.03-6.46)
Hong Kong Chest Service [24]	$6H_3R_3Z_3S_3$	60 +	8/166 (5; 2.08-9.50)
Singapore Tuberculosis Service [25]	2HRZS/4HRZ	93.6 +	1/ 71 (1; 0.04-7.60)
Singapore Tuberculosis Service [26]	2HRZS/4HR	93.6	2/ 67 (3; 0.4 -10.4)

Legenda next page

TABLE 3. Relapse rates of tuberculosis after the completion of treatment reported in selected publications (3-27) grouped according to duration of follow-up in months

follow-up in months after completing treatment	No. of patients	No. of relapses	months after completing of treatment			
			0-6	7-12	13-36	>36
12	1312	17	13	3	1	
18	268	6	4	2		
24	794	20	11	3	6	
30	644	20	12	5	3	
36	334	8	5	0	1	2
48	103	2	0	0	2	
54	882	28	2	7	10	9
60	358	12	6	0	1	5
94	138	3	1	1		1
Total	4833	116	54	21	24	17

been performed on treatment regimens of 6 months or shorter. In view of the strong sterilant effect of pyrazinamide, it should be possible to shorten the duration of treatment. A 9-month treatment regimen without pyrazinamide, but with isoniazid, rifampicin and possibly ethambutol or streptomycin, led to a tuberculosis relapse rate of 3 out of 298 patients, with a bacteriologically confirmed relapse rate of 1% (0.2-2.9) (Table 4) [1]. Although in the literature, reference is often made to the studies reviewed by Fox, it was impossible to make comparisons. They chiefly contained unpublished data on small numbers of patients.

The American Thoracic Society put forward a relapse rate of <5% as a criterion for the effectiveness of a treatment regimen [2]. Owing to the fact that a treatment duration of 4 months with at least isoniazid, rifampicin and pyrazinamide in patients with Ziehl-Neelsen-positive sputum and a positive Löwenstein cul-

Table 2 previous page
95% CI = 95% confidence interval; H=isoniazid; R=rifampicin; Z= pyrazinamide
* The number in front of the letters is the number of months that the chemotherapeutics with those letters were administered. The chemotherapeutics were taken daily. If the chemotherapeutics were taken intermittently (a number of times per week), this is depicted by a number in subscript after the letter of the chemotherapeutic. Example: 4 H_3R_3 means 4 months of isoniazid and rifampicin 3 times per week.
† P.Fujiware and G. Schecter, written communication, 1991
‡ The same regimen, published twice
$ the same regimen, published twice

TABLE 4. 9 month treatment regimens for tuberculosis, including isoniazid and rifampicin, but without pyrazinamide, based on an overview Fox [1]

Study	treatment regimen*	follow-up In months after completing treatment	relapse rates in patientsafter succesfully completing treatment (%)
First British Thoracic Association Study (1978) (unpublished data)	2SHR/7HR 2EHR/7HR	45 45	0/ 48 (0) 0/ 51 (0)
Second British Thoracic Association Study (1981) (unpublished data)	2EHR/7HR	9	1/ 61 (2)
First French Study Brouet & Roussel (1977)	3EHR/6HR 3SHR/6HR	27	0/ 86
Seccond French Study Pretet (1981) (unpublished data)	2EHR/7HR	12	2/ 52 (4)
Total		9-45	3/298 (1) (95% CI: 0.2-2.9)

95% CI = 95% confidence interval; S=streptomycin; H = isoniazid; R=rifampicin; E = ethambutol

* The number in front of the letters is the number of months that the chemotherapeutics with those letters were administered. The chemotherapeutics were taken daily. Example: 2EHR / 7HR means: 2 months of ethambutol, isoniazid and rifampicin, followed by 7 months of isoniazid and rifampicin

ture led to a relapse rate of 12% (9-16%) [1], we only selected treatment regimens with a duration of 6 months. Relapse occurred in a total of 116 out of the 4833 patients, a rate of 2.4% (2.0-2.8), which is less than 5%.

In the Netherlands, no norm has been established for the relapse rate. On the basis of in vitro research by Grosset, it was decided to add pyrazinamide routinely to the treatment regimen in 1978 [32], on the assumption that the existing low rate of relapse could be decreased even further. No prospective studies have been performed in the Netherlands. Alternatively, it would be possible to perform a retrospective analysis on patient records, but the process would be very time-consuming.

With the aid of tuberculosis registration cards on Dutch patients over the period 1984-1990 from the Inspectie voor de Gezondheidszorg van het Staatstoezicht op de Volksgezondheid (IGZ), we calculated a relapse rate of 44/1792 (2.5%; 1.8-3.2) (*M.tuberculosis*) within 5 years after the completion of treatment [31].

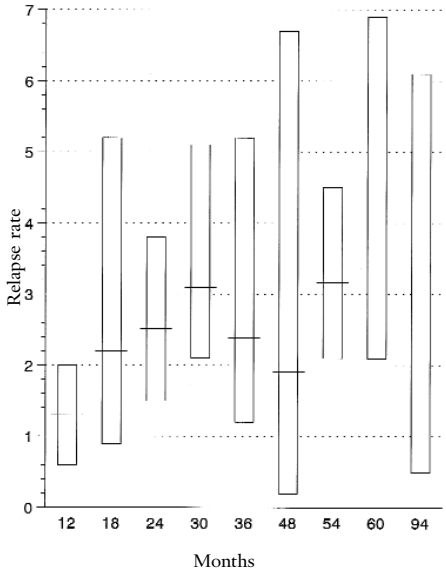

Figure 1A. Relapse rates after various treatment regimens for tuberculosis (see regimens in Table 1) reported in the literature: grouped according to follow up period in months after completing treatment

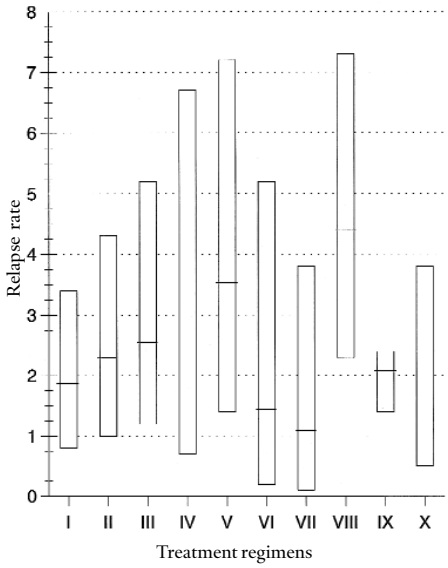

Figure 1B. Relapse rates after various treatment regimens for tuberculosis (see regimens in Table 1) reported in the literature: mean percentages and 95% C.I. (white blocks)

It can never be totally excluded that relapse is the result of reinfection. The risk is greatest in countries with a high tuberculosis prevalence. On the basis of calculations, Styblo showed that in countries with a low tuberculosis prevalence, such as the Netherlands, active tuberculosis can manifest itself for the first time in elderly people as a result of an infection contracted in their youth [33]. This is known as endogenous reactivation. The risk of exogenous reinfection being diagnosed in countries with a high tuberculosis prevalence increases as the length of follow-up after the completion of treatment increases. The majority of papers analysed in this study were performed in countries with a high tuberculosis prevalence. Therefore the risk of exogenous reinfection can be expected to be comparable in the various populations. The relapse rates observed were probably higher than can be expected on the basis of endogenous reactivation alone [34].

It was not possible to calculate a reliable regression curve for the majority of studies, because not all the publications mentioned the month in which the

relapse occurred. In the studies with a follow-up period of 18 to 36 months, 75% of the relapses occurred in the first year after the completion of treatment. Generally, a follow-up period of 24 to 30 months is considered to be sufficient for prospective studies [35]. Nowadays further determination of *M.tuberculosis* is possible using the restriction fragment length polymorphism (RFLP) method; in some cases, distinction can be made between endogenous reactivation and exogenous reinfection.

Isoniazid, rifampicin and pyrazinamide form the corner stones of tuberculosis treatment. Various combination regimens can be administered. On the basis of this study, we cannot state a preference for one particular treatment regimen. In the patient populations analysed, the addition of streptomycin and/or ethambutol was of no additional benefit (see Table 1 and Fig. 1). Self-medication did not lead to a higher relapse rate than the administration of medication under close supervision. This finding disagreed with general expectations. It should be realised that the patients who took part in these studies underwent close supervision. No difference was found between daily and intermittent intake of medication.

Based on our findings, it seems justified to shorten the continuation phase of treatment by 3 months in patients with pulmonary tuberculosis caused by non-resistant *M. tuberculosis* in the Netherlands, on the condition that the patients can be supervised closely. The latter is possible in the Netherlands due to the extensive network of Municipal Health Services in which TB nurses can provide supervision at hospitals and at the patient's home. An advantage of shorter treatment is that the willingness of patients to comply with taking medication, increases as the duration of treatment decreases. The increase in tuberculosis observed since 1987 in the Netherlands can be attributed to the increasing influx of persons from countries with a high tuberculosis prevalence. Owing to the fact that resistance to the usual chemotherapeutics is more common in those countries than in the Netherlands, it may be necessary to administer more than 3 antibiotics in the intensive phase. If sensitivity testing shows that *M. tuberculosis* is sensitive to isoniazid, rifampicin and pyrazinamide, then we recommend limiting the treatment regimen to 2HRZ/4HR. A national guideline has been published [36].

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We thank P. Oude Vrielink, MD, MHS Nijmegen, for his contribution to this study.

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Chapter 3

3.A
DIAGNOSIS OF CERVICAL TUBERCULOUS LYMPHADENITIS

Based on: *van Loenhout-Rooyackers JH, Richter C. De diagnostiek en behandeling van halskliertuberculose. Ned Tijdschr Geneeskd 2000;144:2243-7*

3A.1 ABSTRACT

The incidence of extrapulmonary forms of tuberculosis, which occur predominantly in immigrants and persons infected with HIV, is increasing. Cervical tuberculous lymphadenitis is the most common form: about 200 patients in the Netherlands per year. Fine needle aspiration is the diagnostic procedure of choice. If no acid-fast rods or caseous granulomas are seen, then excision biopsy should be performed. Biopsy specimens must always be cultured for mycobacteria. On the basis of anamnesis, physical examination, epidemiology, laboratory results, acid-fast rods or cytological/histological evidence of caseous granulomas, tuberculostatic treatment should be started while awaiting the culture results.

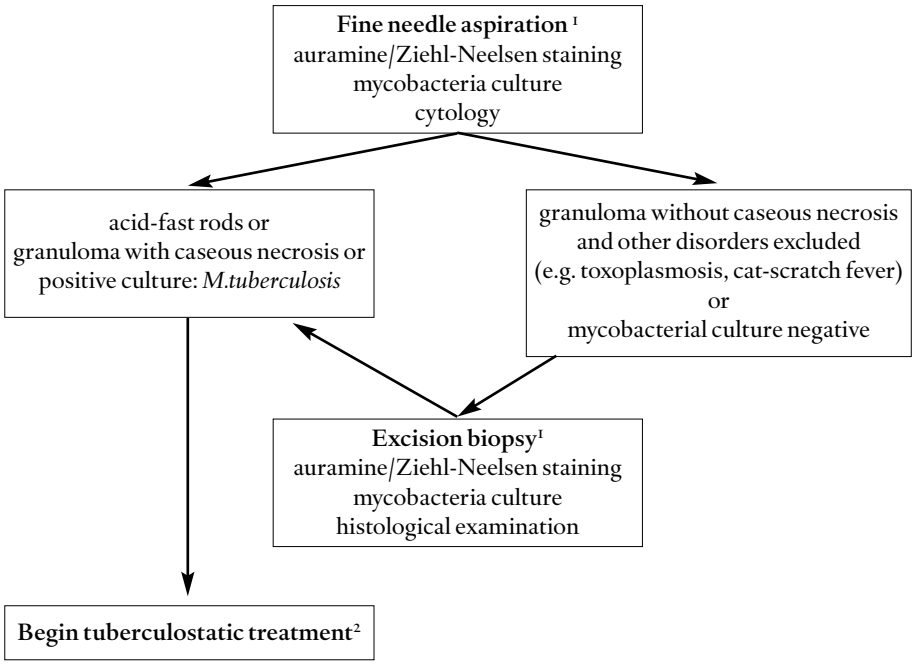
3A.2 INTRODUCTION

Tuberculosis is a generalised infection that can be active in multiple organs simultaneously. During active tuberculosis, lymph drainage from the primary infection site, usually the lungs, spreads bacteria to the nearby lymph nodes: this is referred to as the primary complex.
Below, we address the diagnosis of cervical tuberculous lymphadenitis. This subject was chosen for several reasons. Firstly, cervical tuberculous lymphadenitis is the most common form of extra-pulmonary tuberculosis. Extrapulmonary forms of tuberculosis occur predominantly in immigrants and persons infected with HIV. [1,2,3] Secondly, cervical lymph nodes often form part of the primary complex, because *M. tuberculosis* enters the body via the oropharyngeal mucosa. In many cases, an enlarged cervical lymph node is the chief or only reason why a patient consults a physician. Many of these physicians only have a rudimentary knowledge of tuberculosis. Thirdly, it is often difficult to find bacteriological evidence and/or establish whether a patient has been cured. Before starting tuberculostatic treatment, a diagnosis must be made. On the basis of the literature, a diagnostic decision tree was developed for use in the Dutch situation [4, figure 1].

3A.3 EPIDEMIOLOGY

World-wide, about 70% of the patients with tuberculosis and non-compromised immunity have pulmonary tuberculosis and about 30% have an extra-

FIGURE 1. Diagnosis of cervical tuberculous lymphadenitis in the Netherlands (Richter)



[1] Supply unfixed material; prior consultation with microbiologist and pathologist
[2] If fine needle aspiration and biopsy only show granulomas and other causes have been excluded, then the initiation of tuberculostatic treatment should be considered in persons with risk factors for tuberculosis and in cases of persistent clinical suspicion, supported by a positive Mantoux test

pulmonary form. Risk groups for tuberculosis in the Netherlands are: a) persons from a country or returning home from a country in which there is a high incidence of tuberculosis (the risk is even greater in persons infected with HIV); b) persons who may have been exposed to infection and are therefore invited to take part in source and contact tracing; c) alcoholics and/or drug addicts; d) elderly tuberculosis patients who have never received treatment or have never been treated adequately; e) the homeless; f) detainees; g) health care workers; h) seamen. The frequency of extra-pulmonary tuberculosis and the frequency of organ localisation can vary per population group. Data from the Netherlands Tuberculosis Register (NTR) show that in the period 1993-1997, the incidence of extra-pulmonary tuberculosis increased in the non-Dutch population. World-wide, cervical tuberculous lymphadenitis is the most common form of

TABLE 1. Frequency of tuberculosis localisation in 1486 patients in 1997 in The Netherlands*

Tuberculosis localisation	Absolute numbers (%)** n= 1486
Primary tuberculosis	77 (5.2)
Pulmonary localisation	762 (51.3)
Other forms of tuberculosis of the respiratory tract	229 (15.4)
Meninges and central nervous system	21 (1.4)
Intestinal tract	59 (4.0)
Bones and joints	76 (5.1)
Urogenital tract	47 (3.2)
Other organs	253 (17.0)
Cervical tuberculous lymphadenitis	200 (13.5)
Miliairy tuberulosis	35 (2.4)
Unknown / undetermined	133 (9.0)

* Multiple localisations could be registered per patient
**Source: Netherlands Tuberculosis Register (NTR) and Royal Netherlands Tuberculosis Association, The Hague

extra-pulmonary tuberculosis; in the Netherlands, about 200 patients per year are affected [1,2,3] (Table 1). In patients with compromised immunity, e.g. HIV-positive, tuberculous lymphadenitis often accompanies active tuberculosis in other organs [5]. In such cases, it is important to consider atypical mycobacteria as the pathogen; this occurs commonly in AIDS patients.

3A.4 THE PATHOGEN

Mycobacterial infection of the cervical lymph nodes can be caused by typical or atypical mycobacteria. Cervical tuberculous lymphadenitis only involves infection with members of the *M. tuberculosis* complex (*M. tuberculosis, M. bovis, M. bovis BCG, M. africanum*). *M. africanum* cannot be distinguished clinically or pathogenically from *M. tuberculosis. M. bovis* is resistant to pyrazinamide. Since the pasteurization of milk in 1940, *M. bovis* has rarely been seen in the Netherlands and since 1956, Dutch livestock has been tuberculosis-free [6].
The atypical mycobacteria, e.g. *M. avium* and *M. scrophulaceum*, are encountered in HIV-positive patients, but they can also occur in otherwise healthy young

children in countries such as the Netherlands where tuberculosis is rare and livestock is tuberculosis-free. The atypical mycobacteria fall outside the scope of this paper.

3A.5 CLINICAL PRESENTATION

A patient consults a doctor because of an enlarged cervical lymph node that has appeared gradually and is not painful. In some cases, there may also be other long(er)-term complaints of fever, weight loss and fatigue. Night sweats and coughing are fairly uncommon. General complaints are absent in 30% of the patients. Children and adults up to the age of 30 years are more commonly affected than other age groups. More women than men are affected. It is possible that women are more likely to consult a doctor for cosmetic reasons, but endocrine factors may play a role.

3A.6 PHYSICAL EXAMINATION

In most cases, the cervical lymph nodes are affected, unilaterally or bilaterally. Lymph nodes at other sites may also be affected (axillary, inguinal, mediastinal). One single lymph node might be affected, or several smaller lymph nodes in the vicinity. The lymph nodes can be friable, in which case they will feel soft and be attached to the skin (cold abscesses) or they can be hard and mobile.

3A.7 DIAGNOSIS

Tuberculosis stands high on the list of differential diagnoses when a person has enlarged lymph nodes and belongs to a risk group. Examination with fine needle aspiration is the diagnostic procedure of choice. If the result is inconclusive, excision biopsy is recommended, because incision biopsy can give rise to fistulas. Physicians should always endeavour to obtain bacteriological evidence of infection [7,8] (Figure 1). This means that fine needle aspiration and excision biopsy specimens must be sent for auramine/Ziehl-Neelsen staining and mycobacteria culture. The biopsy specimens should preferably be supplied fresh and unfixed, after contacting the Departments of Microbiology and Pathology. Cytological and histological examination may contribute to making the diagnosis. Granuloma with caseation and necrosis is considered to be evi-

dence of tuberculosis, even when the culture is negative. The value of the polymerase chain reaction (PCR) for demonstrating *M. tuberculosis* complex DNA in extra-pulmonary material has not yet been fully validated. A negative PCR result does not exclude tuberculosis, while a positive PCR result does not form proof of active tuberculosis. Even after a patient has been cured, PCR DNA test results in patient material can remain positive for a long period. Another disadvantage of PCR testing for mycobacteria is that it does not provide any insight into the resistance pattern of the *M.tuberculosis*. If tuberculosis is not considered in the initial stages and it is not possible to repeat fine needle aspiration, PCR on *M. tuberculosis* complex DNA can be performed on fixed material. The genotype can sometimes be determined indirectly by PCR, eg with mixed linked PCR spoligo-typing.

About 30-50% of the patients with cervical tuberculous lymphadenitis also have pulmonary tuberculosis. A chest X-ray is always indicated, as well as sputum collection for Ziehl-Neelsen and Löwenstein culture. Mantoux testing and the skin test have limited value as diagnostic procedures for atypical mycobacteria. Tuberculin conversion in patients with cervical tuberculous lymphadenitis is often stronger than in patients with pulmonary tuberculosis [5,7]. If the direct bacteriological result (auramine/Ziehl-Neelsen culture) of the cervical lymph node is negative or if histological examination does not show caseous necrosis or if the mycobacteria culture is negative, then consideration should be given to other causes for the enlarged cervical lymph node(s), such as toxoplasmosis and cat-scratch fever. If these other causes can be excluded, then the diagnosis of "tuberculosis" should certainly not be dismissed in patients who belong to risk groups for tuberculosis.

3A.8 DISCUSSION

In the Netherlands, fine needle aspiration material and/or excision biopsy material is often fixed before being sent to the microbiologist or pathologist, which makes it impossible to culture mycobacteria. In view of the low number of tuberculosis patients in the Netherlands, hospitals cannot be expected to change their general policy of supplying unfixed biopsy material. The aim of this paper is to indicate the value of macroscopic findings of caseation and granulomatous abscesses during histological examination, as has been observed in countries with limited laboratory facilities and personnel [7,9]. Whether or not a person is HIV-positive does not affect the diagnostic procedure [7]. Not being able to find bacteriological evidence (Ziehl-Neelsen staining, mycobacteria cul-

ture or PCR) must not form a reason for withholding tuberculostatic treatment from patients who belong to risk groups for tuberculosis and have a granulomatous abscess whether or not with caseation. In view of the different social and cultural backgrounds of tuberculosis patients in the Netherlands, there is a high risk that if treatment is postponed, the patient will present later elsewhere with fulminant pulmonary tuberculosis or a disseminated form of tuberculosis.

3A.9 RECOMMENDATIONS

In patients with enlarged cervical lymph nodes who belong to risk groups for tuberculosis, the diagnosis of tuberculosis should be high on the list of differential diagnoses. Great effort should be made to obtain bacteriological evidence of tuberculosis by means of fine needle aspiration or excision biopsy. Material should be sent for examination in an unfixed state and cultured for mycobacteria. If the material has unfortunately been supplied in a fixed state, PCR can be considered, particularly if it is not possible to repeat the biopsies. On the basis of granulomatous abscesses with caseation and necrosis, tuberculostatic treatment can be started, even when the culture result is negative.

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Chapter 3

3.B
SHORTENING THE DURATION OF TREATMENT FOR CERVICAL TUBERCULOUS LYMPHADENITIS

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3B.1 ABSTRACT

The aim of the study was to determine the optimal duration of treatment for patients with tuberculous lymphadenitis.
The Medline database was searched for relevant articles published between 1978-1997. Inclusion criteria were study populations of patients with predominantly cervical tuberculous lymphadenitis in whom the diagnosis had been confirmed bacteriologically and/or histologically, or was made probable by using clinical and laboratory markers. Treatment management had to include at least isoniazid, rifampicin and pyrazinamide and a follow-up of at least 12 months after the end of treatment. Patients with resistance to rifampicin and pyrazinamide and previous treatment for tuberculosis were excluded.
The number of patients who relapsed after treatment was calculated.
The study population in eight out of the 35 articles retrieved were suitable for analysis. Some concerned comparative studies. There were eight treatment schedules of 6 months' duration and three schedules of 9 months' duration. Treatment for 6 months resulted in a tuberculous lymphadenitis relapse rate of 13/422=3.3% (95% confidence interval: 1.7-5.5), with a mean follow-up of 31 months after completion of treatment. Treatment for 9 months resulted in a relapse rate of 3/112= 2.7% (95% confidence interval: 0.6-7.8), with a mean follow-up of 20 months.
Despite the limitations of the literature available, 6 months of therapy is probably sufficient for patients with tuberculous lymphadenitis.

3B.2 INTRODUCTION

Lymph node tuberculosis, occurring predominantly in the cervical region, is the most common manifestation of extrapulmonary tuberculosis [1].
In the Netherlands, the total number of tuberculous patients is about 1600 a year, of whom 530 cases have extrapulmonary tuberculosis[2]. The case definition of extrapulmonary tuberculosis at several sites depends on the site with the most severe disease. Cervical tuberculous lymphadenitis (n=200/year) and pleuritis (n=200/year) are the most common localizations of extrapulmonary tuberculosis [2]. Lymph node tuberculosis is classified as a less severe form of extrapulmonary tuberculosis. Patients feel less ill and there is neither a significant acute threat to life nor a risk of subsequent severe handicap. Considerations for appropriate treatment are disease severity determined by bacillary load, extent of the disease and anatomical site. In the Netherlands, recently the

duration of treatment for pulmonary tuberculosis with sensitive tubercle bacilli (*M. tuberculosis*) has been shortened from 9 to 6 months on the basis of literature data, using the percentage of bacteriologically proven relapses as the criterion [3]. In contrast, in some countries, like the Netherlands, the duration of treatment for lymph node tuberculosis is still 9 months. The authors reviewed the existing literature to determine whether 6 months of treatment for tuberculous lymphadenitis is justifiable.

3B.3 METHODS AND DEFINITIONS

The Medline database was searched for relevant articles published from 1978-1997 using the keywords: tuberculosis; lymph node; and drug therapy, with restriction to the English language. In the 1950s pyrazinamide was used in high doses, but it proved to be toxic. Nowadays it is routinely used in each combination of anti-tuberculosis drugs in the initial phase of treatment, because in 1978, it was discovered that lower doses of pyrazinamide were also effective. All of the retrieved publications were screened for the following six inclusion criteria: 1) isoniazid, rifampicin and pyrazinamide had been included in the treatment schedule, possibly with ethambutol and/or streptomycin in adequate doses [4]; 2) treatment had been applied daily or intermittently, supervised or self-administered; 3) (combinations of) tablets of proven adequate bioavailability had been used; 4) the diagnosis had been confirmed either by detection of acid-fast bacilli in direct smears from fine needle aspiration (FNA) or from biopsy and / or by positive mycobacterial culture of biopsy and / or by histological evidence of caseating or necrotizing granulomas (clinical diagnosis with response to therapy, without bacteriological or histological evidence, was also included) [5]; 5) cases were not resistant to rifampicin and pyrazinamide ; 6) follow-up after the end of treatment had to be at least 12 months. Studies on patients with active pulmonary parenchymal disease (but not isolated mediastinal lymphadenopathy) or active tuberculosis at sites other than lymph nodes, were excluded. Furthermore, patients with concomitant renal, hepatic or haematological disease and patients who had previously received >1 month of treatment for tuberculosis or who had missed > 14 consecutive or cumulative doses, were excluded from the analysis.
Treatment failures were also excluded from the analysis.

Failure was defined as a residual lymph node at the end of treatment, either without any decrease in size or with a size of > 1 cm. Patients with suspicious

residual nodes were only excluded if they had been reassessed by FNA, biopsy or had received additional treatment.

Relapse was defined as recurrence of a (residual) lymph node or the appearance of a new node confirmed to be tuberculous after one full course of medication with a period of initial clinical remission. To explore differences in treatment duration, a stratified analysis was carried out. From each study, the authors calculated the rate of relapse after the end of treatment, with a 95% confidence interval (95% C.I.) [6].

3B.4 RESULTS

Eight out of the 35 articles met the criteria. As some concerned comparative studies, there were eight treatment schedules of 6 month's duration and three schedules of 9 months' duration [7-14]. Two articles used the same study population; one reported the preliminary results, the other the final results [10,11]. The total number of patients was 644 (table 1). In 229 patients FNA had been performed, while in 291 a biopsy (excisional or incisional) had been taken. The diagnosis had been bacteriologically proven by culture in 349 (54%) and histologically proven in 315 (49%). In 259 patients *Mycobacterium tuberculosis* had been susceptible to isoniazid, rifampicin and pyrazinamide; in 346 patients sensitivity had not been tested or reported; 17 patients were resistant to isoniazid, 11 to streptomycin and 11 to isoniazid and streptomycin. Clinical and laboratory parameters were not reported in detail and could therefore not be analysed. The treatment outcome of patients with bacteriologically proven or suspected tuberculosis was not given separately in the studies. The dose of anti-tuberculous drugs used varied and was not reported in one study [14]. In adults, the dose of isoniazid used was 300 mg daily or 10-15 mg/kg intermittently. In children, the isoniazid dose was 15-30 mg/kg twice or thrice weekly [8,9]. The same dose of rifampicin and ethambutol was given to adults and children (mg/kg body weight): rifampicin:10-15 mg/kg, 450 mg < 50 kg and 600 mg > 50 kg; ethambutol: 15 mg/kg. Adults received of pyrazinamide 1.5-2 g < 50 kg and 2-2.5 g > 50 kg while children received 45-60 mg/kg. Adults received streptomycin 1g while children received 40 mg/kg, max. 750 mg. Side-effects were reported in 37 patients, 26 patients were not compliant and 27 were lost to follow-up for other reasons. During treatment, new nodes or enlargement of existing lymph nodes occurred in 79/468 =17% [7,8,10,11,13]. Nodes were present after treatment in 143/423= 34% of the patients [7,8,10,11,13]. The size of the nodes was not report-

TABLE 1. Treatment for patients with tuberculous lymphadenitis based on published data: 6 and 9 months with isoniazid (H), rifampicin (R) and pyrazinamide (Z)

Study	Regimen	Patients	Patients lost			Failures	Cure rate % *		Follow-up (months) treatment supervised or not (+/-)	Relapse rate number of patients (%; 95% C.I.)
			Side-effects	Non-compliant	other		Intention to treat	Per protocol		
6 months' therapy										
Cheung[7]	$6S_3H_3R_3Z_3$	123	3	14	1	0	85	100	36-	4[h]/105 (3.8;1.1-9.5)
Jawahar[8**]	$2S_3H_3R_3Z_3/4S_2H_2$	175	2	3		2[b]	96	99	36+	3[b]/166 (1.9;0.4-5.4)
Kumar[9**]	$2H_2R_2Z_2/4H_2R_2$	15					100	100	24-	0/15
Kumar[9**]	$2HRZ/4H_2R_2$	12			1		100	100	24-	0/11
B.T.S [10,11]	2HRZ/4HR	66	6	2	6	1	77	98	24-	3/51 (5.9;1.2-16.2)
Yuen[12]	$4S_3H_3R_3Z_3/2H_3R_3$	49	4	2		2[b]	84	95	21+	2/41(4.9;0.6-16.5)
McCarthy[13]	2HRZ/4HR	57	5	1	10	2	68	95	20-	1/29 (3.5;0.1-17.8)
Pang[14]	2HRZ(E)/4HR***	4***	1***			0	93***	100***	12-	0/4
9 months' therapy										
B.T.S [10,11]	2HRZ/7HR	70	3	1	9	1	79	98	21-	2/56 (3.6;0.5-12.3)
Yuen[12]	$4S_3H_3R_3Z_3/5H_3R_3$	64	13	3		1[b]	73	98	21+	1/47 (2.1;0.1-11.3)
Pang[14]	2HRZ(E)/7HR***	9				0	93***	100***	12-	0/9

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin.
In the "Regimen " column, numbers before a group of letters represent the number of months on that type of drug, numbers after a letter or group of letters represent the number of doses of the drug(s) per week, and if a letter or group of letters is not followed by any numbers then the drug(s) were given daily.
Data are presented as absolute numbers with percentage and 95% confidence interval in parentheses.
*Cure rate intention to treat: number of patients cured/starters therapy.
Cure rate per protocol: number of patients cured/number of patients who completed therapy as planned.
**children, age < 13 yrs [8], <15 yrs [9].
***4 patients 4HR, 9 patients 7HR and 1 patient > 10HR.
[b] bacteriologically proven.
[h] histologically proven.

ed, or the nodes were not suspected of harbouring disease. If the diameter was > 1 cm and/or clinically suspicious, tissue was sent for culture before treatment was restarted. In 5/9 patients with reported failure, the unfavourable outcome was bacteriologically proven (9/553=1.6%) (Table 1) [8,12]. In one of these patients, the residual lymph node resolved spontaneously within 3 months and another patient with a residual node of 1 cm at the end of treatment was lost to follow-up [13]. A total of 534 patients completed treatment and follow-up as planned (Table 1). After a mean follow-up of 29 months, nodes were still present in 41/378=11% [7,8,10,11]. However, the number of patients with a relapse on clinical grounds after successful treatment of 6 months'duration was 13/422= 3.3% (95% C.I. 1.7-5.5, mean follow-up 31 months). After 9 months of therapy, 3/112 = 2.7% (95% C.I. 0.6-7.8, mean follow-up 20 months) relapsed. In three out of these 16 patients, the relapse was bacteriologically confirmed, while in four it was histologically proven [7,8]. Five patients relapsed during the first year [7,8,13]; three patients relapsed later, and in eight patients there was no further information [7-12].

3B.5 DISCUSSION

The authors addressed the question of whether the duration of treatment for tuberculous lymphadenitis can be safely reduced to 6 months. Most recent national and international treatment guidelines also recommend a 6 month therapy [4,15,16] The current meta-analysis supports these recommendations. The relevant literature was analysed using the relapse rate as the criterion. Follow-up was at least 12 months after the end of treatment. The shortage of literature with well-defined treatment results for tuberculous lymphadenitis made analysis very difficult. Out of necessity, the authors limited the analysis to patients with predominantly cervical tuberculosis. In general, cervical tuberculous lymphadenitis is one of the less severe manifestations of tuberculosis. Active tuberculous disease at other sites cannot always be ruled out completely. It is important for the diagnosis to be bacteriologically confirmed, not only to exclude other diagnoses, but also to obtain material for determination of the organism and susceptibility tests.

In contrast with high-prevalence countries, tuberculosis in low-prevalence countries is not the most frequent cause of lymphadenopathy. Persons infected with human immunodeficiency virus (HIV) have an increased frequency of mycobacterial infections in general, often affecting the lymph nodes. Care providers should be aware that in these patients *M.tuberculosis* is not always the

cause of lymphadenopathy. HIV-positive patients were not included in the present analysis, because the authors could not find any literature with a follow-up of at least 12 months after the end of treatment and no cases of infection were restricted to the lymh nodes [17].

FNA is the diagnostic procedure of choice. If this fails to be conclusive, excisional biopsy is the next step [5,18]. The diagnosis of tuberculosis was confirmed bacteriologically and histologically in 54% and 49% of the cases, respectively. As a result, treatment outcomes in patients with bacteriologically or histologically proven disease and in patients with suspected tuberculosis on clinical grounds, were merged and could not be analysed separately. Rest nodes did not always mean an unfavourable outcome. The latter was defined as treatment failure or relapse not only proven bacteriologically or histologically, but also on clinical grounds. The decision to perform a second diagnostic procedure or start retreatment depended on clinical judgement. The bacteriologically proven diagnosis depended on the bacillary load and the diagnostic approach. In contrast with smear-positive pulmonary tuberculosis, bacteriological confirmation of a cure is not available. However an immunological response to the antigens released from the dead bacilli may be reflected by the development of new nodes, increases in diameter, or complications such as sinus and abscess formation during treatment or follow-up [11].

The recommendations of the World Health Organisation (WHO) for antituberculous drugs were not strictly adhered to [7-9]. Doses (mg/kg body weight) of essential drugs for the treatment of tuberculosis should be the same in adults and children [4]. Resistance may have been induced by human failure (incompliance) when treatment was not supervised. Nevertheless the clinical outcome was satisfactory in most cases. Such favourable outcomes may be explained by the small number of bacilli in such patients and the low resistance rate. In the group of patients with tuberculous lymphadenitis treated for 6 months 3.3% relapsed, while those treated for 9 months had a relapse rate of 2.7%. Treatment for pulmonary tuberculosis for 6 months with a regimen including isoniazid, rifampicin and pyrazinamide resulted in a relapse rate of 116/4833 =2.4% (95% C.I. 2.0-2.8, follow-up 12-94 months) [3]. Differences were not statistically significant.

In studies on pulmonary tuberculosis, only patients with bacteriologically proven, fully sensitive tuberculosis are analysed. Treatment failures and relapses can be bacteriologically proven [3]. The suggestion that a low bacillary load may justify an even shorter length of treatment, e.g. 4 months, needs to be investigated [19]. However, sterilisation of lesions depends on the persistence of (semi)dormant bacilli, but on theoretical grounds this may be unrelated to the bacterial load.

In pulmonary tuberculosis, relapses mostly occur within 12 months after the end of treatment. Therefore, for prospective studies, a follow-up of 24-30 months is generally enough [3]. The risk of relapse in lymph node tuberculosis is unknown, but the small number of relapses during follow-up in the retrieved articles confirms the advice given by the Joint Tuberculosis Committee of the British Thoracic Society: after successful treatment, follow-up is not required but patients should be re-referred if symptoms recur [15].

In conclusion, it seems justified to administer medication for 6 months, including isoniazid, rifampicin and pyrazinamide, for tuberculous lymphadenitis (as the individual authors of the retrieved articles suggested). A large proportion of patients had rest nodes. Relapses occurred within 12 months after the end of treatment, but later was also possible. The small number of patients described in the literature makes consensus about diagnostic procedures and treatment schedules important, because investigators have to depend on pooled data and office-based analyses. Therefore data must be gathered in the same way to enable sound clinical judgements and to formulate therapeutic guidelines.

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Chapter 4

TUBERCULOUS MENINGITIS: IS A 6-MONTH TREATMENT REGIMEN SUFFICIENT?

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4.1 SUMMARY

Background The British Thoracic Society and the American Thoracic Society advise 12 months treatment for tuberculous meningitis, with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z).
Objective To establish whether 6 months treatment for tuberculous meningitis is equally as effective as longer treatment.
Method Medline search for papers published between 1978 and 1999. Inclusion criteria: study populations of patients with tuberculous meningitis, in whom the diagnosis was confirmed with clinical, cerebrospinal fluid and epidemiological findings; a treatment regimen with at least isoniazid, rifampicin and pyrazinamide and at least 12 months follow-up after the completion of treatment. Outcome measure: the number of relapses.
Results There were four 6-month treatment regimens (G6) and seven longer treatment regimens (G>6); 160/197 (81%) patients completed the 6-month treatment regimens, while 577/675 (85%) completed the longer-term treatment regimens. The clinical stage in G6 was poorer than in G>6. Relapse occurred in 2 out of 131 (1.5%) in G6 and in 0 out of 591 in G>6.
Conclusion Although no studies have compared 6-months treatment with longer treatment, it can be concluded on the basis of this literature review that 6-months treatment is sufficient for tuberculous meningitis with fully susceptible mycobacteria.

4.2 INTRODUCTION

Tuberculosis is an infectious disease that can be active in many organs simultaneously. Recommended treatment duration differs from one organ site to another [1,2]. For tuberculous meningitis with fully susceptible mycobacteria, the recommended treatment duration is 12 months, whereas the advised duration for pulmonary tuberculosis is 6 months with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) [1,2]. The following explanations can be put forward for this difference: 1) tuberculous meningitis is difficult to diagnose; 2) morbidity and mortality are high; 3) reliable parameters to evaluate the effect of therapy are lacking, such as bacteriology of cerebrospinal fluid (CSF); 4) it is unclear whether rifampicin is effective in the central nervous system; 5) the penetration of ethambutol and aminoglycosides is poor, particularly when the meninges are non-inflamed; 6) there is a risk of relapse and cerebral damage if therapy is stopped prematurely; and 7) the available studies are not considered to have reliable methodology.

The longer the duration of therapy, the greater the risk of non-compliance, especially if the patient does not experience signs of clinical recovery. Moreover, if a shorter treatment duration is equally as effective, it will obviously be cheaper.
We performed a literature review based on relapse rates of tuberculous meningitis to evaluate the effectiveness of 6 months treatment with a regimen that included at least isoniazid, rifampicin and pyrazinamide.

4.3 DEFINITIONS AND METHOD

Medline was used to search for relevant papers in the English language that had been published between 1978 and 1999. Reference lists were checked and authors contacted. Keywords were spinal tuberculosis, meningeal tuberculosis, miliary tuberculosis, intracranial and spinal tuberculomas, tuberculous encephalitis and myelitis, tuberculous abscess of the brain and spinal cord, isoniazid, rifampicin and pyrazinamide.
Inclusion criteria for the literature study were:

1) the diagnosis of tuberculous meningitis was based on clinical findings, CSF analysis and epidemiological data;
2) treatment included at least isoniazid, rifampicin and pyrazinamide, possibly in combination with ethambutol and/or streptomycin in adequate doses [3];
3) follow-up after treatment was at least 12 months.

The patients had to be classified into classes according to the clinical severity of their disease, because this is of importance for the prognosis [4,5].
Stage I: the patient has non-specific complaints (headaches, nausea, vomiting) without any changes in the level of consciousness.
Stage II: the patient shows changes in the level of consciousness, but there is no coma or delirium. Physical examination reveals slight focal neurological symptoms.
Stage III: the patient is stuporous or comatose whether or not in combination with severe neurological deficits; epileptic fits, extrapyramidal disturbances and hemiplegia may be present.
The papers were also required to contain information about CSF analysis. Lymphocytic pleocytosis, strongly elevated CSF protein and a decreased glucose CSF:blood ratio were considered to correlate with tuberculosis.
Important epidemiological data to help confirm the final diagnosis were signs

of direct contact with a patient with a contagious form of tuberculosis in the anamnesis.
The diagnosis of tuberculous meningitis is "definite" when acid-fast rods are found in the CSF, when the culture in Löwenstein-Jensen medium is positive, or when autopsy findings are in line with tuberculosis.
The diagnosis is "probable" when *M.tuberculosis* is cultured from another organ. The suspicion of tuberculous meningitis can be supported by: 1) cerebral computed tomography (CT) findings that correlate with tuberculous meningitis; 2) a chest radiograph with signs of tuberculosis; 3) a positive Mantoux test; or 4) good response to tuberculous chemotherapy.
In this study, the following measures were employed to evaluate the effectiveness of the treatment: number of patients who completed treatment and follow-up according to the original treatment plan, the number of patients who died, the number of patients who were cured, the number of patients who were cured but still had residual neurological symptoms and the number of patients who relapsed after completing treatment.

4.4 RESULTS

A total of 71 papers were found, but 60 could not be included in our review, because the treatment regimen did not contain pyrazinamide, or it was not clear how many patients had been treated with which drugs, or the follow-up period was too short. One of the 11 remaining papers reported on tuberculomas [6], while 10 reported on tuberculous meningitis [7-16]. Two papers described the same study population, with short-term and longer-term follow-up periods. Relevant details were extracted from both papers [15,16]. The studies included in our analysis were published between 1961 and 1994. Three had been performed in Thailand, three in India, one in Ecuador, one in South Africa, one in Turkey and one in China.
The paper on tuberculomas of the brain [6] reported on 108 patients, all aged over 5 years, in whom the diagnosis had been made on the basis of clinical and CT findings. Treatment duration was 9 months. A total of 105 patients completed treatment according to the original plan; 97 were cured and eight had residual neurological symptoms; all of them completed 15 months follow-up. At the end of the follow-up period, 94 patients were cured, 11 had residual symptoms and no relapses had occurred.
The papers on tuberculous meningitis described patients who had been treated for 6 months (referred to as G6) or longer (G>6) [7-16]. The following information was recorded (also see Table 1):

TABLE 1. Results on the basis of data from the literature on ≥ 6 months treatment for tuberculous meningitis. Treatment included at least isoniazid (H), rifampicin (R) and pyrazinamide (Z). Numbers in so far as mentioned in the review studies (%)

	6 months treatment		> 6 months treatment	
Population				
Number of studies	4		5	
Authors	Cotmongkol [7] Alarcon [8] Jacobs [9] Donald [10]		Doğanay [11] Phuapradit [12] Goel [13] Humphries [14] Ramachandran [15,16]	
Number of patients	197		1176	
Analysed	197		675	
Age				
< 16 years	147		515	
≥ 16 years	50		160	
Diagnosis				
Clinical stage				
I	27	(14%)	138	(18%)
II	95	(48%)	434	(58%)
III	75	(38%)	178	(24%)
CSF testing				
Ziehl-Neelsen Positive /number of specimens	17/61	(28%)	36/103	(35%)
Löwenstein culture positive / number of specimens	45/187	(24%)	105/330	(32%)
Other diagnostic criteria				
Contact with known TB patient	109/176	(62%)	84/180	(47%)
CT-scan positive	112/141	(79%)	35/45	(80%)
Hydrocephalus	89/113	(79%)	42	
Tuberculoma	10		7	
Chest X-Ray positive for TB	107/197	(54%)	243/479	(51%)
Miliary pattern	17		48	
Mantoux > 10 mm	117/176	(66%)	90/180	(50%)
Treatment regimen [1]	2HRZ/4HR 2HRZS/4HR 2HRZE/4HR 6HRZetionamide		2HRZS/6-7HR 4-6HRZS/8-10HR 4-6HRZE/8-10HR HRZS ethionamide, cycloserine, PAS 3HRZS/6HRE/15HE 2HRZS/10HE $2HR_2ZS$/10HE	

	6 months treatment	> 6 months treatment
During treatment		
Number of failures		2
Non-compliant	4	66
Side-effects	1	1
Died	32/197 (16%)	41/675 (6%)
Treatment completed	160/197 (81%)	577/675 (85%)
On completion of treatment: *cured*	120/160 (75%)	91/148 (61%)
residual neurological deficits	40/160 (25%)	57/148 (39%)
During follow-up		
Duration of follow-up	mean 15 months range 4-33 months 85% at least 12 months	mean 15 months range 4-36 months 92% at least 12 months
On completion of follow-up, absolute numbers and rates who completed treatment	131 82%	591[2] ≥ 85%
Relapse[3]	2	0
Died	2	24
On completion of follow-up *cured*	33/39 (85%)	188/307 (61%)
residual neurological deficits	6/39 (15%)	119/307 (39%)

[1] isoniazid (H), rifampicin (R) pyrazinamide (Z) ethambutol (E) streptomycin (S)
[2] including 100 patients [ref 15,16]: a maximum of 68 had received Z, while a minimum of 32 patients had not received Z
[3] Goel et al. described 37 patients, who dropped out (non-compliant); 25 children and 10 adults suffered relapse; 20 had received < 6 months treatment, 15 > 6 months treatment [13]

Patient population

Numbers: Four studies reported on 197 G6 patients [7-10] and five studies reported on 1176 G>6 patients; 675 G>6 patients were included in the analysis [11-16], while 501 G>6 patients were excluded, because there was insufficient information [13].

Age: in both the G6 and G>6 groups there were almost three times as many children as adults.

Sero-positivity for the human immunodeficiency virus:

Human immunodeficiency virus (HIV) status was not mentioned.

Diagnosis: The distribution of G6 and G>6 patients over the clinical stages is shown in Table 1. The clinical stage of G6 patients was poorer than that of G >6 patients. Distributions of children and adults over the clinical stages were equal.

CSF analysis: In the G6 group, 95% had undergone Löwenstein-Jensen culture and 24% were positive. In the G>6 group, these percentages were 49% and 32%, respectively.

Details about the diagnosis reported in the papers are listed in Table 1.

Resistance: the sensitivity of *M.tuberculosis* in vitro was reported in 42 G6 patients and in 56 G>6 patients [10,15]. Resistance to streptomycin, isoniazid, ethambutol and a combination of isoniazid and streptomycin was found in one, three, one and nine patients, respectively [15].

Treatment regimen: There were 4 G6 [7-10] and 7 G>6 regimens [11-16] (Table 1).

The treatment regimen mostly comprised an intensive phase of at least two months with isoniazid, rifampicin and pyrazinamide, whether or not in combination with ethambutol or streptomycin, followed by at least four months of isoniazid and rifampicin [7-9,11,12]. In two studies, ethionamide was also used [10,14]. In the study by Humphries et al. it was administered in addition to cycloserine and para-amino salicyl acid (PAS) [14]. Neither study made a distinction between an intensive phase and a continuation phase [10,14]. Ramachandran et al. did not administer rifampicin in the continuation phase, but ethambutol [15,16]. After an intensive phase of 3 months, Goel et al. administered isoniazid, rifampicin and ethambutol for 6 months and continued treatment with isoniazid and ethambutol for a further 15 months; their total treatment period was 2 years [13]. The medication was taken daily in all the treatment regimens except for one, in which rifampicin was taken twice a week during an intensive phase of 2 months duration [15,16].

Dosage: Isoniazid was administered in a dose of 300 mg/day, or the dose varied between 5-12 mg/kg/day. Rifampicin was administered in a dose of 450 mg to patients with a body weight of < 50 kg and 600 mg > 50 kg, or the dose varied

between 10-15 mg/kg/day. Pyrazinamide was administered in a dose of 20-40 mg/kg/day. The only difference in dosage between G6 and G>6 patients was that for 6 months, Jacobs et al. and Donald et al. gave a higher dose of isoniazid (15 mg/kg) and a higher dose of rifampicin (20 mg/kg/day) to children [9,10]. Dosage was not mentioned in the study by Humphries et al. [14].

Medication under supervision

Patients were either hospitalized for the total treatment period of 6 months [10] or for the first 2 to 3 months [8,15], or until they showed clinical improvement [12,13]. Treatment was completed by 81% of the G6 patients and by 86% of the G>6 patients.

Other medication

Prednisone (1-3 mg/kg or 30-60 mg/day) or dexamethasone (0.3-0.5 mg/kg) were administered to patients with spinal arachnoiditis, high CSF protein level, mental changes and focal neurological abnormalities. Donald et al. administered steroids to 40 patients within the framework of their study [10], while Ramachandran et al. administered steroids to all their patients [15,16]. The paper by Goel et al. did not mention steroids [13]. Vitamin B6 was administered in three studies in a dosage that varied between 10-100 mg/day [8,11,13]. Ramachandran et al. [15,16] reported that they had administered vitamins without any further specification, whereas a number of other papers did not mention vitamins at all [7,9,10,12,14].

Surgical intervention

All the authors reported that lumbar punctures were performed regularly in patients with increased CSF pressure (>200 mm H_2O). If this was insufficient, ventriculostomy or a ventrico-peritoneal shunt was applied; 32/197 (16%) G6 patients received a ventrico-peritoneal shunt versus 126/674 (19%) G>6 patients [7,8,10-16].

Parameters to monitor the course of recovery

After the completion of treatment, distinction was made between "cured" and "cured but with residual neurological deficits" in all of the G6 patients and in 26% of the G>6 patients. In 429 G>6 patients, no distinction was made between "cured" and "cured but with residual neurological deficits" [13,14]. None of the papers mentioned criteria on which to base the decision of whether patients should be treated for longer than 6 months. In the study by Alarcon et al., CSF was normal in all 20 patients who completed treatment [8]; in the study by

TABLE 2. Results in **children** with tuberculous meningitis after ≥ 6 months treatment with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) on completion of treatment and on completion of ≥ 12 months follow-up

Number (%) 6 months treatment		> 6 months treatment
Starters	147	515
Completed treatment	127 (86%)	447 (87%)
Completed follow-up	99 (78%)	472[1] (≥ 83%)
Relapse	1	0
After treatment cured	93/127 (73%)	32/68 (47%)
After treatment residual neurological deficits	34/127 (27%)	36/68 (53%)
After follow-up cured	6/7 (86%)	170/286 (59%)
After follow-up residual neurological deficits	1/7 (14%)	116 / 286 (41%)

[1] Including 100 patients [ref 15,16]: a maximum of 68 had received Z

Chotmongkol, this was the case in nine out of the 15 patients tested [7]. The remaining papers did not mention CSF analysis findings at the completion of treatment.

Mortality was 16% (32/197) in G6 patients and 6% (41/675) in G>6 patients (Table 1). More than 50% of all the cases died in the first three months; six patients died in the seventh to fourteenth month of treatment [7-16]. The clinical stage on admission of the 91 patients who died was: stage I 2%, stage II 43% and stage III 55%.

Follow-up after the completion of treatment (Table 1)

Mean follow-up after the completion of treatment was 15 months in the G6 and G>6 patients. Follow-up was at least 12 months in 85% of the patients who completed follow-up.

It was not possible to indicate how many patients who received H, R and Z also actually completed follow-up, because one study [15, 16] reported the results of 100 patients, but this group also included patients who had not received Z. This means that a minimum of 85% (491/577) and a maximum of 97% (559/577) of the patients who completed treatment also completed follow-up. Relapse occurred in 2/131 (1.5%) in G 6 and in 0/591 in G >6. One G6 patient with stage III on admission suffered relapse and died 3 months after completing treatment [8]. The other G6 patient (stage I on admission) suffered relapse 3 weeks after completing treatment and received a further 6 months treatment [10]. The clinical stage on admission in G 6 patients was poorer than in G >6 patients.

Relapse was also reported by Goel et al. [13]. Their paper mentioned 37 drop-outs; relapse occurred in 35 of them: 25 children and 10 adults; 20 of them had received treatment for less than 6 months and 15 for more than 6 months. During follow-up, two G6 patients and 24 G>6 patients died; 18 of these patients had residual neurological deficits and eight died of other causes [10,16,14].

At least 82% of the G6 patients and at least 85% of the G>6 patients completed follow-up after treatment. The percentage of patients who were cured or were cured but had residual neurological deficits was not mentioned in all of the papers: results were reported for 30% of the G6 patients and 52% of the G>6 patients. In the G6 group, 83% of the patients were cured and 15% had residual neurological deficits [7,8]. No outcomes were mentioned in 87 patients [9,10]. In the G>6 group, 61% were cured and 39% had residual neurological deficits [12-16]. Outcome was not mentioned for 260 patients [11,13].

Effectiveness in adults and children

A young age is believed to be an unfavourable prognostic factor [14]. In the G6 group, treatment was completed by 86% of the children and by 66% of the adults, while in the G>6 group, the completion rates were very similar at 83% and 81%, respectively (Table 2 and 3). Mortality in the G6 children was lower than in the adults (14% and 24%, respectively). In the G>6 group, mortality was 11% in the children and 2% in the adults. It should be noted that the clinical stage on admission was poorer in G 6 than in G >6.

In the G6 group, outcomes were mentioned for all the children and adults who completed treatment; 73% of the children were cured, while 27% were cured but had residual neurological deficits. In the adults, these rates were 82% and 18%, respectively. In the G>6 group, the percentages of patients who were cured and/or had residual neurological deficits after completing treatment were not mentioned in all of the papers: outcomes were mentioned for only 15% of the

TABLE 3. Results in **adults** with tuberculous meningitis after ≥ 6 months treatment with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) on completion of treatment and on completion of ≥ 12 months follow-up

Number (%) 6 months treatment		> 6 months treatment
Starters	50	160
Completed treatment	33 (66%)	130 (81%)
Completed follow-up	32 (97%)	119 (92%)
Relapse	1	0
After treatment cured	27/33 (82%)	59/80 (73%)
After treatment residual neurological deficits	6/33 (18%)	21/80 (27%)
After follow-up cured	27/32 (84%)	18/21 (86%)
After follow-up residual neurological deficits	5/32 (16%)	3/21 (14%)

children and in 62% of the adults. In the G>6 group, 47% of the children were cured and 53% were cured but had residual neurological deficits. In the adults, these rates were 73% and 27%, respectively. The large percentage of children who were cured with residual neurological deficits is based solely on the studies by Ramachandran et al.; This was the only study population in which rifampicin was not administered in the continuation phase of treatment[15,16].

High percentages of children and adults completed follow-up in accordance with the original treatment plan; completion did not depend on the duration of treatment. In the G6 group, relapse occurred in one adult and one child. The percentages of patients who were cured or were cured but had residual neurological deficits at the end of follow-up were reported for all adults and for 7% of the children. In the adult G6 patients, the results after follow-up were not different from the results at the end of treatment. In the G>6 group, outcomes at the end of follow-up were mentioned for 18% of the adults and 61% of the children.

4.5 DISCUSSION

In a literature study, we reviewed 10 papers that met our inclusion criteria regarding the treatment of tuberculous meningitis, in order to analyse the risk of relapse in relation to treatment duration. The patients had been treated for 6 months or longer. Although a 6-month treatment has never been compared to longer treatment in one study, we could conclude that a treatment duration of 6 months for tuberculous meningitis with normal drug sensitivity was equally as effective as longer treatment. However, for this conclusion to be valid, treatment had to include a 2-month intensive phase consisting of isoniazid, rifampicin and pyrazinamide and a further 4 months of isoniazid and rifampicin.

It was not possible to make a satisfactory comparison between the number of patients in G6 and in G>6 who were cured or were cured but had residual neurological symptoms at the time of completing treatment and at the time of completing follow-up, because not all of the papers reviewed reported the results after completing treatment and after completing follow-up. Similary, it was not possible to establish the degree of spontaneous recovery or deterioration of neurological deficits after completion of treatment. Nevertheless the data reported in the review studies and presented in Tables 1 and 2 seem to indicate that in any case, a 6-month treatment regimen did not lead to poorer results than one of more than 6 months, either at the time of completing treatment or at the time of completing follow-up.

The treatment regimens applied in the review studies could be considered equivalent, except for Ramachandran et al. who discontinued rifampicin after the intensive phase [15,16]. These authors suggested that the high rate of residual neurological symptoms may have been caused by the extremely poor nutritional state of their patients. Nothing was mentioned about nutritional state in the other studies.

The treatment results as a whole show that tuberculous meningitis is a very dramatic form of tuberculosis. Between 10-50% of the patients were cured but had residual neurological deficits, while mortality was between 10-30% [17]. At the start of treatment, patients were commonly suffering from irreversible brain damage. It may be possible to optimise treatment so that no further damage occurs.

An important theoretical question regarding the regimens applied in the studies reviewed, is whether the drugs adequately reached the focus of infection. In the literature as a whole, analyses on CSF concentrations of tuberculostatic agents were performed in only a small number of patients. However, the outcome of treatment cannot be expected to be directly proportional to tuberculostatic drug concentrations in the CSF.

Owing to the fact that tuberculous meningitis also implies tuberculous meningo-encephalitis, the tuberculous infection can be focused in the CSF, meningeal tissue and/or cerebral parenchyma. Depending on the infection site, consideration must be given to how and whether chemotherapy crosses the blood-CSF barrier and/or the blood-brain barrier. The brain and CSF cannot be considered as one pharmacokinetic compartment [18]. For example, active transport of chemotherapy plays a role in crossing the blood-CSF barrier, while diffusion plays a key role in the blood-brain barrier. Small molecular size, high lipophilia and low binding to plasma proteins facilitate diffusion, but the influence of these mechanisms on penetration into brain tissue and CSF decreases as the severity of the TB infection increases.

Pyrazinamide and ethionamide have a low molecular weight, high lipophilia and low protein binding in plasma. They easily cross the blood-CSF barrier in the presence and absence of meningeal inflammation [9,13,17-21]. Rifampicin binds to plasma proteins for 80%, but it has a very long half-life in CSF [18]. Isoniazid is hydrophilic, but easily crosses the blood-brain barrier in infected meninges; the concentration also exceeds the minimum inhibitory concentration (MIC) value in non-infected meninges [18,22]. It is debatable whether ethambutol is worthwhile in the continuation phase of treatment, because in line with the aminoglycosides, its penetration is poor, especially when the meninges are no longer infected [13-16,22]. Ofloxacin is the quinoline with the best penetration of infected meninges [17,18].

In patients who are suspected of having tuberculous meningitis with drug resistance, preference might be given to a highly penetrative chemotherapeutic agent such as ethionamide as a fourth agent in the initial treatment phase, instead of ethambutol and the aminoglycosides [10].

Another reason for administering a fourth tuberculostatic in the intensive treatment phase is a high concentration of *M.tuberculosis*, because this involves an increased risk of spontaneous mutation into a resistant strain. It is unclear whether there is a high bacterial load in tuberculous meningo-encephalitis. Persistently "dormant" bacteria require sterilisation therapy with rifampicin and pyrazinamide. If these two agents cannot be administered, then long-term treatment with isoniazid is necessary. It is unclear how many "dormant" bacteria are present and how well they can be reached in the central nervous system.

In the studies reviewed, good results were achieved with 2 HRZ/4HR. The majority of studies were performed during the period that there was little risk of primary resistance.

Another factor that can affect treatment outcome is dosage. [23] In the treatment of other bacterial infections, a great deal of data have recently become

available on time-dependent and concentration-dependent bactericide of antibiotics [24]. High dosage alone does not appear to be a valid option in the case of poor transport capacity. If a high peak concentration can be reached this does not lead to more rapid bactericide or sterilisation owing to the long replication time of *M.tuberculosis*. It might be worthwhile to administer frequent very high dosages, but this would increase the risk of side-effects and treatment compliance is known to decrease with multiple daily intakes.

Another important issue is the potential interaction with other medication prescribed for the patient. Remarkably, the penetration of tuberculostatics is not impaired by the simultaneous use of corticosteroids [25,26]. Vitamins are often given in high dosages. However, a dose of 10 mg vitamin B6 per day is sufficient to counteract the neuropathy induced by isoniazid, while a high dose of vitamin B6 might have an antagonistic effect on isoniazid [27,28,29]. It was not possible to analyse the effect of vitamin B6 dosage on the outcomes of treatment in the studies reviewed. In order for treatment to be effective, it is important that the tuberculostatics are actually taken by the patient. More than 80% of the patients in the review studies completed treatment irrespective of whether it was short-term or longer-term. However, this does not mean that the tuberculostatics were taken under supervision over the whole treatment period. Information about supervision was scarce, except in the study by Donald et al. [10]. Longer-term treatment will have little effect unless compliance can be guaranteed: motivation is known to diminish if the patient does not experience steady clinical improvement.

The aim of treatment is not only to cure the patients and avoid residual symptoms, but also to prevent relapse. Although a large number of children have tuberculous meningitis, a disproportionately small number of studies have addressed the relapse rate. A possible explanation is that follow-up is difficult in tuberculosis endemic regions.

According to the literature, clinical and laboratory findings are the same in HIV-infected and non-infected individuals [30,31]. Tuberculous meningitis in HIV patients is treated in the same way. In HIV-infected children, the results are poorer than in infected adults. The more severe clinical and neuroradiological abnormalities in children are associated with HIV encephalopathy [31].

None of the review studies mentioned comorbid HIV seropositivity in their tuberculous meningitis patients.

4.6 CONCLUSIONS AND RECOMMENDATIONS

It can be concluded that 2HRZ/4HR is adequate treatment for tuberculous meningitis with fully susceptible organism. If there is a suspicion of resistance, four tuberculostatics should be administered; the fourth agent might comprise ethambutol, an aminoglycoside, ethionamide or a quinoline. In patients with an unknown resistance pattern or isoniazid resistance, pyrazinamide should be administered during the total treatment period (2HRZE/4HRZ). In the case of rifampicin resistance or multidrug-resistance, the treatment regimen should include at least 2 tuberculostatics to which the bacteria are sensitive and the treatment should be continued for longer than 6 months.

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Chapter 5

ISONIAZID DOSAGE IN THE TREATMENT OF CHILDREN WITH TUBERCULOSIS

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Dosering van isoniazide bij behandeling van kinderen met tuberculose. Tijdschr Kindergeneeskd 1998;66:182-5

5.1 SUMMARY

In 1997, a written survey was conducted among Municipal Health Service tuberculosis physicians. Information was requested on the isoniazid dosage in children with active tuberculosis treated in 1993, 1994 and 1995 and the relapse rates after the completion of treatment. The period 1993 to 1995 was chosen because a computer-based tuberculosis registration system was introduced nationally in 1993. More than 75% of relapses occur within the first year after the completion of treatment. In the period 1993 to 1995, 289 children aged 0 to 14 years were registered with active tuberculosis. Data on 176 children (61%) could be analysed. Isoniazid dosage was 4-8 mg/kg body weight (mean 5 mg per kg body weight) in 166/176 children (94%) and ± 10 mg/kg body weight in 10 children. Clinical and radiological response to treatment was good in all the children. The mean treatment duration was 9 months, in conformity with the guidelines valid at that time. Mean follow-up duration after the completion of treatment was approximately 24 months (12-36). None of the 176 children relapsed after the completion of treatment. It can be concluded that the Dutch policy of administering 4-8 mg/kg body weight of isoniazid was adequate.

5.2 INTRODUCTION

Recently it has been recommended in this journal to administer 10-20 mg/kg body weight of isoniazid per day to children, in conformity with the American literature [1-3]. In the Netherlands, the National Tuberculosis Policy Committee (CPT) advises a mean isoniazid dosage for children and adults of 5 mg/kg per day (4-8 mg/kg/day) to a maximum of 10 mg/kg, in accordance with the guidelines of the International Union Against Tuberculosis and Lung Disease (IUATLD). The maximum dose of isoniazid is 300 mg per day [4]. During treatment, the dosage should be adjusted regularly to the child' weight.

This study evaluated the INH dosage administered to children aged 0 to 14 years with active tuberculosis in the Netherlands in 1993, 1994 and 1995 and the relapse rate after the completion of treatment.

TABLE 1. Number of children with a first diagnosis of active tuberculosis in 1993, 1994 and 1995. Netherlands Tuberculosis Registry data (NTR)

Localisation	0-4 yrs	5-14 yrs	total
Pulmonary	61	169	200
Pulmonary and extrapulmonary	4	16	20
Extrapulmonary	26	43	69
Total	91	198	289

5.3 PATIENTS AND METHODS

In 1993, 1994 and 1995, 289 children were diagnosed for the first time with active tuberculosis in the Netherlands (Table 1).
The dosage of anti-mycobacterial medication is not registered nationally. Therefore, in April 1997, a questionnaire was sent to 29 tuberculosis physicians working at Dutch Municipal Health Services, to obtain information on children aged 0 to 14 years registered in 1993, 1994 and 1995 with active tuberculosis.
Active tuberculosis was diagnosed when the diagnostic criteria of the American Thoracic Society (Table 2) were met, or when contact tracing in a child without complaints revealed a positive Mantoux test and an abnormal chest X-ray that improved after the start of treatment. Owing to the fact that the standard treatment duration for children with TB was 9 months, no information was obtained about the duration of treatment.

5.4 RESULTS

A total of 22 out of the 29 physicians responded, which yielded information on 193 patients. In 17 patients, the data was not suitable for analysis: 14 patients did not have active tuberculosis; one patient showed resistance to isoniazid and it had been discontinued almost immediately; one patient had *Mycobacterium bovis*; one patient had *Mycobacterium avium*.
Data were analysed on 176 out of the 289 (61%) children registered with active tuberculosis for the first time. Age was 0-4 years in 54 children and 5-14 years in 122 children. Nationality was unknown in 34 children; 60 children had Dutch parents and 82 had non-Dutch parents. Seventy-seven children were found by contact tracing; they did not have any complaints, but they did have a positive

TABLE 2. Criteria for active tuberculosis according to the American Thoracic Society

Response to treatment for tuberculosis and at least 2 out of the following 3 criteria must be met:
1. One or more of the following clinical findings: - fever > 38°C for at least one week - night sweats for longer than one week - more than 20% weight loss - coughing - dyspnoea - haemoptysis - lymphadenopathy for longer than 4 weeks
2. One of the following microbiological criteria: - acid-fast rods in sputum, pleural fluid or both - positive Löwenstein culture - histopathological findings correspond with tuberculosis
3. Radiological criterion - chest X-ray findings correspond with tuberculosis (infiltrate, pleural fluid or hilar adenopathy

Mantoux test and radiological abnormalities on the chest X-ray that improved with treatment.

In the group of 176 children, 114 had been treated by MHS physicians and 62 by hospital specialists. In 34 out of these 62 children, the chief treating physician had been a paediatrician. In 10 children, the hospital specialist had consulted a pulmonologist.

In 94% of the children (166/176) the isoniazid dosage was 4-8 mg/kg body weight per day (mean 5 mg/kg). In 10 children a higher dosage was administered (mean 10.8 mg/kg body weight). In one patient with tuberculous meningitis, it was decided to perform concentration of isoniazid in serum on the basis of the clinical reaction and to adjust the dosage accordingly. The mean treatment duration of the 176 children was 9 months, in conformity with the guidelines valid at that time. An intensive phase of 2 months with daily isoniazid, rifampicin and pyrazinamide, if necessary supplemented by ethambutol, was followed by 7 months of daily isoniazid and rifampicin. Treatment was successful in all 176 children. None of the children suffered relapse after the completion of treatment.

In 139 questionnaires, the year of starting treatment was mentioned. The estimated follow-up period after the completion of treatment varied in 79% of the patients from 12 to 36 months.

5.5 DISCUSSION

The recommended isoniazid dosage for children varies. In the American literature, 10-20 mg/kg per day is advised. When isoniazid is combined with rifampicin, isoniazid is administered in a dosage of 10 mg/kg per day to prevent liver function disturbances [3,5]. The same dosage is prescribed in the UK [6]. In accordance with the IUATLD guidelines, an isoniazid dosage of 5 mg/kg per day is advised in the Netherlands, the neighbouring countries and in the majority of countries with a high tuberculosis prevalence [7-9].

Arguments in favour of administering a higher isoniazid dosage to children include: differences in pharmacokinetics compared to adults; poorer tissue penetration; an assumed lower number of bacteria; the more frequent presence of caseomas than cavernae; higher prevalence of extrapulmonary tuberculosis; children tolerate high dosages and the limitations in the available means of administration, so that one dose is often larger than 5 mg/kg body weight [10].

A study by the IUATLD on the serum concentration of isoniazid showed that in children, a dosage of 5 mg/kg achieved a sufficiently high and therapeutic serum concentration [11,12]. It was concluded that correspondingly, the dosage in children does not need to be higher than that in adults.

The penetration of isoniazid through the blood-brain barrier is excellent, both in healthy meninges and in meningitis. Therefore, it is not necessary to increase the dosage for the treatment of tuberculous meningitis. An isoniazid serum concentration analysis can be indicated in infants and young children in the case of liver function disturbances, strong weight increase, decreased sensitivity of mycobacteria to isoniazid, if there is no clinical improvement and in serious forms of tuberculosis, such as miliary tuberculosis, meningitis and encephalitis [13]. In the above-described survey, the dosage was adjusted on the basis of the serum isoniazid concentration in one child with tuberculous meningitis.

The daily dose of isoniazid is taken in one go, preferably on an empty stomach. In the case of gastrointestinal disturbances, it is recommended to take the isoniazid with a light breakfast. Although food delays the time until maximum serum concentration is reached, this does not usually have any therapeutic consequences. It is only worthwhile to perform serum concentration analysis if the patient's recovery does not follow the expected pattern. The questionnaires showed than none of the 176 children suffered tuberculosis relapse. The mean follow-up period was 24 months (12-36). The relapse rate is a gauge for the effectiveness of treatment. In general, a follow-up period of 24 to 30 months after the completion of treatment is considered to be adequate for a prospective study. More than 75% of recurrences occur within the first year after the com-

pletion of treatment [15]. Tuberculosis is a notifiable disease and the registration system is watertight. Therefore, if any cases of relapse occur, they will be registered.

5.6 CONCLUSION

The policy in the Netherlands of administering an isoniazid dose of 4-8 mg/kg body weight per day in conformity with the guidelines of the IUATLD, did not lead to treatment failure. At present, there do not appear to be any arguments in favour of adopting the American policy of administering 10-20 mg/kg body weight.

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Chapter 6

CHEMOTHERAPEUTIC TREATMENT FOR SPINAL TUBERCULOSIS

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6.1 ABSTRACT

Aim: to evaluate whether 6 months of chemotherapy for patients with spinal tuberculosis prevents relapse as effectively as > 6 months of chemotherapy.
Method: literature review. Medline search including references, from January 1978 to November 2000. Inclusion criteria for publications: diagnosis of spinal tuberculosis confirmed bacteriologically and/or histologically, or was probable on the basis of clinical and radiological parameters; treatment regimen (whether or not in combination with surgery) included isoniazid (H), rifampicin (R) and pyrazinamide (Z); follow-up period after completion of treatment of ≥ 12 months. Exclusion criteria: patients with relapse who had previously been treated adequately for tuberculosis.
Outcome parameters: relapse rate.
Results: 4 publications were found with HRZ regimens of 6 months duration and 10 publications with HRZ regimens of > 6 months duration. A number of patients had received HRE (E=ethambutol) for ≥ 9 months. In the results, no distinction was made between treatment groups. HRZ for 6 months led to a relapse rate of 0% (0/56)(95% C.I. 0.0-6.4); follow-up after surgical intervention ranged from 6 to 108 months. HRZ for ≥ 9 months (≥119 patients) or HRE for ≥ 9 months (≤71 patients) led to a relapse rate of 2% (4/218)(95% C.I. 0.6-5.0); follow-up after surgical intervention was 6-168 months. Despite the small number of studies 6 months of therapy is probably sufficient for patients with spinal tuberculosis.

6.2 INTRODUCTION

In the literature, there is no uniformity in the duration of chemotherapeutic treatment for spinal tuberculosis. The American Thoracic Society (ATS) recommends 6 months treatment for spinal tuberculosis and osteoarticular tuberculosis in adults, but 12 months in children, because reliable data on shorter treatment durations are lacking [1]. The British Thoracic Society (BTS) recommends 6 months treatment, irrespective of the age of the patient [2]. The Netherlands Tuberculosis Register (NTR) shows that in the period 1993-1998, 384 patients were treated for osteoarticular tuberculosis (55% had spinal tuberculosis); 22% (86/384) were treated for 6-9 months, 31% (119/384) were treated for 10-12 months and 32% (123/384) were treated for ≥ 13 months. The treatment regimens included isoniazid (H), rifampicin (R) and pyrazinamide (Z).
In patients with spinal tuberculosis, surgical intervention is very important. It

may comprise abscess drainage, debridement, laminectomy, anterior and/or posterior stabilisation with bone grafts or metal implants. The following circumstances are generally considered to form indications for surgical intervention: (1) neurological deficits (with an acute or non-acute onset) caused by compression of the spinal cord, (2) spinal instability caused by collapse or destruction of vertebrae, or kyphosis of more than 30°; (3) no response to chemotherapeutic treatment; (4) non-diagnostic biopsy; (5) large paraspinal abscesses [3,4,5].

The aim of this study was to investigate whether 6 months of chemotherapeutic treatment with a regimen including isoniazid (H), rifampicin (R) and pyrazinamide (Z) (6HRZ), with or without surgery, was equally as effective as a longer treatment regimen (> 6 months). Outcome was evaluated in terms of relapse rates after successful treatment.

6.3 METHODS

A search was made of the English, German and French literature published subsequent to 1978 (i.e. after the introduction of pyrazinamide) using Medline; the references were checked for additional relevant publications. The most recent search was performed in November 2000.
Keywords were osteoarticular, miliary, spinal tuberculosis, drug therapy; searches were also made under Pott's disease, vertebral tuberculosis, bone, joint tuberculosis, treatment, antitubercular agents, isoniazid (H), rifampicin (R) and pyrazinamide (Z).
Inclusion criteria were: study populations of patients with spinal tuberculosis whose treatment had included isoniazid (H), rifampicin (R) and pyrazinamide (Z) and in whom the follow-up period after the completion of treatment was at least 12 months.
Exclusion criterion was: patients with tuberculosis relapse who had previously received adequate treatment with chemotherapy.

Definitions
The diagnosis of spinal tuberculosis is certain when Löwenstein culture of biopsy specimens obtained from the vertebrae are positive; the diagnosis is almost certain in the case of a histological profile with caseating granulomas; the diagnosis is probable when there is no bacteriological and/or histological evidence of tuberculosis in the vertebral column, but active tuberculosis has

been proven biologically in other body compartments (e.g. positive urine culture, positive sputum or positive stomach contents after fasting) in combination with clinical or radiological manifestations (X-ray, CT scan, MRI) that correlate with spinal tuberculosis and a good reaction to chemotherapy.
Clinical symptoms vary widely, but usually comprise pain with an acute or gradual onset, whether or not in combination with neurological deficits, fever and elevated ESR. It is common for several vertebrae to be affected, including the vertebral discs. Paraspinal and/or epidural abscesses may be present.
The diagnosis should be considered in patients who belong to the risk groups for tuberculosis and have corresponding clinical and radiological symptoms with a good reaction to chemotherapy.

Successful treatment
Treatment is considered to be successful when the symptoms have subsided or the patient is complaint-free, the neurological deficits have improved or disappeared, there are no longer any clinical signs of abscesses or sinuses, the vertebral column is stable and the patient is able to resume full activities.
Radiological characteristics of successful treatment are: radiologically quiescent lesion, bony fusion with little or no deformity.
During (sufficiently long) follow-up, there must be no signs of progression of the kyphosis and no relapse of the tuberculosis [6,7]. It should be realised that the risk of kyphosis and paraplegia also depends on the surgical intervention at an earlier stage [6,8,9]. There is a risk of kyphotic deterioration until bony fusion has occurred, even when the clinical profile is stable [6]. In children in the growth phase, the risk of kyphotic deterioration is greater than in adults.

Failure
Failure means that the complaints deteriorate during treatment and changes have to be made to the chemotherapy regimen. Failure does not necessarily have to be proven bacteriologically and/or histologically.

Relapse
Relapse refers to the situation in which the complaints recur after the completion of successful treatment and on the basis of the complaints, radiodiagnostics, CT scan and MRI, whether or not in combination with biopsy, it is necessary to start a new course of chemotherapy.

6.4 RESULTS

Publications with a 6-month treatment regimen

There were 4 publications with a 6-month treatment regimen of isoniazid, rifampicin and pyrazinamide (6 HRZ) (Tables 1 and 2) [10,11,12,13]. In each publication, a number of patients also received 18 months treatment with isoniazid, rifampicin and ethambutol (18 HRE). When discussing the results, no distinction was made between the patients who had followed different treatment regimens. In the publications, there was a total of 82 adult patients (68% men, 32% women). There was no mention of whether HIV testing had been performed. Chemotherapy was dosed according to the WHO guidelines [10,11,12,14]. Nothing was mentioned about administering the chemotherapy under supervision. All the patients had undergone surgical intervention, usually within 3-4 weeks of starting chemotherapy. The interval between the onset of complaints and intervention varied from 1-12 months in 67% of the patients [12,13] and from 6-12 months in 33% [10,11].

The localisation of the affected vertebrae was as follows: cervical 23%; thoracic 21%; thoracolumbar 17%; lumbar 40% and lumbosacral 1/82; there were double localisations in 3 patients [12]. In 48% of the patients, 1 vertebra was affected; in 34% of the patients, 2 vertebrae were affected and in 18% of the patients, 3 vertebrae were affected.

Neurological deficits were present in 60% of the patients; 18% were known to have an abscess preoperatively and 6 had a fistula [13]. The diagnosis had not been proven bacteriologically in any of the patients, but the histological profile corresponded with tuberculosis in 55%.

After the completion of treatment, all the patients were declared cured. The neurological deficits had improved in 48/49 patients, but 8 patients had not recovered completely. In 3/6 patients the fistula persisted; surgical intervention was necessary in 2 of them [13]. The interval until radiological consolidation was 3-5 months in all the patients. All 82 patients completed postoperative follow-up (duration: 6-108 months). The relapse rate was 0%.

Publications with a > 6-month treatment regimen

There were 10 publications with a > 6-month treatment regimen of isoniazid, rifampicin and pyrazinamide (≥ 9 HRZ) (Tables 1 and 2) [4,5,15-22]. Three publications also reported on patients who had not received Z [16,21,22]. When presenting the results, no distinction had been made between the patients who had received Z and those who had not.

The results of these 10 studies were as follows.

In a total of 344 patients (56% men, 44% women), 274 had spinal tuberculosis. Only one publication mentioned HIV testing: none of the 7 patients tested were found to be HIV-positive [18]. Age distribution was as follows: 79% (216/274) were adults [4,16,17,20,21,22]; 2% (6/274) were < 12 years [15]; 19% (52/274) comprised adults and children [5,18,19]. In 4/10 publications, chemotherapy was dosed according to the WHO guidelines [14,4,17,18,20]. The actual treatment regimen was not mentioned in 2/10 [5,18]. Nothing was mentioned about administering the chemotherapy under supervision. A proportion of the patients had undergone surgical intervention (162/274) and a proportion had not (112/274). The interval between the onset of symptoms and chemotherapy and/or surgery varied from 2 weeks to 39 months; in 60% (165/274), the average duration was 6 months [4,5,20,16,22]. The time of surgery in relation with the start of chemotherapy was not always mentioned [4,5,15,16,18,19,21].

The localisation of the affected vertebrae was as follows: cervical 4% (7/199); cervicothoracic 1 patient (1/199); thoracic 51% (102/199); thoracolumbar 14% (27/199); lumbar 29% (57/199); lumbosacral in 1 patient; double localisations were present (thoracic and cervical) in 4 patients. In one publication on 75 patients with spondylitis, the precise localisations were not mentioned [22]. The number of affected vertebrae was not mentioned in 64 patients [5,16,18]. One vertebra was affected in 24% of the 210 patients, while more than one was affected in 76%. Neurological deficits were reported in 53% (144/274); paravertebral abscesses were present in 102 patients and epidural abscesses in 41 [4,5,15,17,18,21,22].

On the basis of the vertebral biopsy specimens, the diagnosis was confirmed bacteriologically in 62% (114/183), histologically in 72% (87/121) [19,21,22] and bacteriologically and/or histologically in 50/58 patients [4,17]. The diagnosis was confirmed bacteriologically and histologically from a biopsy specimen obtained from a different location in 26 and 3 patients, respectively [5,16,20,21]. Isoniazid resistance was present in 5/70 patients [4,22]. Failures occurred in 10/42 patients, whether or not they received Z and whether or not they received surgery [21]. Nussbaum stated that a treatment duration of < 6 months led to relapse. [5]. His patients received varying combinations of H,R,Z,E,S for at least 3 months. Progression of the symptoms was observed in a total of 13/29 patients 2 months to 14 years after diagnosis; no distinction was made between failures and relapse and it was not mentioned whether a new course of chemotherapy had been started. One patient died within one month of starting treatment. The average follow-up period in the 28 remaining patients was 7.4 years (1-20 years); one patient died, 17 patients had mild or no residual neurological deficits and 10 patients had severe residual neurological deficits [5].

TABLE 1. Publications with study populations of patients with spinal tuberculosis, whether or not in combination with surgery, treated for 6 months or ≥ 9 months with isoniazid (H), rifampicin (R) and pyrazinamide (Z), whether or not in combination with ethambutol (E) and/or streptomycin (S). The number preceding the treatment regimen is the treatment duration in months. The cure rate in the patients who started treatment and the relapse rate are shown. Postoperative follow-up period is given in months.

Author	Regimen	Surgery	No. of patients	Cure rate	Follow-up months mean (range)	Relapse
Loembe [10]	6HRZE 18 HRE	+ +	3 2	100% 100%	32 (8-96)	0/3 0/2
Loembe [11]	6HRZE 18 HRE	+ +	14 8	100% 100%	23.7 (8-96)	0/14 0/8
Loembe [12]	6HRZE 18HRE	+ +	18 8	100% 100%	6-108	0/18 0/8
Ghadouane [13]	6HRZS 12-18HRE	+ +	21 8	100% 100%	15.6 (8-60)	0/21 0/8
Rezai [4]	≥18HRZE 12HRZE RZE (H resistant)	- + +	9 9 2	100% 78%, 2 deaths tb-	12 (12-60)	0/18
Nussbaum [5]	≥3 months HRZES combinations	+ 25 - 4	29	1 death < 1 months treatment	7.4 yrs (1-20)	13 patients readmitted 2 months -14 year after initial diagnosis
Journeau [15]	3HRZE/ 2HRE/7HR	+	6	100%	12-168	0/6

When the 29 patients who had received ≥ 3 HRZSE in the study by Nussbaum were omitted from the analyses, the results were as follows: 3% of the patients died before completing treatment (8/245); 7 out of these 8 patients died of other causes [4,17,21,22]. A total of 93% were cured (227/245). After the completion of treatment, 9% had residual neurological deficits [4,15,19,21]. Bony fusion had occurred in all the cases (16/16) [15,20], in 36/57 within 3 months and in 56/57 within 6 months [17,19].

Author	Regimen	Surgery	No. of patients	Cure rate	Follow-up months mean (range)	Relapse
Peronne [16]	3HRZE/HR 3HRE/HR (9-18HR median 12HR)	+1 -22 -8	23 8	100% 100%	>12	0/22 (9/31 lost)
Yilmaz [17]	2HRZS/ 7HR	+	38	97% 1 death tb-	29 (24-76)	0/37
Vohra [18]	>9HRZE	+19 -6	4/25 spinal tbc	100%	41 (13-96)	0/4 (0/25)
Louw [19]	12HRZE	+	19	100%	25.5 (6-47)	0/19
Güven [20]	HRZ mean 11 months	+	10	100%	24.2 (17-36)	0/10
Colmenero [21]	2HR(Z) (E)/7-10HR	+32 -10	42	69% 10 failures, 3 deaths tb-	6 months, after completion of treatment	3/29
Pertuiset [22]	3HRZE/& 3HRE/& mean 14.7 ± 3.4 months	+20 -55	52 21	97% 2 deaths, 1tb+ and 1 tb-	12.3 ± 21	1/73

Follow-up duration after surgical intervention varied from 6-168 months. Relapse occurred in 2% (4/218). It is unclear whether they had received pyrazinamide and/or surgery [21,22]. Colmenero [21] reported relapse in 3 patients (3/29=10%); follow-up duration was 6 months after the completion of treatment. Pertuiset reported relapse in 1 patient (1/73=1%); follow-up duration was 12.3 months $\pm$ 21 months. The patient was treated for 9 months [22].

TABLE 2. Spinal tuberculosis patient characteristics and treatment regimens with isoniazid (H), rifampicin (R) and pyrazinamide (Z), whether or not in combination with ethambutol (E) and/or streptomycin (S) [4,5,10-22]

	6HRZ	≥9HRZ
No. of patients	56/82	274/344
Age		
Adults	82	79% (216/274)
Children < 12 yrs		2% (6/274)
Adults and children		19% (52/274)
Male:female	68%:32% (56:26, n=82)	56%:44% (192:152, n=344)
Delay		
1-12 months	67% (55/82)	
6-12 months	33% (27/82)	
mean 6 months		60% (165/274)
Localisation of affected vertebra		
Cervical	23% (19/82)	4% (7/199)
Cervico-thoracic		1 patient
Thoracic	21% (17/82)	51% (102/199)
Thoracic-lumbar	17% (14/82)	14% (27/199)
Lumbar	40% (32/82)	29% (57/199)
Lumbosacral	1 patient	1 patient 4 patients cervical and thoracic
unknown		75
No. of affected vertebrae		
1 vertebra	48% (39/820)	24% (51/210)
> 1		76% (159/210)
2 vertebrae	34% (28/82)	
3 vertebrae	18% (15/82)	
unknown		64 patients (n=274)
Neurological deficits	60% (49/82)	53% (144/274)
Abscess paravertebral/epidural	18% (15/82)	62% (143/229)
fistula	6 patients	

	6HRZ	≥9HRZ
No. of patients	56/82	274/344
Diagnosis tuberculosis vertebra		
Bacteriological	0/82	62% (114/183)
Histological	55% (45/82)	72% (87/121)
Bacteriological and/or histological		50 patients (n=58)
Tuberculosis elsewhere	10% (8/82)	27% (81/295)
Treatment		
Surgery	100% (82/82)	61% (181/295)
chemotherapeutic		
HRZ		10 patients
HRZE	35 patients	122
HRZS	21	38
HRE	26	29
RZE		2
HR(Z)(E)		42
Different combinations of HRZES		29
No. of deaths	0%	3% (8/245)
Reason tbc		1
Radiological consolidation after 3-6 months	100% (82/82)	99% (72/73)
Treatment completed as planned	100% (82/82)	93% (227/245)
Cure rate No. of patients treatment completed	100%	100%
Follow-up in months after surgery, range	6-108	6-168
Follow-up completed as planned	100% (82/82)	96% (218/227)
Relapse	0% (0/56) 95% C.I. 0.0-6.4	2% (4/218) 95% C.I. 0.6-5.0

6.5 DISCUSSION

Very few reports have been published on the results of 6 months treatment with HRZ in spinal tuberculosis patients [10-13]. This might be because surgical intervention forms an essential part of treatment and the literature has focused more attention on this aspect [4-9]. It is unclear whether there is overlap in the

patients described by Loembe [11,12]. In most cases, the follow-up duration after surgical intervention is mentioned, not the duration after the completion of chemotherapy. It was not possible to establish how many patients had completed a follow-up of ≥ 12 months after chemotherapy. All the patients who received 6 months chemotherapy had also received surgery. Relapse only occurred in the group that had been treated for longer than 6 months. It was unclear whether the patients with relapse had received pyrazinamide, whether they had undergone surgery or had an indication for surgery. On the other hand, the relapse rate of 2% (95% C.I. 0.6-5.0) is so low that this does not justify treatment for a period longer than 6 months, especially in view of the good result in the group of patients who were treated during 6 months. HRZ for 6 months led to a relapse rate of 0% (95% C.I. 0.0-6.4). In as far as data are available, the penetration of chemotherapy in spinal tuberculosis lesions is good [23]. Surgery accelerates the resolution of sinuses and abscesses and reduces the risk of their development [24]. In the case of progression or persistence of abscesses and/or neurological deficits during chemotherapy, surgical intervention should be considered [4,25]. Not only the risk of relapse, but also the risk of kyphotic deterioration and late neurological complications justify a long follow-up period. [6,9].

Another explanation for the small number of studies might be that even after treatment with 6 HR and a follow-up of ≥ 3 years, the relapse rate was low [26,27].

The question arises as to why patients are treated for longer than 6 months. A possible explanation is that there is doubt about the parameters for declaring a patient "cured". There might be doubt about the radiological quiescence of the affected vertebra. The clinical profile can be stable even when bony fusion is incomplete [6].

The BMRC studies have shown that further improvement of the radiological profile occurs even after the chemotherapy has stopped, but the kyphosis can still deteriorate [26,28]. The risk of kyphotic deterioration is greatest (i) in children of younger than 15 years, in whom ≥ 3 thoracic vertebrae are affected, (ii) in patients in whom the disease spreads from 1-2 vertebrae to 3-4 vertebrae and (iii) in patients with an initial angle of > 30° [9]. Chemotherapy in patients with spinal tuberculosis is obligatory, but careful monitoring is necessary in order to perform surgery as soon as there is an indication [4,6,9,24]. It may be possible to administer fewer chemotherapeutics to patients with spinal tuberculosis, because the bacterial load is much lower than that in lung tuberculosis [26,29]. The risk of primary resistance developing through spontaneous mutation is lower in the case of low bacterial concentration. However, tuberculosis can be

active in several organs simultaneously, which necessitates an intensive phase with 3 chemotherapeutics (HRZ) for *M. tuberculosis* with normal sensitivity. Moreover, in contrast with the period in which the BMRC studies were performed, there is a greater risk nowadays of becoming infected with a primary resistant strain. An intensive phase with 4 chemotherapeutics (HRZE) is necessary if the resistance pattern is unknown.
It is very unlikely that this literature analysis included patients known to be HIV-positive. The clinical profile and chemotherapeutic regimen would be the same as that in HIV-negative patients [30].

6.6 CONCLUSIONS AND RECOMMENDATIONS

On the basis of this literature analysis, it can be concluded that the treatment for spinal tuberculosis does not differ from that for lung tuberculosis. The treatment regimen comprised 2HRZ/4HR for *M. tuberculosis* with normal sensitivity. If there are indications of resistance, 4 chemotherapeutics (HRZE) should be administered while awaiting the result of the resistance pattern. If the resistance pattern remains unknown, then ethambutol should be continued throughout treatment (2HRZE/4HRE). The necessity for surgical intervention should be considered per individual [3]. A separate study on the effectiveness of surgical intervention in combination with chemotherapeutics is planned.

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Chapter 7

CHEMOTHERAPEUTIC TREATMENT FOR RENAL AND URINARY TRACT TUBERCULOSIS

7.1 SUMMARY

Aim: to evaluate whether 6 months treatment for patients with renal tuberculosis prevents relapse as effectively as >6 months treatment.
Method: literature study. Medline search and relevant publications in the period 1978 to November 2000.
Inclusion criteria: studies on patients whose chief diagnosis was genitourinary tuberculosis, in whom the diagnosis was confirmed bacteriologically and/or histologically or was probable on the grounds of clinical and/or radiological findings and who responded well to chemotherapeutic treatment. The treatment regimen had to include isoniazid, rifampicin and pyrazinamide (whether or not in combination with surgery). Follow-up after the completion of treatment had to be at least 12 months.
Exclusion criteria: patients with tuberculosis relapse who had been treated adequately with chemotherapy in the past and studies that only described genital tuberculosis.
Outcome parameter: patients with tuberculosis relapse.
Results: five publications were found with a total of 334 adult patients who had been treated with isoniazid, rifampicin and pyrazinamide. Fifty-four patients (16%) had been treated for four months; 187 patients (56%) had been treated for six months and 93 patients (28%) had been treated for eight to eleven months. Follow-up after concluding treatment varied from six to 120 months and had been completed by more than 90% of the 334 patients. There was one relapse in the group who had been treated for six months (0.6%, 95% CI: 0.0-3.2), but no relapses in the group who had been treated for >6 months (0%; 95% CI: 0.0-4.5). It can be concluded that six months treatment for patients with renal tuberculosis caused by *M. tuberculosis* with normal sensitivity is sufficient.

7.2 INTRODUCTION

Renal tuberculosis is a late complication of tuberculosis. In general, it can still occur 20 to 50 years after primary infection. Renal tuberculosis is registered under tuberculosis of the genitourinary tract, together with tuberculosis of the bladder, ureter, epididymis, other male genital organs, ovary, fallopian tube, cervix and endometrium. In the period 1993 to and including 1999, a total of 11059 patients were registered with tuberculosis in the Netherlands, including 6205 (56%) non-Dutch patients (data from the Netherlands Tuberculosis Register (NTR), Royal Netherlands Tuberculosis Association (KNCV). In 267 patients (2.4%) a diagnosis of genitourinary tuberculosis was made; 103 of them

had renal tuberculosis (63 Dutch and 40 non-Dutch patients). The male:female ratio among the Dutch patients and non-Dutch patients was about 1:1 for genitourinary tuberculosis and renal tuberculosis. The age peak among the Dutch patients lay between 45 and 84 years; in the non-Dutch patients, the peak lay between 25 and 44 years. In the period 1993 to and including 1999, the diagnosis of renal tuberculosis was made in only one child (non-Dutch nationality; age category 5 to 14 years). Genitourinary tuberculosis and renal tuberculosis in combination with active tuberculosis in other organs was present in 33% (88/267) and 42% (43/103) of the patients, respectively. Genitourinary tuberculosis and renal tuberculosis in combination with bacteriologically proven pulmonary tuberculosis was present in 17% (45/267) and 14% (14/103) of the patients, respectively. In 15% (40/267) of the patients with genitourinary tuberculosis, the diagnosis of tuberculosis had also been made in the past (NTR). In the Netherlands, the diagnosis of renal tuberculosis was bacteriologically confirmed in 76% to 80% of the patients. Chemotherapeutic treatment was administered to 38% of the Dutch renal tuberculosis patients and to 43% of the non-Dutch renal tuberculosis patients for a duration of six to nine months and to the same percentages for ten to twelve months (NTR).

The literature showed that the most common complaints in genitourinary tuberculosis are unexplained micturition disorders, haematuria and sterile pyuria. These complaints were present in 50%, 21-30% and 15% of the patients, respectively [1,2,3]. Bacterial super-infection can occur: E. coli infection was found in 30% of the patients [2]. The percentage of patients with renal calcification varied from 13-52% [1,3]. At the time that genitourinary tuberculosis was diagnosed, only 2% (2/87) and 6.3% (10/160) of the patients also had active pulmonary tuberculosis [1,3]. The suspicion of tuberculosis in the past varied from 30%-49.3% [2,3,4].

The clinical symptoms of this rare disorder are vague; physicians are unlikely to consider tuberculosis and the diagnosis is often made after severe renal damage has occurred. This means that besides chemotherapeutic treatment, surgical intervention might be necessary to resolve the excretory impairment or to try to improve renal function.

We determined whether on the basis of the literature, judgement could be made about the efficacy of six months treatment with at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) for renal tuberculosis.

7.3 METHOD AND DEFINITIONS

Using Medline, the literature was searched for relevant publications in the period 1978 to 2000. Keywords were genitourinary tuberculosis, drug therapy, antitubercular agents. No restrictions were made regarding language.
Inclusion criteria: populations of patients with the chief diagnosis of genitourinary tuberculosis whose diagnosis was confirmed bacteriologically and/or histologically or was considered probable on the basis of clinical and/or radiological findings and who responded well to chemotherapeutic treatment. The treatment regimen, whether or not in combination with surgical intervention, had to include at least isoniazid (H) rifampicin (R) and pyrazinamide (Z), possibly in combination with ethambutol and/or streptomycin. Follow-up after the completion of treatment had to be at least 12 months.
Exclusion criteria: patients with tuberculosis relapse who had been treated adequately in the past with chemotherapy and studies which only described patients with genital tuberculosis.
Outcome parameter was the number of patients with tuberculosis relapse.
Definitions: Treatment was considered to have failed if after 12 weeks of treatment, 2 or more positive cultures were found within an interval of at least 1 month. Treatment was considered to be successful if the patient was complaint-free and the urine did not contain *M. tuberculosis*. Genitourinary tuberculosis relapse was defined as symptom recurrence after the completion of treatment and the presence of *M. tuberculosis* in the urine.

7.4 RESULTS

A total of five publications were found, containing 1586 adult patients with genitourinary tuberculosis. It was not possible to distinguish patients with renal tuberculosis in combination with genital tuberculosis from patients with renal tuberculosis alone on the basis of the data presented in the publications. There were two prospective studies [5,6] and three retrospective studies [3,4,7]. In 21% (334/1580), treatment had comprised at least isoniazid (H), rifampicin (R) and pyrazinamide (Z) [3-7]. Treatment regimens without rifampicin or pyrazinamide were not included in the analyses [3,4,7]. The study by Benchekroun et al. which described 40 patients who had received isoniazid and rifampicin during six months with pyrazinamide during the first two months (2HRZ/4HR) and 16 patients who had received isoniazid, rifampicin, pyrazinamide and streptomycin for the first two months and isoniazid and rifampicin during the next

TABLE 1. Treatment for genitourinary tuberculosis in the literature with treatment regimens comprising at least isoniazid (H), rifampicin (R) and pyrazinamide (Z)

Author period	Gow [4] 1961-1981	Wong [5] 1975-1983	Škutil [6] 1979-1980	Bennani [7] 1976-1993	Poulios [3] 1976-1986	Total No. of patients (pts)
No. of pts	1117	110	113	86	160	1586
Age (yrs)	7-8 (20-50)	19-79	23-72	14-82 (mean 34)	18-82 (mean 50)	
Male: female	2:1	2:1	2:1	1.4:1	2:1	
Diagnosis bacterio-logically and/or histolo-gically confirmed	100%	100%	100%	?	57%	
Surgery: Radical Recon-structive	 58% 13%	 43% 32%	 22% 1%	 36% 20%	 39% 4%	
Drug therapy alone	29%	25%	77%	44%	57%	
Pts with HRZ (+/- surgery) 4 months 6 months 8-11 months	74 48 26	110 27 83	113 113	31 21 10	6 6 	334 54 187 93

seven months (2HRZS/7HR), was not included in the analyses because no follow-up data were presented [2]. The diagnosis had been confirmed bacteriologically or histologically in 1431 patients [3-6]. *M. tuberculosis* had normal sensitivity, in as far as this detail was mentioned [4]. Chemotherapy dosage had been administered according to the World Health Organisation (WHO) guidelines, with the exception of the low dosage of pyrazinamide (1000 mg/day) administered by Škutil et al. [6]. Poulios and Malovrounas did not mention anything about dosage [3]. Gow and Barbosa reported that the dosage had been adjusted according to renal function and that a creatinine clearance of 100 ml/minute was considered to be normal, but they did not mention the specific chemotherapeutic agent. If clearance fell below this level, the dosage was adjusted in terms of percentage [4]. The medication was administered under full supervision by

TABLE 2. Studies in the literature that mention relapse rates after treatment for genitourinary tuberculosis with treatment regimens comprising at least isoniazid (H), rifampicin (R) and pyrazinamide (Z), possibly in combination with ethambutol (E) and streptomycin (S). The figure in front of the letter is the number of months that the agent was administered. Medication was administered daily. When the medication was administered intermittently (a number of times per week), the number of times is given in subscript after the agent

Author	Regimen	No. of patients who started treatment	No. of patients, who discontinued treatment (because of side-effects)	Follow-up duration in months after completing treatment	No. of patients who completed follow-up / started treatment (no. of patients with relapse)
Gow [4]	2HRZ/ $2H_3R_3$ 2HRZS/ $2H_3R_3$	48	1(1)	>12	130/135 (0)
	2HRZ/4RZ	26			
	3HRE/6HR	4			
	3HRE 3HRE/3HR	57			
Wong [5]	2HRZE/ $4H_3R_3Z_3$ no surgery	27	5(3)	mean 35 months	22/27 (0)
	2HRZE before and after surgery/			mean 49 (6-82)	
	after ablative surgery $4H_3R_3Z_3$ and	48	6(6)		42/48 (0)
	after reconstructive surgery $7H_3R_3Z_3$	35	7(5)		28/35 (0)
Škutil [6]	2HRZ/4HR	113	7(7)	45-63	106/113 (1)
Bennani [7]	2HRZ/4HR	21		12-120	31/31 (0)
	2HRZS/ 7HR	10			
Poulios [3]	4HRZ	6		18	6/6 (0)

Škutil et al. during the first two months [6]. The percentage of patients who had to discontinue treatment because of side-effects varied from 2-14% (Table 2). Ethambutol had to be stopped in 8% (5/61) [1]. There were no treatment failures [3-7]. After two months of treatment, *M. tuberculosis* could no longer be demonstrated in the urine [4,6]. After one to two months of chemotherapeutic treatment, Wong et al. demonstrated *M. tuberculosis* in 17.9% of the patients who had undergone ablative surgery. In some of the patients who underwent reconstructive surgery, the urine was still positive one month after surgery, i.e. three months after the start of chemotherapeutic treatment [5]. In general, surgery was performed four to six weeks after the start of chemotherapeutic treatment [4,5].
More than 90% (304/334) of the patients who had received HRZ completed the follow-up period, which varied from 6 to 120 months after concluding chemotherapeutic treatment (Table 2). Only one bacteriologically confirmed relapse occurred six months after the completion of six months treatment (1/170=0.6%; 95% C.I. 0.0-3.2). The patient had *M. tuberculosis* with normal sensitivity [6]. In the groups that were treated for four months and for 8-11 months, the relapse rates were 0/54=0% (95% C.I. 0.0-6.6) and 0/80=0% (95% C.I. 0.0-4.5), respectively.

7.5 DISCUSSION

On the basis of the perhaps limited literature data, we can conclude that in general, a treatment duration of six months was sufficient for patients with renal and urinary tract tuberculosis. In such cases, adequate surgical intervention is necessary. The low number of publications on the treatment of urinogenital tuberculosis since the introduction of pyrazinamide can probably be explained by the good results of even four months treatment [4,9]. As explanations for the effectiveness of four to six month treatment regimens, the following arguments have been put forward [1,10]: (1) the number of *M.tuberculosis* in the kidneys is probably low in comparison with the bacterial load in patients with pulmonary tuberculosis; (2) owing to the rich blood supply, concentrations of isoniazid, rifampicin and pyrazinamide in the kidneys are much higher than the minimum inhibitory concentrations. In a non-functional kidney, chemotherapeutics will not be able to reach the focus of infection and renal resection might be considered. Only Wong et al. based the duration of chemotherapeutic treatment on the degree of organ damage and the type of surgical intervention (Table 2) [5]. The clinical symptoms of this rare disorder are vague, which means that many

patients present with severe and very advanced disease. The studies included in our analyses did not mention the severity of renal dysfunction or how often this required treatment adjustment. It was not possible to evaluate the relation between the dosage of ethambutol, pyrazinamide, the severity of renal dysfunction and the occurrence of side-effects [4,5].

The dosage of ethambutol and pyrazinamide must be adjusted in the case of impaired renal function [8,11-13]. Ethambutol is administered as the fourth chemotherapeutic agent in the intensive phase, while awaiting the resistance pattern of the *M. tuberculosis*. The studies included in the analyses were performed in the period that resistance to *M. tuberculosis* seldom occurred. Ethambutol had been administered to 33% (110/334) of the patients. A total of 13% (14/110) of the patients suffered from side-effects, but no mention was made of the specific chemotherapeutic agent(s) [5]. Close ophthalmological monitoring has been recommended in patients with renal dysfunction while they are receiving ethambutol [14]. Although it is possible to determine serum chemotherapeutic levels in the Netherlands, there is insufficient experience to interpret the data adequately. A rapid test to determine rifampicin resistance might reduce the need to include ethambutol at the start of treatment. *M. tuberculosis* can easily be detected in the urine. In experienced hands, Ziehl-Neelsen staining of morning urine can produce reliable results [15]. However, it is important to take into consideration that the antibiotics used for common bacterial super-infections, such as aminoglycosides, rifampicin and ciproxin, must be stopped for the Löwenstein culture to be reliable.

The percentage of patients in the studies included in our analyses who received chemotherapeutic treatment alone varied from 25% to 77%. In patients with an abnormal IVP, the investigation was repeated every three months, combined with isotope renography, in order to detect the earliest possible indications for surgical intervention. A proportion of the cases of stricture were caused by oedema, which responded well to chemotherapeutic treatment. Corticosteroids are only worthwhile in the acute phase and are not the medication of first choice [4]. There are two types of surgery: radical and reconstructive. Radical operations included (partial) nephrectomy, cavernectomy and epididymectomy. Reconstructive operations included resolution of the ureter-urethral stricture and bladder enlargement. After the completion of chemotherapeutic treatment, it has been recommended to send morning urine for Löwenstein culture on three separate occasions and to repeat this procedure every three months up to a total follow-up of 12 months after the completion of treatment. The IVP should be repeated after the completion of treatment and at follow-up visits if the previous investigation showed abnormalities [4]. Patients with large

renal calcifications should be follow-up once a year, in order to monitor indications for surgery [4].

7.6 CONCLUSION

On the basis of this literature study, it can be concluded that treatment for renal and urinary tract tuberculosis need not differ from that for pulmonary tuberculosis. Treatment should comprise 2HRZ/4HR in patients who have *M. tuberculosis* with normal sensitivity. On the suspicion of resistance, four chemotherapeutic agents must be administered while awaiting the resistance pattern (HRZE).
Surgical intervention may be necessary in combination with chemotherapeutic treatment.

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Chapter 8

PYRAZINAMIDE USE AS A METHOD TO ESTIMATE UNDER-REPORTING OF TUBERCULOSIS

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8.1 SUMMARY

Objective: to develop a method of validating the notification of active tuberculosis by physicians in the Netherlands.
Method: the chemotherapeutic agent pyrazinamide was used as a "marker" for the occurrence of tuberculosis. On the basis of Defined Daily Doses (DDD) of pyrazinamide dispensed to out-patients, an estimate was made of the number of patients with tuberculosis in the Netherlands in the period 1994-1998. DDD is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. Usually it is based on the average dosage per day for the main indication in adults with normal organ function. The Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ) provided the DDD data. Based on the notification of tuberculosis patients to the Netherlands Tuberculosis Register (NTR) we calculated how much pyrazinamide (measured in DDDs) these patients would have used depending on their body weight.
Results: the number of DDDs prescribed according to the GIP pharmacy records differed by only 8% from the number of DDDs calculated on the basis of notification to the NTR; 6889 patients should have been registered instead of 6349.
Conclusion: the close correlation between the use of pyrazinamide measured by means of the GIP and NTR provides strong evidence that in the Netherlands, tuberculosis is reported in conformity with the guidelines for notifiable diseases. The method was simple to apply and may deserve following-up in other countries.

8.2 INTRODUCTION

In the Netherlands, tuberculosis is a notifiable disease [1,2]. A case is notifiable when *M.tuberculosis* complex is present in patient material, or when a physician makes the diagnosis of tuberculosis on the basis of symptoms, clinical and radiological signs and decides to start curative treatment with anti-tuberculosis drugs. A medical microbiology laboratory or a treating physician is obliged by law to notify the Municipal Health Service in the region where the patient lives. After receiving notification, the staff at the Municipal Health Service fill in registration forms for the Inspectie voor de Gezondheidszorg (IGZ) and for the Royal Netherlands Tuberculosis Association (KNCV). The KNCV keeps the Netherlands Tuberculosis Register (NTR). The register holds anonymous

detailed information on every tuberculosis patient reported to the Municipal Health Service. After notification, the staff at the Municipal Health Service record the data for epidemiological purposes and also start source and/or contact tracing. In addition, the patient is monitored by a TB nurse from the Municipal Health Service to prevent resistance induction from treatment errors.
The number of patients with tuberculosis in the Netherlands is closely associated with the influx of persons from countries where tuberculosis is highly endemic. More of these persons have extra-pulmonary forms of tuberculosis than Dutch tuberculosis patients. In the case of non-infectious forms of tuberculosis, there is a greater risk of under-reporting by the treating physician, because there is no need for contact tracing. In addition, if the diagnosis has not been confirmed bacteriologically, the laboratory cannot notify the Municipal Health Service.
To estimate under-reporting, this study compared the number of days of pyrazinamide use registered by the NTR, to the number of days of pyrazinamide use measured on the basis of data from the Dutch Drug Information Project (GIP) of the Health Insurance Board (CVZ) in the period 1994-1998.
Pyrazinamide was chosen as a "marker" for tuberculosis, because this medication is used solely for the treatment of tuberculosis and moreover, it usually forms part of the treatment [3-5].

8.3 MATERIAL AND METHODS

The use of pyrazinamide derived from notification to the NTR was compared to the quantity of pyrazinamide supplied on prescription by Dutch pharmacies. Since 1993, the NTR has been computer automated. Therefore, we chose the period 1994 to and including 1998 for this study.
In the NTR the following patients data are included: age, number of days that the patient was hospitalized and number of days that the patient took medication, including isoniazid, rifampin, pyrazinamide or alternatively other antituberculosis drugs.
The standard treatment of tuberculosis is a six-month regimen consisting of daily isoniazid, rifampin, pyrazinamide and ethambutol given for two months followed by isoniazid and rifampin for four months. Pyrazinamide is always given for at least 2 months, but administration of pyrazinamide is continued after this period if no sputum conversion has occurred. Pyrazinamide treatment can also be continued after 2 months if the final typing and the resistance pattern have not been determined yet, pending the results of the cultures.

In the Netherlands the advised dosage pyrazinamide is 30 mg/kg body weight per day, with a maximum of 2 grams per day for 2 months.
Data on the out-patient use of pyrazinamide were made available by the GIP over this period. Pyrazinamide use was calculated as the number of DDDs per year. Defined Daily Doses (DDD) is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. Usually it is based on the average dosage per day for the main indication in adults with normal organ function [6-9]. On the basis of population data from the GIP and the total Dutch population, an estimate was made of the number of patients with tuberculosis in the whole of the Netherlands.
According to the World Health Organisation (WHO), the DDD of pyrazinamide is 1500 mg per day [5]. The actual dosage prescribed (Prescribed Daily Dose = PDD) may deviate, for example on the basis of the patient's weight. Therefore, a correction factor was determined.
Distinction was made between patients < 16 years and $\geq$ 16 years, because children < 16 years usually weigh $\leq$ 50 kg. That means that for children < 16 year 1 DDD = 1500 mg pyrazinamide per day is prescribed and that for patients $\geq$ 16 years 2000 mg pyrazinamide per day is prescribed. In the Netherlands tuberculosis patients > 16 years usually weigh more than 60 kg. A survey held by the first author among 36 tuberculosis physicians at Municipal Health Services revealed that a dose of 2 gram of pyrazinamide is prescribed for the majority of patients. A survey of tuberculosis patients' medical files in the Municipal Health Service Nijmegen showed that in the period 1994-1998, 60% (100/163) of the patients received prescriptions for 2 gram of pyrazinamide. It was assumed that in at least 60% of the adult patients, the PDD = 1.3333 DDD and that for 40% of the adults and for children younger than 16 years the PDD = 1 DDD.
In the NTR, selection was made of days of pyrazinamide use, excluding the number of days that the patient was hospitalized.

8.4 RESULTS

The following data were extracted from the NTR: in the period 1994-1998, 6349 patients were registered with tuberculosis in the Netherlands; 58% were not of Dutch origin. Pulmonary tuberculosis was present in 60%, extrapulmonary tuberculosis in 33% and a combination of pulmonary and extrapulmonary tuberculosis in 7%. Diagnosis of the pulmonary form of tuberculosis was confirmed bacteriologically in 77% of the patients using Löwenstein Jensen medium for culture; Ziehl-Neelsen stain was positive in 21%.

TABLE 1. Number of tuberculosis patients treated with anti-tuberculosis drugs including pyrazinamide (Z) with duration in days according to 1994-1998 Netherlands Tuberculosis Register (NTR) data and calculated Defined Daily Doses (DDD), compared to data on Z use of the Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ)

	Year of diagnosis					Total
	1994	1995	1996	1997	1998	
No. of tuberculosis patients	1396	1258	1404	1256	1035	6349
Age and days of Z use						
< 16 years	8070	8805	8905	8908	6162	40850
>= 16 years	141497	120345	121888	111784	86706	582220
Treatment duration of Z in days (all ages)	149567	129150	130793	120692	92868	623070
Percentage of completed Part 3 of the NTR form	96.2	92.5	97.6	96.5	86.5	93.9
No.of days of Z after correction for 100% Part 3 completion						663546
Corrected DDD based on body weight						
< 16 year x 1 DDD	8070	8805	8905	8908	6162	40850
>= 16 year x 1.3333DDD (60%)	113195	96274	97508	89425	69363	465765
>= 16 year x 1 DDD (40%)	56599	48138	48755	44714	34682	232888
Total DDD corrected for body weight	177864	153217	155168	143047	110207	739503
DDD corrected for body weight and after correction for 100% Part 3 (NTR) completion	184889	165640	158984	148235	127407	787543
Total No. of DDDs pyrazinamide (GIP)	200837 108.6%	191496 115.6%	187579 118.0%	140136 94.5%	134240 105.4%	854288 108.4%
No. of prescriptions	4789	4521	4484	3520	3394	20708
DDD per prescription	41.9	42.4	41.8	39.8	39.6	41.3

Extra-pulmonary forms were confirmed bacteriologically in 74%, while ZN was positive in 2%. A combination of pulmonary and extra-pulmonary forms was confirmed bacteriologically in 82%, while ZN was positive in 16%.
The number of days of pyrazinamide use is reported in Part 3 of the NTR form. Part 3 had been filled in for 93.3% of the cases: the 6349 tuberculosis patients had been treated with pyrazinamide (Z) for 623070 days (Table 1). Correction for 100% completion of Part 3 led to 663546 days of Z in the 6349 patients.
According to the GIP, 854288 DDDs had been supplied (Table 1). According to Dutch regulations, drugs for chronic diseases, like pyrazinamide, can only be prescribed for a maximum period of one month. By dividing the number of DDDs by the number of prescriptions, we found that on average, the patients had received a one month supply of Z per prescription and that the PDD was equal to 1.3333 DDD (Table 1). This means that according to the GIP, Z was dispensed for 640732 days (854288÷1.3333). The difference between the number of days of Z use according to the NTR and number of days according to the GIP was 4%.
If we assume that all the patients aged < 16 years and 40% of the patients ≥ 16 years used 1 DDD Z per day, and that 60% of the patients aged ≥ 16 years used 1.3333 DDD Z per day, then on the basis of the NTR data, the 6349 patients used 739503 DDDs of Z. After correction for 100% completion of Part 3, this means 787543 DDDs. In this case, the difference between the number of days of Z use according to the NTR and the number of days according to the GIP (854288 DDDs) was 8%. According to the NTR, a patient used an average of 124 DDDs (787543÷6349), while according to the GIP, 854288 DDDs were dispensed (Table 1). This means that notification should have been received by the NTR for 6889 patients (854288 DDDs ÷ 124 DDDs per patient). Thus, under-reporting was 8.5%.
By dividing the number of days of Z use according to the NTR by the number of tuberculosis patients, we found that each tuberculosis patient used Z for an average of 105 days (663546 days of Z ÷ 6349 tuberculosis patients).

8.5 DISCUSSION

Our study showed that pyrazinamide as a "marker" for tuberculosis made a valid estimate of the number of patients with tuberculosis in the Netherlands [6-9]. In this way, it was possible to investigate under-reporting of a notifiable disease by Dutch physicians. Choosing a period of several years automatically corrected for the patients who were diagnosed in the last few days of

one year and actually started treatment on anti-tuberculosis drugs in the following year. In addition, the wide time frame covered any doses of pyrazinamide that might have been obtained but not used, and later given to patients without health insurance by tuberculosis physicians from Municipal Health Services.
Our calculations showed that the patients had used pyrazinamide for an average of 3.5 months, instead of the minimum of 2 months advised by protocol. The NTR data from 1998 show that 53% (582/1090) of the patients used pyrazinamide for 2 months, 19% (208/1090) for 3 months and 20% (218/1090) for a period longer than 3 months. No information on the use of pyrazinamide is available from 19% (251/1341) of the patients.

A possible explanation for the longer treatment period is that the resistance pattern would still have been unknown at 2 months, so pyrazinamide was continued while awaiting the result of the resistance pattern.
Although only a very small proportion of patients take their medication under the supervision of a TB nurse in the Netherlands, so-called Direct Observed Therapy (DOT), treatment compliance is monitored very thoroughly. A TB nurse visits the patients regularly at home, checks the medication prescribed by the doctor and checks that the correct medication has been dispensed by the pharmacy. The same TB nurse fills in the number of days of pyrazinamide use on the registration forms.
It is possible that the GIP gave an under-estimation of pyrazinamide use among asylum seekers in the Netherlands, because these persons fall under the care of the agency for the reception of asylum seekers (COA). In the period 1994-1998, asylum seekers spent an average of 15 months under the care of the COA [10]. It is not clear whether asylum seekers have an increased tuberculosis risk compared to the other tuberculosis risk groups. In the period 1994-1998, 21% (1335/6349) of the tuberculosis patients were asylum seekers; 54% (723/1335) of them had been in the Netherlands for less than 2 years (NTR/KNCV).
Underestimation of pyrazinamide use in relation with discharge from hospital and the patients taking a supply with them was considered to be negligible, because hospitals in the Netherlands are budgeted. Patients probably only received sufficient medication for the first day. In the period 1994-1998, it was not yet customary to use pyrazinamide as a prophylactic. Pyrazinamide use on the basis of the GIP data may have led to overestimation of the number of patients with active tuberculosis, because treatment is also started on the *suspicion* of tuberculosis, although later, culture might show that the tuberculosis is caused by non-tuberculous mycobacteria.

8.6 CONCLUSION AND RECOMMENDATIONS

On the basis of the number of days of pyrazinamide use by patients with active tuberculosis as reported on Part 3 of the NTR forms in the period 1994-1998 and on the basis of data from the GIP of the CVZ on the number of DDD of pyrazinamide supplied to out-patients, it can be concluded that in the Netherlands, there is only a small amount of under-reporting of the number of patients with tuberculosis. In addition, it can be concluded that TB nurses generally monitor and record treatment accurately. From an epidemiological point of view, employing data on pyrazinamide use proved to be a good and simple method of validating notification of tuberculosis patients. The method may also be suitable for validation purposes in other countries.

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Chapter 9

9.A
RISK OF TUBERCULOSIS AT TEMPORARY SHELTERS FOR ASPIRANT ASYLUM SEEKERS

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Risico van tuberculose bij inadequate opvang van aspirant-asielzoekers.
Ned Tijdschr Geneeskd 1994;138:2496-2500

9A.1 ABSTRACT

Objective: descriptive study on tuberculosis screening at a temporary shelter for aspirant asylum seekers and contact tracing around infected patients.
Design: descriptive.
Setting: Municipal Health Service Nijmegen.
Method: 3 River Rhine cruisers (with inadequate ventilation facilities) served as a temporary shelter for aspirant asylum seekers in the winter months from November 1993 to April 1994. Residents were screened for tuberculosis by means of chest X-ray after an average of 10 days. In the case of radiological abnormalities, sputum was tested (Ziehl-Neelsen staining and Löwenstein culture). Mantoux testing was performed on the shelter staff.
Results: 4 out of the 834 screened persons had open tuberculosis. Contact tracing yielded 3 infected cases in the first ring (n=5) and 11 infected cases and two other patients with infiltrative and cavernous lung tuberculosis in the second ring (n=215); 14 of these cases were shelter staff. The bacteria were not resistant to tuberculostatics.
Conclusion: Rapid transmission of tuberculosis occurred due to inadequate ventilation facilities and delayed screening. Tuberculosis among aspirant asylum seekers is a major problem that requires serious attention.

9A.2 INTRODUCTION

Since 1987, there has been an increase in the number of patients with tuberculosis in the Netherlands. This increase can largely be attributed to the increasing influx of asylum seekers from countries with a high tuberculosis prevalence (S.T. Keizer, Royal Netherlands Tuberculosis Association, written statement, 1994). The incidence of tuberculosis in the Dutch population is 10 per 100,000 per year. The prevalence of tuberculosis among immigrants is about 300 per 100,000, whereas the prevalence among asylum seekers is 400 per 100,000. In view of the large influx of asylum seekers, the number of patients with tuberculosis can be expected to increase sharply. In 1994, 50,000 asylum seekers were expected, which means about 200 tuberculosis patients. An extra problem is the possible import of tuberculosis strains that are resistant to current tuberculostatics.

Tuberculosis surveillance among aspirant asylum seekers at the so-called River Waal Harbour Temporary Shelter (Dutch abbreviation: POC) by the Municipal

Health Service Nijmegen in the period November 1993 to April 1994, revealed that there is a real danger of infection transmission to the Dutch population. The POC comprised 3 River Rhine cruisers. Insufficient ventilation led to the infection of persons in the direct vicinity. The authorities responsible for receiving the asylum seekers neglected to obtain advice from the Municipal Health Service.
This study wishes to draw attention to the problem of tuberculosis among asylum seekers and to demonstrate how inadequate (temporary) shelter facilities and poor execution of policy can lead to secondary cases of infection.

Reception of aspirant asylum seekers and tuberculosis screening
In the Netherlands, the reception of aspirant asylum seekers is organised nationally by the Agency for the Reception of Asylum Seekers (COA). While awaiting accommodation at an official Reception Centre where the first legal hearing will take place, it is sometimes necessary for asylum seekers to be placed in temporary shelter facilities for several weeks. National policy is to screen asylum seekers for tuberculosis directly on arrival in the Netherlands and to continue screening for 2 years at 6-monthly intervals. Municipal Health Services (MHSs) are responsible for carrying out this policy. Screening can take place at the MHS building or a mobile X-ray unit can be placed at the shelter facilities once a week. The MHS in Tilburg and Lelystad coordinate screening for tuberculosis with the aid of mobile X-ray units.

9A.3 METHOD

The POC Waal Harbour procedure was as follows:
Reception of aspirant asylum seekers During the period November 1993 to April 1994, a total of 928 aspirant asylum seekers were accommodated aboard 3 River Rhine cruisers moored in the Waal Harbour. Each had accommodation for 100 persons. These cruisers were not suitable for permanent residence. The Inspection of Shipping Inland Waters does not have ventilation norms for hotel ships / river cruisers. In view of the fact that these river cruisers were used in the winter months, it could be expected that the asylum seekers would spend most of their time indoors aboard the cruisers. On inspection of the quarters, the MHS found that the cabins were small and only suitable for sleeping in. A number of cabins did not admit daylight, while 14 cabins did not have any ventilation facilities at all. Aboard all the cruisers, the height of the ceilings was less than 2 metres and the ventilation facilities were inadequate. The dining rooms (nor-

mal capacity: 100 persons) each had to accommodate 300 asylum seekers and the shelter staff. In the cold winter months, these dining rooms were not ventilated at all; but even if the ventilation facilities had been in operation, they would not have been sufficient to prevent aerogenic infection by a patient with undiagnosed open tuberculosis.

Accommodation for the shelter staff, ship's crew and medical team Although the shelter staff and asylum seekers made communal use of the dining rooms, the ship's crew had separate recreation rooms. Smoking was only permitted in the dining rooms or recreation rooms. The medical team (doctors, nurses and administration staff) had offices and care facilities in barracks on the quay.
At the POC, the first medical examination comprised triage. The asylum seekers received a written call-up notice. During the triage, the anamnesis list was checked that the residents had received and filled-in beforehand. A nurse went through the list with the residents and if necessary, made an appointment with the doctor. The doctor could then refer residents to a general practitioner or medical specialist.
Owing to the unexpectedly high water level in the River Waal, the medical team had to abandon the barracks on the quay and create medical care facilities on the lower deck of one of the river cruisers. Therefore, intake and examination of newly arrived asylum seekers took place below deck, where there was no daylight or ventilation. Despite serious complaints from the shelter staff and the MHS, these conditions had to be endured from December 1993 to April 1994.

Tuberculosis examination procedures
Before opening the Waal Harbour shelter, the following agreements were made between the MHS and the medical team regarding the tuberculosis examination procedure:
- Procedure for aspirant asylum seekers: each asylum seeker will be called-up for chest X-ray by the medical team within one week of arrival aboard a river cruiser. The X-ray will be taken in the mobile X-ray unit. Use of the mobile X-ray unit will be coordinated by Tilburg MHS.
The mobile X-ray unit will be parked on the Waal Harbour quay every Wednesday, provided that there are at least 15 new arrivals. The X-rays will be developed on the same day at Tilburg MHS and be read on the following day by the Community Health Officer for TB & Infectious Diseases at the MHS Tilburg. In the case of abnormalities, the shelter will be informed immediately by telephone, so that the patient can attend the tuberculosis out-patient clinic at the Nijmegen MHS on the same day. In the case of open tuberculosis, the patient can immedi-

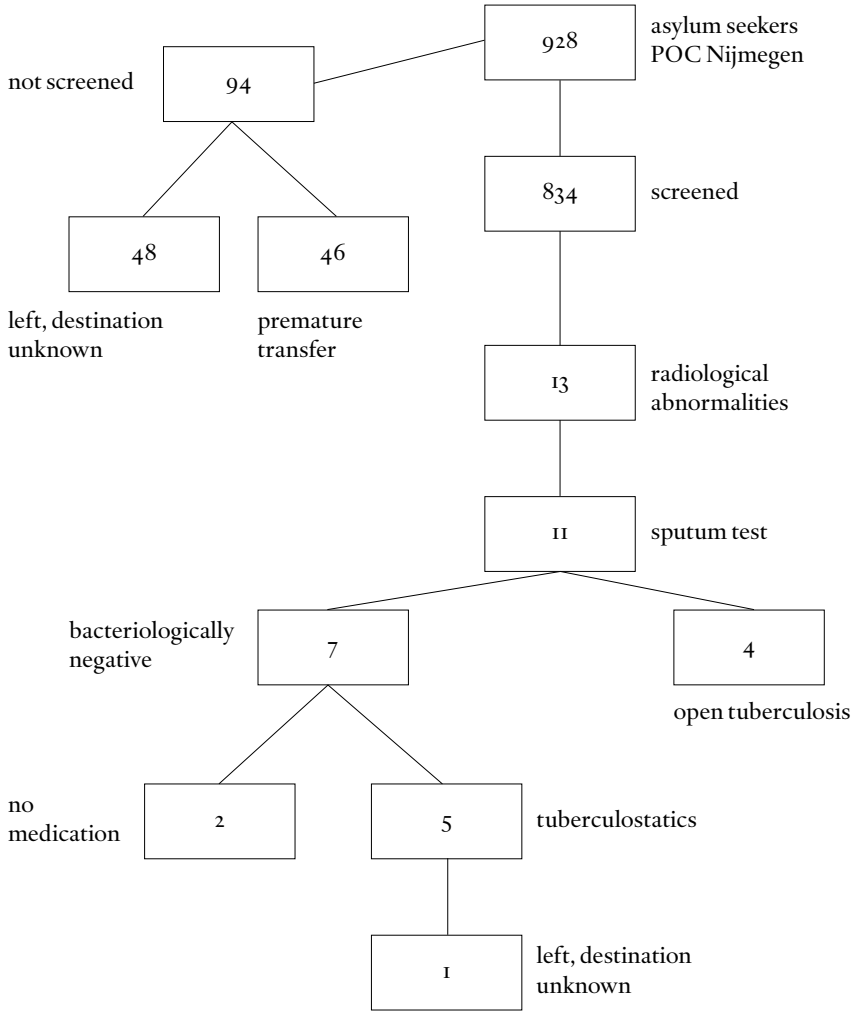
ately be admitted to the Chest Clinic Dekkerswald of the University Hospital Nijmegen, which has an isolation ward. In the case of suspected tuberculosis, the patient should be accommodated in a single cabin that can be ventilated. The importance of good coughing hygiene should be emphasized.
Second reading of the chest X-rays will be performed by the Community Health Officer for TB & Infectious Diseases at the Nijmegen MHS within 7 days. The doctor on the medical team could also send residents to the MHS for chest X-ray in the intervening period.
- Procedure for shelter staff: the shelter staff will be advised to undergo screening for tuberculosis (Mantoux test) before starting work at the shelter in November 1993 and to repeat the screening 2 months after the last contact (in view of the incubation period) in June 1994. In addition, contact tracing will be performed if one of the residents is diagnosed with an infectious form of tuberculosis. Information sessions about tuberculosis will be provided by the MHS for the shelter staff and ship's crew.

9A.4 RESULTS

Results of the first screening
A total of 834 aspirant asylum seekers (90% of all the shelter residents) were screened for tuberculosis (Figure 1). The estimated response rate after one written call-up was 70%. Mean interval between arrival aboard a river cruiser and the first chest X-ray was 10 days according to the medical team. Ninety-four persons (10%) were not screened: 48 (5%) left with destination unknown and 46 (4%) were transferred prematurely.
Radiological abnormalities possibly associated with tuberculosis were present in 13 (1.5%) of the aspirant asylum seekers. A sputum test was performed in 11 of them. In 7 persons, Ziehl-Neelsen staining and Löwenstein culture were negative; 5 of these persons nevertheless started extramural tuberculostatic treatment on the grounds of the radiological abnormalities. One of them left with destination unknown.

Four asylum seekers had open tuberculosis. Löwenstein culture showed human tubercle bacillus growth with good sensitivity to the usual tuberculostatics. One of these 4 patients with open tuberculosis had visited the doctor on the medical team directly on arrival because of health complaints; the doctor immediately referred him to the MHS. Another of these 4 patients with open tuberculosis had been transferred from a different shelter to the Waal POC by

FIGURE 1. Results of the first screening for tuberculosis in 928 asylum seekers at the River Waal Harbour Temporary Shelter (POC) in Nijmegen



the COA without any form of prior consultation. The intervals between arrival aboard a cruiser and the first chest X-ray in the 4 patients with an infectious form of tuberculosis were 2, 1, 9 and 19 days, respectively. Due to circumstances, the chest X-ray of the first patient was not read on the day after it was taken, but 4 days later. The 4 patients were admitted to the Nijmegen University Chest Clinic Dekkerswald. The first patient arrived at the POC Waal Harbour in mid-November. Contact tracing around this patient was performed 2

months after the last contact (in mid-February) in view of the incubation period. The remaining 3 patients with open tuberculosis arrived in mid-February. It was decided that contact tracing in their case would coincide with the screening examinations planned at shelter closure in June 1994.

Contact tracing around the first patient with open tuberculosis

First ring: Contact tracing around the patients with an infectious form of tuberculosis was performed in the usual way according to the ring principle [1]. Contact tracing around the first patient was performed in February 1994 (Table 1). In this patient the first ring comprised the cabinmate and 5 shelter staff. In 3 out of these 5 shelter staff, a positive Mantoux reaction was found, i.e. an increase in tuberculin conversion of at least 10 mm (baseline value 0-2 mm) within a period of one year. This indicated an infection rate of 60% among the shelter staff in the first ring. Therefore, contact tracing was extended to the second ring.

Second ring: The second ring comprised 105 shelter employees/ visitors and 110 asylum seekers residing aboard the same river cruiser.

- Shelter employees/visitors included shelter staff from the Agency for the Reception of Asylum Seekers, ship's crew, security personnel, Refugee Workers Nijmegen, Alien Registration Officers, drivers from a taxi company, family members of the shelter staff who visited the cruisers and lawyers. The work force had been changing constantly since the shelter opened; the Agency for the Reception of Asylum Seekers did not have a complete list of employees. In a number of cases, this contact tracing formed the first screening test, because medical examinations had not been performed before they started work at the shelter.

In the group of 105 employees/visitors, 29 were considered to have an indication for chest X-ray and 76 underwent Mantoux testing (the rule employed was: persons born prior to 1945 and persons with a history of positive tuberculin conversion or BCG vaccination were screened with a chest X-ray, while the others were screened with a Mantoux test). Eleven employees / visitors had a positive Mantoux test. This meant an infection rate of 10.5% in the second ring. Five out of the 11 Mantoux-positive persons showed positive tuberculin conversion; in the other 6 persons, recent infection and therefore actual tuberculin conversion could be assumed in view of their young age [1].

The group of 14 infected employees/visitors (the total number from the first and second ring) comprised 5 ship's crew and one person from security; 5 out of these 6 persons had a positive Mantoux test; they had not had any direct contact with the residents, but they had used the communal dining room. The remaining 8 persons were all employees from the Agency for the Reception of Asylum

TABLE 1. Results of contact tracing around the first of 4 patients diagnosed with open tuberculosis at the temporary shelter for aspirant asylum seekers (Waal Harbour POC, Nijmegen) in mid-February 1994

	No. of persons total	No. of persons with positive Mantoux test	No. of persons with open tuberculosis	Tuberculosis infection rate (%)
Direct employees*	5	3	-	60
Other employees**	105	11	-	10.5
Aspirant asylum seekers	110	-	2†	1.8

* Staff at the temporary shelter

**Personnel from the Agency for the reception of Asylum Seekers, ship's crew, security personnel, Refugee Workers Nijmegen, Alien Registration Officers, drivers from a taxi company, family members of the shelter staff who visited the cruiserd, lawyers

† One person left with destination unknown

Seekers. The 14 persons with a positive Mantoux reaction had a normal chest X-ray. They were advised to take 300 mg of isoniazid per day for 6 months as prophylactic treatment. Later, 2 of them had to stop the medication prematurely owing to liver function disturbances. In addition, one person withdrew from the control visits, which made therapy compliance doubtful.

- Residents. The 110 fellow-residents in the second ring of the first patient had been transferred to other shelters for asylum seekers in the meantime. With the aid of 16 different MHSs, these persons were traced and approached personally. Two of them had consulted a doctor in March and April 1994, respectively. One had infiltrative lung tuberculosis and the other had cavernous tuberculosis. Human tubercle bacillus were found with good sensitivity. The first screening of the patient with cavernous tuberculosis in November 1993 had revealed radiological abnormalities that may have been caused by a previous tuberculosis infection. The patient had never received treatment. Further determination of *M.tuberculosis* with restriction fragmentation polymorphism by the National Institute of Public Health and the Environment (RIVM) showed that the *M.tuberculosis* of both these patients matched that of the first patient. Before tuberculostatic could be started, the asylum seeker with cavernous tuberculosis left with destination unknown.

9A.5 DISCUSSION

During the reception of aspirant asylum seekers at the Waal Harbour POC, a great deal went wrong with prevention and control of tuberculosis in the initial stages. There was a high rate of infections in the first and second ring, because of delayed diagnosis of patients with open tuberculosis. This was caused by inadequate accommodation facilities and sluggish surveillance. In view of this high infection rate, we feel it worthwhile to briefly summarize the transmission mode of tuberculosis and the preventive measures.

Infection Infection with tuberculosis occurs by means of aerogenic transmission. Droplet nuclei with a diameter of 1-5 μm can reach the lower airways after inhalation. In the case of equal immunological resistance, the risk of actual infection is directly proportional to the concentration of airway particles and the duration of exposure. One out of every 25-30 patients with cavernous lung tuberculosis is highly infectious.

Prior to World War II, before adequate tuberculostatics became available, good coughing hygiene and ventilation were considered to be the most effective means of preventing tuberculosis infection. Studies at sanatoria showed that it took an average of 6 to 18 months for the staff to become infected. One study on an outbreak of tuberculosis that might have been related with the air circulation system within a building, showed that being inside the building for ≥ 40 hours per week was the largest only risk factor [2,3]. After adequate tuberculostatics became available, less attention was paid to good coughing hygiene and ventilation. However, the current threat of imported tubercle bacillus that is resistant to medication has reawakened the need to prevent droplet infection. It is generally accepted that if bodily odours can be dispelled by the ventilation system, then the ventilation is adequate. The degree to which aerogenic transmission can be prevented by ventilation is limited. Natural ventilation varies with the weather conditions, the construction of the building and the behaviour of the people inside. Ventilation must be compatible with the work situation and be regarded as acceptable by the users of the building. Many people suffer from respiratory infections during the winter months. Coughing contributes to the spread of bacteria and viruses through a building. Exogenic reinfection with tuberculosis can lead to an active form of tuberculosis in persons who have suffered from tuberculosis is the past. The risk is greater in the case of decreased psychological or physical resistance [4].

It is certain that the poor ventilation in the Waal Harbour POC and the fact that the asylum seekers were not screened for an infectious form of tuberculosis

before being permitted to board the river cruisers led to an unnecessarily high number of tuberculosis infections. In view of the risk of asylum seekers introducing resistant tuberculosis, conscious exposure of staff and fellow-residents to potential patients with open tuberculosis is irresponsible. Moreover, it is a spine-chilling thought that potentially infectious patients are able to "disappear". In the meantime, the MHS Nijmegen has alerted the Agency for the Reception of Asylum Seekers, the Inspectorate of Health, the Royal Netherlands Tuberculosis Association and the municipality.

Prevention Based on the above-described experience, the MHS gave the following advice to the Agency for the Reception of Asylum Seekers:

- Accommodation facilities of limited size with poor ventilation and little daylight can only be used for asylum seekers in whom active pulmonary tuberculosis has been excluded. Obviously, it would be better never to use such facilities.
- Consideration must be given to whether a sanction policy should be introduced for asylum seekers who ignore the first written call-up for compulsory tuberculosis screening.
- Asylum seekers cannot be transferred to other shelter accommodation by the Agency for the Reception of Asylum Seekers until it has been established that they do not have open tuberculosis. This is necessary to prevent infections at multiple shelters.
- To promote treatment compliance, it is important for asylum seekers who are taking tuberculostatics to remain at the same shelter for the total duration of treatment. In this way, the patient can be monitored by one and the same MHS.
- Isolation facilities should be available at shelters for asylum seekers.
- Personnel and volunteers who apply for work at shelters for asylum seekers should be approached personally and/or provided with written information by the Industrial Health Authority. Screening for tuberculosis directly after work acceptance and every 6 months thereafter must be made compulsory.

Furthermore, the MHS emphasizes that tuberculosis in asylum seekers is a major problem that requires serious attention.

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Chapter 9

9.B
DNA FINGERPRINTING IN CONTACT TRACING AROUND AN ASYLUM SEEKER WITH PULMONARY TUBERCULOSIS

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Submitted

9B.1 ABSTRACT

Background: in asylum seekers with open tuberculosis, contact tracing is always performed by the Municipal Health Service (MHS). We investigated whether any further patients had been registered after regular contact tracing around an asylum seeker with open tuberculosis had closed.
Methods: data from the Fingerprinting Surveillance Project after regular contact tracing had closed.
Results: there were four further contacts. They all had bacteriologically confirmed *Mycobacterium tuberculosis,* whose DNA fingerprint was identical to that of the index patient and they all manifested active tuberculosis after regular MHS contact tracing had closed. No further contacts with a bacteriologically confirmed form of tuberculosis were found around these four new patients.
Conclusion: DNA fingerprinting contributed to tracing further patients after regular contact tracing had closed.

9B.2 INTRODUCTION

In the period 1993-1998, an average of 32986 asylum seekers per year entered the Netherlands [1]. The annual percentage of people screened for tuberculosis by means of a chest X-ray on entry varied from 90-98%. Pulmonary tuberculosis was diagnosed in an average of 93 asylum seekers per year, a prevalence of 300 per 100,000; in 37 persons, the diagnosis was confirmed bacteriologically, an average prevalence of 124 per 100,000 [1]. Since 1993, all *M. tuberculosis* cultures have been sent to the National Institute of Public Health and the Environment (RIVM) for DNA fingerprinting [2]. A specific characteristic of the bacteria is revealed by DNA fingerprinting. This technique provides a routine means of monitoring which tuberculosis patients in the Netherlands have been infected with the same *M. tuberculosis*. This is of importance for source and contact tracing. It has also led to new insights into the epidemiology of tuberculosis in broader terms [2]. Patients with 100% identical DNA fingerprints belong to one cluster [2].
This article presents an example from clinical practice.
Firstly, the results of the regular contact tracing performed in 1993/1994 by the MHS are summarized [3].
In November 1993, an infectious form of pulmonary tuberculosis was diagnosed in an aspirant asylum seeker from Algeria who was staying at the Tempory Shelter (POC) Waalhaven. Examination took place within the framework

of the compulsory screening for tuberculosis, valid for asylum seekers after entering the Netherlands. The ventilation facilities at the POC Waalhaven were totally inadequate [3]. Contact tracing was performed by the MHS according to the usual ring principle [4].
Contact tracing around the persons who belonged to the first ring of the asylum seeker, revealed an infection rate of 60%. Therefore, it was decided to extend the contact tracing to the second ring. The second ring comprised 110 other co-tenants at the POC Waalhaven, all aspirant asylum seekers [3]. In the meantime, these asylum seekers had been transferred to other shelters. With the cooperation of 16 different MHSs, these persons could be approached personally. Special care was taken to ensure their participation in the voluntary half-yearly follow-up screening for tuberculosis during the first two years of their stay in the Netherlands, as recommended for persons from countries with high rates of endemic tuberculosis. The asylum seekers had received BCG vaccination in their countries of origin, which made detection of a latent tuberculosis infection impossible with a Mantoux test. Screening for tuberculosis was only possible by means of a chest X-ray and on the basis of symptoms. After regular contact tracing by the MHS had closed in February 1994, but before the first half-yearly follow-up screening in May 1994, two asylum seekers (one from Afghanistan and one from Bosnia) consulted a physician because of symptoms. In contrast with the results of screening performed on entry to the Netherlands in November 1993 and the results of contact tracing, active pulmonary tuberculosis was diagnosed in these two asylum seekers. Determination of the mycobacterium by the RIVM revealed that both patients had tuberculous bacteria with normal sensitivity and 100% identical DNA fingerprints to the index patient who came from Algeria and had been a co-tenant at the POC Waalhaven in November 1993.
Below we discuss how with the aid of data from the DNA Fingerprinting Surveillance Project over the period 1994 to January 2001, patients were identified with bacteriologically proven tuberculosis, whose *M. tuberculosis* had an identical DNA fingerprint to that of the index patient.

9B.3 METHODS

DNA typing of the *M. tuberculosis* was performed by means of the Restriction Fragment Length Polymorphism (RFLP) technique. Different *M. tuberculosis* stems contain a varying number of IS6110 insertion elements. In addition, there is wide variation in the position in the genome of the bacteria where the ele-

ments are inserted. During RFLP typing, DNA fragments are identified that contain IS6110 DNA.
In order to establish whether patients with an identical *M. tuberculosis* (100% identical DNA fingerprints) had indeed been in contact with each other, a nurse from the Royal Netherlands Tuberculosis Association (KNCV) contacted a TB nurse at the MHS where the patients with 100% identical DNA fingerprints had been found, in the framework of the DNA Fingerprinting Surveillance Project [5].
In order to make an epidemiological link, consultation took place between the TB nurse from the MHS and the individual patients, while observing the privacy regulations.

9B.4 RESULTS

The asylum seeker from Algeria who was diagnosed with an infectious form of pulmonary tuberculosis in November 1993 during his stay at the POC Waalhaven, belonged to a cluster of 14 persons whose *M. tuberculosis* DNA fingerprints were identical. Within this cluster, three groups of patients could be distinguished, containing five, three and six persons each. No epidemiological links could be established between the three different groups, or between the six patients in group 3, which makes cross-contamination unlikely. Below, we briefly discuss the countries of origin and the possibility of cross-contamination in the countries of origin or in the Netherlands of the different persons in this cluster.
Group 1 of the cluster comprised five persons: the asylum seeker from Algeria who was diagnosed with an infectious form of pulmonary tuberculosis at the POC Waalhaven and four asylum seekers from Afghanistan (n=1), Bosnia (n=1) and Somalia (n=2). The latter four asylum seekers were staying at the POC Waalhaven in November 1993 and belonged to the second ring of the patient from Algeria. In these four asylum seekers, there were no signs of active tuberculosis in November 1993 or in February 1994. After the regular contact tracing had closed, an infectious form of pulmonary tuberculosis was diagnosed in three of them after they had contacted a physician of their own accord, because of symptoms; this occurred in March 1994, April 1994 and September 1996, respectively. In the remaining asylum seeker, infectious tuberculosis was diagnosed in April 1994 during the recommended half-yearly screening programme for tuberculosis that applies to asylum seekers and immigrants during their first two years in the Netherlands [6]. Screening was performed by means of a chest X-ray.

In group 2 of the cluster, three patients had been in contact with each other: two were members of a family from Somalia and the remaining person was a Dutch nurse. The link between the nurse and her index patient (from Somalia) was made after it became known that the DNA fingerprints were identical; this was later confirmed by anamnesis.
Group 3 of the cluster comprised six patients who had not shared accommodation or shelter facilities. They indicated that they had never met any of the other persons in the group or any of the other 8 patients in the cluster with an identical DNA fingerprint. One came from Algeria, 2 from Iran, 1 from the Netherlands, 1 from Somalia and 1 from Syria.

9B.5 DISCUSSION

In the Netherlands, the IS6110 RFLP patterns of *M. tuberculosis* stems are extremely polymorphic. An identical fingerprint does not form indisputable evidence that contact has taken place between patients in the same cluster, because there can be a non-identified index patient or an external source. The finding of identical DNA fingerprints in immigrants means that the patients must have had a common source in the Netherlands or in their country of origin, or that they infected each other in their country of origin or in the Netherlands.
Regular contact tracing by the MHS is conducted according to the ring principle [4]. If infections are found, for example, in co-tenants, i.e. the first ring, then contact tracing is extended to the next ring and so on until no more cases of infection are found.
On the basis of contact tracing by TB nurses from MHSs (period 1997-1999), an epidemiological link was suspected in 22% of the patients in the same clusters. Using unpublished data from the DNA Fingerprinting Surveillance Project (M. Šebek) over the period 1997-1999 on 1673 patients, a definite epidemiological link was made in 26% of the patients and a suspected link in 21% with the aid of the RFLP technique and supplementary anamnesis. Therefore RFLP typing contributed to demonstrating links that were not found by means of regular contact tracing.
These findings support the results of the present study. None of the four contacts with the index patient at the POC Waalhaven were detected by means of regular contact tracing in February 1994. Three out of these four patients consulted a physical because of symptoms. Patients who might have been exposed to infection and have therefore been invited for contact tracing belong to risk

groups for tuberculosis. In persons known to have a positive Mantoux test and in persons who have received a BCG vaccination in the past, it is no longer possible to make a diagnosis of latent tuberculosis by means of a Mantoux test. A Mantoux test can also give a false-negative result. Three out of the four contacts became ill within two years of infection. This rate agrees with data in the literature. Although the incubation period for tuberculosis is lifelong, the majority of patients manifest active tuberculosis within two years of infection [7]. Endeavouring to achieve optimal compliance with the voluntary half-yearly screening for tuberculosis by means of a chest X-ray during the first two years of an asylum seeker's stay in the Netherlands is therefore extremely desirable [6]: on the one hand because the risk of developing active tuberculosis is greatest in the first two to five years after immigration and on the other hand because it is possible for a person to become infected while staying at a shelter for asylum seekers [8]. The risk of infection is greatest when the ventilation facilities at a shelter are deficient and a (too) large group of people who have not been screened for tuberculosis are sharing such accommodation. Regular contact tracing every three months after the last contact cannot always be performed, because it is common practice for asylum seekers to be transferred from one shelter to another.

9B.6 SUMMARY AND CONCLUSION

On the basis of 100% identical DNA fingerprints and anamnestic findings, it is very likely that one patient caused bacteriologically proven active tuberculosis in four other persons. At the time of regular contact tracing, none of these four asylum seekers had any signs of active tuberculosis. Three out of these four persons became ill within two years of infection and one became ill within three years. Three out of the four patients were detected as a result of symptoms and one was detected by screening. No further patients with a bacteriologically proven form of tuberculosis were found around these four new patients. DNA fingerprinting contributed to making links that were not made using regular contact tracing.

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Chapter 10

CONCLUSIONS AND DISCUSSION

THE IMPLEMENTATION PROCESS REGARDING
THE SHORTENING OF THE TREATMENT DURATION
OF TUBERCULOSIS IN THE NETHERLANDS

10.1 CONCLUSIONS AND DISCUSSION

A 6 months treatment of tuberculosis in which isoniazid, rifampicin and pyrazinamide are administered during the first two months, followed by 4 months on isoniazid and rifampicin, suffices irrespective of the organ in which the disease is most active. *M.tuberculosis* has to be normally sensitive in this case, i.e. it should not be a resistant bacterium.
After 6 months the patient is cured, and the chance of relapse is less than 3.3%. This is the most important conclusion to be drawn from this study of the literature, which systematically charts the results of a 6 months treatment of non-immunocompromised patients primarily diagnosed with lung-, cervical lymph node-, meningitis-, bone- or kidney tuberculosis.
These findings do not imply that the duration of treatment cannot be shortened still further. Some knowledge of the history is needed to understand why the effectiveness of therapy plans shorter than 6 months has not been considered here. Tuberculosis is a severe infectious disease, which may be contagious. The condition may be contracted unwillingly and unwittingly. Even before chemotherapeutics became available after World War II, the number of patients in the Netherlands decreased as a result of better food and housing. The tuberculostatics that became available in the period 1940-1945 turned ambulatory treatment into an option to replace (several) year's hospitalisation in a sanatorium. Since treatment with a single remedy soon led to resistance, and short-term treatment led to an unacceptably high relapse percentage, patient compliance was stressed for protracted ambulatory treatment. Depending on the availability and right combination of tuberculostatics, therapy duration could be reduced from 18-24 to 9 months. As a result of this, and of the effective network of Dutch organisations fighting tuberculosis, the number of patients with tuberculosis in the Netherlands has decreased annually, ranking the Netherlands among the countries with the lowest incidence of tuberculosis and a low level of resistance. This result, together with the lack of a truly effective remedy, explains why in the early 90s in the Netherlands, research was limited to the effectiveness of a 6 months treatment. The treatment duration is arbitrary. What relapse percentage is still acceptable is debateable. Treatment with isoniazid, rifampicin, pyrazinamide and streptomycin for 4.5-5 months, of patients with tuberculosis of the lungs (*M.tuberculosis*, normal sensitivity) resulted in a 4% relapse (95% C.I. 3-6), 4 months therapy in a 12% relapse (95% C.I. 9-16) and 3 months therapy in a 16% relapse (95% C.I. 12-20) [1,2]. This actually means that 80% of the patients were cured within 3 months. After 3 months of successful therapy, it is impossible to determine which of the

patients should receive continued treatment up to a total treatment duration of 6 months [1].

At present, the increasing migration is the determining factor for the number of tuberculosis patients in the Netherlands. Worldwide the increase of tuberculosis is related to the population growth and the high incidence of HIV in areas highly endemic to tuberculosis. For the Dutch situation, in which more than half of the tuberculosis patients are foreigners, this means that screening for tuberculosis should take place as soon as possible after entry. The risk of importation resistance is realistic with persons from countries that had no adequate tuberculosis programmes. The reception of these persons should be such that spreading of the disease is prevented and intensive therapy monitoring is safeguarded, especially during the first 2-3 months of treatment. Concentration of patients and concentration of tuberculosis experts is necessary if sufficient experience is to be gained in the Netherlands. Only a combination of research results from areas that are highly endemic to tuberculosis with sufficient in-country clinical experience will promote a correct interpretation of the guidelines regarding treatment.

There is no longer any space for guidelines specific to the Dutch endemic form of tuberculosis, e.g. a low incidence of tuberculosis and no resistance. This is a challenge for the future.

10.2 INTRODUCTION

From 1978, international research has shown that a 6 months treatment of lung tuberculosis will suffice on condition that medication is taken faithfully [3]. In the late 80s, based on studies of patients with lung tuberculosis (normal sensitive *M.tuberculosis*) both the American Thoracic Society (ATS) and the British Thoracic Society (BTS) advised a 6 months treatment [4,5]. The common treatment duration in the Netherlands was 9 months. Possible missed doses of tuberculostatics in the first 6 months were to be compensated by the longer therapy, so that the number of patients with relapse caused by non-compliance would be low. Particularly in the Netherlands, where the 44 well-functioning tuberculosis units of the Municipal Health Service (MHS) safeguard proper care for tuberculosis patients, shorter treatment duration of tuberculosis should be possible. The shorter the treatment, the bigger the chance that patients would comply fully with the therapy.

The immediate cause for the study into the treatment duration of tuberculosis was the difference between the treatment duration of lung tuberculosis in the Netherlands and in other countries [4,5]. In view of the good treatment results of tuberculosis in the Netherlands there was an unwillingness to simply adopt the advice of the ATS and BTS. A systematic survey of the clinical trials about the treatment duration of tuberculosis might provide basis for therapy advice [6]. Not only for lung tuberculosis, but also for the extra-pulmonary forms of tuberculosis, a need for such a systematic survey of clinical trials was felt. An organ specialist may be called for in the case of extra-pulmonary forms like bone- and kidney tuberculosis. Beside the obligatory medicinal treatment, surgical intervention may be necessary.

The diagnosis for extra-pulmonary tuberculosis is harder to prove bacteriologically, moreover, the effect of the therapy is more difficult to evaluate bacteriologically. In addition to this, extra-pulmonary forms of tuberculosis occur far less often than lung tuberculosis, so that there is less clinical experience as well.

In 1992, at the start of the study of the literature about the treatment duration of tuberculosis, the aims were: 1) to develop guidelines about treatment duration, based on reliable scientific publications. 2) to contribute to the implementation of these guidelines, which should also be used in practice by the doctors that treat tuberculosis patients. 3) to evaluate progress as regards the implementation of the guidelines. This might take place on the basis of the data in the Netherlands Tuberculosis Register (NTR).

In this chapter, a description will be given of the way in which, at the start and during the study of the literature about the treatment duration of tuberculosis,

based on literature and practical experience, consideration was given to any factors that could possibly play a part in the implementation of the guidelines resulting from this research [7-10].

10.3 PROFESSIONALS, ORGANISATIONS AND PATIENT GROUPS INVOLVED

Professionals involved

The annual number of patients with tuberculosis varies, from 1192 in 1987 to 1811 in 1994 [11]. In the period 1993-1998, 6511 patients in the Netherlands were registered as having been diagnosed with lung tuberculosis. In 37% of these cases, the diagnosis was made by a tuberculosis doctor working for the MHS. There are 35 such doctors, which amounts to 11.3 patients a year per MHS doctor. Most patients go to a clinical lung specialist with their symptoms; there are 344 of such specialists in the Netherlands, who diagnosed 53% of the patients with lung tuberculosis. On average, therefore, a clinical lung specialist treats 1.7 tuberculosis patients a year. For 6% of the patients the diagnosis was made by an internist-infectiologist. There are 40 such doctors in the Netherlands, which amounts to 1.6 patients with lung tuberculosis each a year. Other specialists made the diagnosis lung tuberculosis for 3% of the other patients; of the remaining 1% this was unknown (data NTR/KNCV 2000).

Organisations involved

The tuberculosis doctors working for the MHS are lung specialists or medical officers. All tuberculosis doctors working for the MHS are members of the National Tuberculosis Policy Committee (CPT). This Committee is part of the KNCV. The KNCV was founded as a private initiative in 1903 and has developed into an international organisation, partly because of its successful programmes to combat tuberculosis. This organisation wants to organise the fight against tuberculosis taken up by the MHS as a coherent national programme; in order to achieve this, it functions as a data bank and coordination centre. The KNCV safeguards and supports the national consensus consultation inside the CPT. Not only the doctors working at the tuberculosis units of the MHS are members of this Committee, but also a representative of the nurses that work at these tuberculosis units, as well as a representative of the clinical lung specialists (nominated by the Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose, NVALT), the clinical consultant for tuberculosis (a clinical lung specialist appointed by the KNCV), a representative of the National Institute of

Public Health and the Environment (RIVM) and a representative of the Inspectie voor de Gezondheidszorg van het Staatstoezicht op de Volksgezondheid (IGZ). Topics regarding both prevention and cure are discussed in the CPT. Apart from its representative in the CPT, the NVALT has its own tuberculosis committee, whose members include members of the CPT. In this way, an effort is made to reach consensus about therapy policy between the tuberculosis doctors working for the MHS and the clinical lung specialists.

Patient groups involved

The population of tuberculosis patients in the Netherlands has changed gradually. From 1992, more than half of the patients have come from abroad. These tuberculosis patients are migrants and asylum seekers. Patients who reside illegally in the Netherlands, as well as uninsured homeless people, are treated by the MHS. The language barrier and the different socio-cultural backgrounds may have their influence on the therapy compliance of these patients. Moreover, asylum seekers frequently move during treatment, which means that they encounter several different doctors for treatment. This makes it difficult to provide optimum care, the more so if the therapy advice is not unequivocal. Therapy mistakes may induce resistance. A normally sensitive *M.tuberculosis* is easy to treat, but the treatment of resistant strains is more complex. Also in patients who have contracted HIV and tuberculosis at the same time, the treatment of tuberculosis, but also of HIV, is more difficult.

The risk of importation of resistance is realistic with persons from countries that have no adequate tuberculosis programmes. Simultaneous infection with HIV and tuberculosis is seen particularly in persons from countries where tuberculosis occurs frequently. In the Netherlands, the more complex tuberculosis problems clearly occur in the patient groups that are hard to reach.

10.4 CURRENT PRACTICE AND PROFESSIONAL CONDUCT

In the Netherlands, there is an obligation to notify the authorities of any case of tuberculosis [12]. The hospital laboratories and/or the clinical doctors contact the MHS as soon as there is proof of the diagnosis tuberculosis or as soon as symptoms and radiological findings seem to indicate tuberculosis and treatment is started. The MHS passes such reports on to the IGZ. In addition to this, the MHS records the tuberculosis data for each patient as part of the NTR [11]. This register is administered by the KNCV. After a tuberculosis patient is regis-

tered, the MHS will do any source- and contact studies necessary, and in consultation with the doctor the patient will be monitored to safeguard therapy compliance. The diagnosis tuberculosis may also be made at the MHS unit, after which treatment will take place from there. In this way, the tuberculosis doctors of the MHS have an overview of all the patients with tuberculosis in their working area. Since they are in such close contact with the NTR, they can follow the epidemiological development of the tuberculosis [11]. The tuberculosis doctors of the MHS are specialised in the treatment and monitoring of patients with tuberculosis. Unlike that of the individual clinical lung specialist or internist-infectiologist, this is their principal task.

10.5 FACTORS IMPEDING AND PROMOTING CHANGE

Impediments to the implementation of new treatment guidelines

In view of the very limited numbers of tuberculosis patients in the Netherlands, it is hard for the individual doctor to gain sufficient experience with tuberculosis. This makes it impossible to experience the necessity and advantage of change first-hand. Chances are that treatment remains based on familiar but outdated knowledge. As a result of the decreasing number of tuberculosis patients after World War II, the lung specialist working in the hospitals stood out less clearly as tuberculosis specialists. It became less natural for doctors to be knowledgeable about the organisation of the fight against tuberculosis in the Netherlands, about the methods of the KNCV and the operating procedures in the tuberculosis units of the MHS.

If it is impossible to gain experience first-hand, proposals for change will have to be made by persons or organisations well known and well trusted [9,10]. The initiative to issue guidelines for the treatment of tuberculosis on the basis of a systematic study of clinical trials was initiated by the CPT, a committee not well known by the clinicians. The CPT has taken into account the fact that foundations that underlie a proposition for change have to be transparent; the advantages must be visible.

Favourable factors for the implementation of the advice to shorten the treatment duration of lung tuberculosis by 3 months

In the same period that the research into the treatment duration in the Netherlands took place, worldwide an increase of tuberculosis was seen in patients with simultaneous infections of HIV and *M.tuberculosis*. In addition to this, in countries without adequate tuberculosis programmes *M.tuberculosis* turned out

to have become resistant to the commonly used tuberculostatics. In the Netherlands, the number of patients with tuberculosis increased as a result of migration of persons from areas highly endemic to tuberculosis. This meant that the importation of resistant tuberculosis strains into the Netherlands became a realistic risk. In the same period that the study into the optimum treatment duration of lung tuberculosis was finished, the committee "Multiresistente Tuberculose" (Lambrechts-van Weezenbeek CSB) [13] issued a report entitled "Richtlijnen met betrekking tot de behandeling en preventie van multiresistente tuberculose in Nederland". Instead of starting treatment with the 3 medicines commonly used up to that point, if resistance was suspected treatment would have to begin with four types of medication.

In the Netherlands, much more attention was bestowed on the report about multi-resistant tuberculosis than on the results of the study into shorter treatment duration [13,14]. The chance of infection with a multi-resistant strain of *M.tuberculosis* in hospitals led to discussions inside these hospitals. The medical microbiologist in a hospital is often in charge of the department for hygiene and infection prevention. Besides the lung specialists and the internist-infectiologists, he is involved in the tuberculosis policy of the hospital. The influx of asylum seekers grew rapidly and their inadequate reception led to heated political discussion, in which the risk of importation of tuberculosis was pointed out [15].

Tuberculosis occurs early in the course of an HIV infection. Patients with HIV infections come to the surgery of the internist-infectiologist. The latter treats AIDS patients with tuberculosis. Interaction of anti-retroviral therapy with tuberculostatics complicates the treatment of even a normally sensitive *M.tuberculosis*, so that internist-infectiologists and lung specialist will need to know about the treatment of tuberculosis.

In spite of the small numbers of patients, the combination of AIDS and tuberculosis, the threat of multi- resistance and the attention paid by the media to the issue of tuberculosis in asylum seekers and the interest in HIV in general, have put tuberculosis back on the lung specialist's agenda.

Who wanted shorter treatment and for whom was this relevant?

The need to change the treatment duration of tuberculosis was increasingly felt in the Netherlands by the tuberculosis doctors working for the MHS, though not by clinical specialists. If, on the basis of research, a decision was to be taken to shorten the duration of treatment with three months also in the Netherlands, this would facilitate monitoring of the tuberculosis patients, decrease the chance of side effects, increase patient compliance, and be cheaper as well.

Clearly, establishing a new treatment protocol, supported by tuberculosis specialists working for the MHS and clinical specialists alike, was of the highest priority.

10.6 THE WAY THE KNCV HAS DRAWN THE ATTENTION OF THE TREATMENT PROVIDERS FOR THE RESULTS OF THE STUDY INTO THE OPTIMUM TREATMENT DURATION OF TUBERCULOSIS

All during the study, the issue at stake was brought to the attention of clinical specialists at local and national referee evenings. In this way, both the topic and the methods were elucidated. Most studies about treatment duration were done on patients with lung tuberculosis, the most common form of tuberculosis. The diagnosis for this has been bacteriologically proven more often than with extra-pulmonary forms of tuberculosis. This means that, due to sufficiently large numbers of patients with bacteriologically proven lung tuberculosis, convincing statements could be made. The systematic reviews of the treatment of the extra-pulmonary forms of tuberculosis did not clarify why a 6 months therapy was effective, but did show that a 6 months therapy was certainly no worse than a longer therapy. The result of the first study was that the treatment of lung tuberculosis (normal sensitive *M.tuberculosis*) could be shortened by three months [14].

The results of the first literature study about shorter treatment duration of lung tuberculosis and the report about multi-resistant tuberculosis prompted the CPT to set up the study group "Therapiebeleid" [13,14]. This study group was assigned to advise on the treatment of lung tuberculosis in the Netherlands: in short, a guideline for the treatment of lung tuberculosis.

A conscious effort was made to include in this study group representatives of the MHS as well as clinical chest-physicians and internist-infectiologists. The concept advice, i.e. to start with 4 types of medication if resistance was suspected, and to treat for 6 instead of 9 months in case of a normally sensitive *M.tuberculosis*, was discussed both within the CPT (June 1995) and at an open meeting of the tuberculosis study group (the later committee) of the NVALT. After the treatment advice of the CPT had been established (November 1995) it was published as a report of the KNCV [16]. Distribution took place from the KNCV among all the tuberculosis doctors and lung specialists in the Netherlands (February 1996).

In close consultation with the NVALT, the KNCV decided to pay extensive

attention to the new treatment advice in the Nederlands Tijdschift voor Geneeskunde [17,3,18,19]. Subsequently, the new therapy policy was consistently brought to the attention of the specialists [20,21].

10.7 IMPLEMENTATION OF SHORTER TREATMENT DURATION

Evaluation of the implementation of the advice of the study group Therapiebeleid has now taken place (inspection study results; data are being published, J.Veen, KNCV. Data from the NTR show that as early as June 1995, patients with bacteriologically proven tuberculosis, normally sensitive *M.tuberculosis*, were treated for 6 instead of 9 months by the tuberculosis doctors; from the beginning of 1997 also by the clinical lung specialists (data J. Veen). The advice about shorter treatment duration for the extra-pulmonary forms of tuberculosis was issued only recently; evaluation based on data from the NTR is not yet possible, therefore.

10.8 POSSIBLE FUTURE IMPLEMENTATION STRATEGIES

Establishing the safety and effectivity of a specific treatment is a necessary step. Establishing guidelines and protocols is the next step. After these steps, the actual implementation process takes place. Tuberculosis is an issue several disciplines are confronted, but have little to do with. This sets clear limits to the amount of time they can devote to this issue. A questionnaire in which clinical lung specialists were asked about their involvement with tuberculosis revealed that their interest in tuberculosis is considerable [22]. The Kwaliteitswet Zorginstellingen makes specific demands of responsible medical conduct [23]. The treatment advice a patient gets should not depend on the doctor he consults [23]. Guidelines help doctors to give the correct advice. If they want to divert from the guidelines, they have to substantiate their reasons. During the general meeting on 9 October 1998, within the NVALT a decision was made to set up a Commissie Richtlijnen Longziekten (CRL). In 2001, the Tuberculosis Committee of the NVALT (the earlier tuberculosis study group of the NVALT) decided to develop guidelines for tuberculosis policy. Clinical conduct based on evidence, the treatment and the correct implementation of the guidelines are topics for discussion [24,8,9,10]. It is to be expected that, apart from those regarding the treatment of lung tuberculosis, guidelines will also be defined for

the treatment of the extra-pulmonary forms of tuberculosis. The quality guidelines and the CRL should safeguard a qualitatively responsible tuberculosis policy in the future.

During the study into and the definition of the advice regarding the optimum treatment duration of (lung) tuberculosis, the CPT and the KNCV have taken into account the implementation, and the realisation that the target group of tuberculosis doctors of the MHS would have to be approached in a different manner from the target group of clinical specialists. Refresher courses, written information and involvement of the target groups in developing the advice and guidelines were emphasised. The lung specialists, for their part, structurally put the topic tuberculosis on the agenda of the NVALT meetings. The involvement with tuberculosis of clinical lung specialists was increased during the study, since the HIV- and tuberculosis resistance problems that result from the growing migration of people from countries with a high incidence of tuberculosis have turned tuberculosis into a problem inside the Dutch hospitals as well. This factor has contributed to making the implementation of the advice concerning the treatment duration of lung tuberculosis possible.

Permanent refresher courses or an individual refresher course with reference to a specific patient is an implementation strategy. On the other hand, tuberculosis care should perhaps be concentrated more with specific specialists. The various parties involved see the problem from different perspectives, related to their backgrounds and patient populations, which makes regional multi-disciplinary cooperation another issue that needs work. Since segments of the patient population, such as migrants, asylum seekers and HIV-positive persons, have specific characteristics, these will have to be taken into account in order to optimalise therapy compliance.

In the Netherlands tuberculosis has become an import disease that is difficult to treat. Its incidence may be expected to remain low, if the organisation of the care for tuberculosis is adjusted. Sufficient own clinical experience is necessary if every individual patient is to be treated optimally and in accordance with guidelines. This pleads for transmural tuberculosis centres that provide integrated care.

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Chapter 11

SUMMARY

SUMMARY

Tuberculosis is an infectious disease caused by the *Mycobacterium tuberculosis*, which can induce symptoms of the disease in all organs. Of all forms of tuberculosis, pulmonary tuberculosis is the most common form. It accounts for 70% of all cases of tuberculosis. The pulmonary form is also the best known form of tuberculosis, since patients can infect other people in the environment by coughing. Treatment aims at patients to be cured as soon as possible without having relapses of the disease later on. Chemotherapeutic treatment for tuberculosis was developed during the 1940s and 1950s: streptomycin (1941), PAS (1948), isoniazid (1952), ethambutol (1961), rifampicin (1965) en pyrazinamide (1978). In the fifties, pyrazinamide was applied in high doses, which led to unacceptable side effects. Since 1978 therapeutically adequate doses have been applied. It is not possible to eliminate all tubercle bacteria at once, i.e. in one treatment. The reason for this is that tubercle bacteria in a patient with tuberculosis are present at various levels of metabolic activity. The duration of the treatment does depend on the types of tuberculostatics that are used. A treatment regimen of 9 months duration with isoniazid and rifampicin resulted in a relapse rate of 1%. Soon after the use of pyrazinamide had been reintroduced in 1978, it became clear that the 9 months treatment including only isoniazid and rifampicin could be shortened, if pyrazinamide was given in addition during the first two months. Considering the working mechanism of the tuberculostatics, administration of pyrazinamide can be stopped after two months, but the question remains for how long administration of isoniazid en rifampicin should be continued after those two months. A shorter therapy is obviously cheaper and easier for the patient to go through with it. In the eighties several studies have been performed on treatment regimens of 6 months or even shorter, in countries where tuberculosis is endemic. At that time AIDS and resistance to antibiotics were no issues yet. Most studies were performed on patients with pulmonary tuberculosis. Based on the results of these studies, a treatment duration of 6 months for patients with pulmonary tuberculosis was recommended internationally at the end of the eighties. For extrapulmonary forms of tuberculosis a longer duration of the treatment used to be advised, due to the fact that for these forms less research data were available. In the Netherlands patients with pulmonary tuberculosis continued to be treated with isoniazid en rifampicin for 9 months as before, while pyrazinamide was added to the medication during the first two months.

Since 1987 a worldwide increase in the number of patients with tuberculosis has been observed. These patients with tuberculosis are mostly AIDS patients

from countries where tuberculosis already was endemic. The increase in tuberculosis observed since 1987 in the Netherlands can be attributed to the increasing influx of persons from countries where tuberculosis is endemic and highly prevalent. In the Netherlands there are yearly about 1500 newly diagnosed patients with tuberculosis. Social and cultural differences as well as increased mobility especially of asylum seekers in the Netherlands hamper optimal supervision of the therapy. Therefore the question has arisen whether also in the Netherlands the treatment duration should be shortened from 9 to 6 months. If the treating physicians at the Municipal Health Services and in hospitals employ unambiguous and short treatment regimens, treatment compliance will increase. The importance of treatment compliance with regard to the prevention of resistance induction, combined with the fact that internationally a 6 months treatment regimen had been employed for a long time already, led to the decision to perform a methodical study on the effectiveness of regimens with a duration of 6 months or longer for the treatment of tuberculosis. Treatment regimens had to include isoniazid, rifampicin and pyrazinamide. The results of the methodical literature studies have been described in chapters 2, 3b, 4, 6 and 7.

In all studies the same method was applied. A comprehensive literature search was performed using the Medline database, collecting only studies published after 1978 (when pyrazinamide was introduced). References were investigated. Publications were selected and retrieved on the basis of the abstracts, without any language restriction. Because a 9 months treatment regimen with isoniazid and rifampicin was known to give good results, no comparative studies have been performed internationally on the effectiveness of 9 months and 6 months treatment regimens including isoniazid, rifampicin and pyrazinamide, for patients with lung-, meningitis-, bone- and kidney tuberculosis. Only for patients with cervical lymph node tuberculosis one study has been performed in which treatment effectiveness was compared of 66 patients who had received treatment during 6 months and 70 patients who had received treatment during 9 months. Since it appeared impossible to compare the effectiveness of 9 and 6 months treatments on the basis of randomised controlled studies we choose to compare groups of patients who met some predetermined inclusion- and exclusion criteria. With the help of a checklist we only included those studies in our analysis in which patients data as well as therapy regimens and treatment results had been described accurately. Only in those cases it was possible to make an accurate description and comparison of the results for patient groups from different studies. This method is called a meta-analysis and it enables one to draw conclusions just as if all studies were part of one big study. Most papers that

could be included in the analysis were written in English. Only for one paper on meningitis tuberculosis the authors have been contacted, because it was not clearly understood from the paper on which grounds the authors had recommended a treatment regimen of longer than 6 months. As a measure for treatment effectiveness we determined the number of patients with tuberculosis relapse during a follow-up period of at least 12 months after completion of a successful treatment. The relapse rate as well as the 95% confidence interval has been calculated. An absolute norm for the relapse rate has not been established. Although children as well as adults were included in the studies, for pulmonary and kidney tuberculosis only adults were involved. To the extent that it was tested, no patients were found to be infected with HIV (human immunodeficiency virus). For pulmonary and kidney tuberculosis, we were able to make a comparison between groups of patients who all had bacteriologically confirmed diagnoses, while treatment results were evaluated bacteriologically as well. For patients with lymph node, meningitis and bone tuberculosis the diagnoses were confirmed bacteriologically in 50%, 28% and 31% respectively. To the extent that it was tested no resistant strains were found. When the diagnosis had not been confirmed bacteriologically, it was made on the basis of histological, epidemiological, clinical, laboratory and radiological data.

After a 6 months treatment, tuberculosis relapse occurred in 116/4833 (2.4%; 95% C.I. 2.0-2.8) of the patients with pulmonary tuberculosis, 13/422 (3.3%; 95% C.I. 1.7-5.5) of the patients with cervical lymph node tuberculosis, 2/131 (1.5%; 95% C.I. 0.2-5.5) of the patients with meningitis tuberculosis, 0/56 (0%; 95% C.I. 0.0-6.4) of the patients with bone tuberculosis and 1/170 (0.6%; 95% C.I. 0.0-3.2) of the patients with kidney tuberculosis. In the studies of patients with pulmonary tuberculosis with a follow-up period of 18-36 months after completion of the treatment, 75% of the relapses occurred in the first year after completion of the treatment. Irrespective of the main diagnosis, no patient group with a 6 months treatment regimen had lower treatment results than the patient group with treatment regimens of longer than 6 months duration. In all studies the importance of bacteriological confirmation was emphasized. After having performed the final typing of the tubercle bacteria, the sensitivity for the usual tuberculostatics can be tested. To the extent that those tests have been performed for patients with tuberculosis relapses, a normal sensitivity of the tubercle bacteria was found in all cases. Most studies have been performed in countries where tuberculosis is endemic and highly prevalent, and where the laboratory facilities are far from similar to those in the Netherlands. Nevertheless, in those countries it was of equally great importance for an adequate diagnosis to give tuberculosis a high ranking in the differential diagnosis. The

occurrence of a granulomatous infection with caseous necrosis in a puncture or biopsy always led to starting treatment with tuberculostatics. Postponing the start of the treatment, pending the results of the bacterial cultures, can cause a progression of the clinical picture and possibly irreversible damage to the organs. Continuing the administration of tuberculostatics for a longer period after a late start can never undo the sustained damage. For this reason the importance of macroscopical and histological observations of the puncture or biopsy, also valid for the situation in the Netherlands, has been pointed out in chapter 3a.

Medicinal treatment of tuberculosis is obligatory for all forms of the disease, but serious remaining damage might make surgery necessary, especially in the case of bone and kidney tuberculosis. This fact probably explains why in papers on bone tuberculosis the emphasis is mainly put on technologies of surgical interventions. Existing doubts about the tuberculostatics reaching the foci of infection were reason for mapping the treatment results per organ. The same doubts explain the fact that especially for meningitis tuberculosis higher doses of medication were given than for other forms of tuberculosis. The treatment results of Dutch children with tuberculosis, as described in chapter 5, show that isoniazid dosages of 4-8 mg/kg bodyweight are sufficient. The results of the studies give indeed no answer on the question why the treatment is effective, however they do answer the question whether it is effective or not.

The studies have been performed in countries with high tuberculosis prevalence. That means that there is a chance that after successful treatment a patient is reinfected by the environment and thus develops active tuberculosis. This disease will be erroneously classified as relapse tuberculosis, which means a failure of previous treatment. DNA fingerprinting techniques, as described in chapter 9b, can be used to determine whether a patient is reinfected with the same or with different tubercle bacteria. By this method a tuberculosis relapse caused by endogenous reactivation can be distinguished from one caused by exogenous reinfection. In addition, these techniques can help to gain an insight into the import and distribution of tubercle bacteria in the Netherlands. This appeared not only to be an indicator for the quality of treatment effectiveness for patients with tuberculosis, it could also reveal relations between patients that had not been found by traditional source and contact tracing made by the Municipal Health Service. Conventional source and contact tracing has been described in chapter 9a. This study concentrated on one asylum seeker who had been diagnosed to have pulmonary tuberculosis as he entered the country. The absolutely inadequate reception of a group of asylum seekers, including this patient, in poorly ventilated rooms led to the infection of some fellow asylum

seekers and some Dutch social workers. This reception policy is irresponsible, even more considering the present chances on the import of resistant tubercle bacteria.

Apart from the patient's own interest, in tuberculosis there is also the general interest of public health. Therefore in the Netherlands tuberculosis is a notifiable disease. Every case of tuberculosis has to be reported to the Municipal Health Service (GGD) that will then start source and contact tracing. In addition, the patient gets support from the GGD during the treatment period. In the analysed studies on treatment results of patients with tuberculosis, medication was generally given without close supervision. However, patients were thoroughly informed and monitored.

In chapter 8 it is described how a comparison of data from the Netherlands Tuberculosis Register (NTR) and data from the Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ) showed that a close correlation exists between the number of days of pyrazinamide use as registered in the NTR and the daily dosage of pyrazinamide supplied on prescription by Dutch pharmacies. On the basis of this close correlation it was concluded that in the Netherlands patients with tuberculosis are indeed reported and thus known to the Municipal Health Services. That means that consultations between physicians working in hospital and physicians and TB nurses from the Municipal Health Services do take place. In chapter 10 the factors are described that possibly played a part in the implemention of the recommendation to shorten the treatment duration of pulmonary tuberculosis with three months. Also general factors, that are always coming into a process of change, were playing a part in here as well. Those factors include the scale of the problem, the unfamiliarity with the matter, the lack of belief in the necessity as well as the fact that tuberculosis treating physicians and nurses are members of various different organisations, as there are the Municipal Health Service (GGD), the Royal Netherlands Tuberculosis Association (KNCV) and the hospitals. It can be foreseen that, when people gain insight into these aspects and into the grounds on which the treatment recommendation has been established, also given the current legal quality standards for treating physicians, the implementation of the treatment recommendation for extrapulmonary forms of tuberculosis will soon be established.

Chapter 12

SAMENVATTING

SAMENVATTING

Tuberculose is een infectieziekte veroorzaakt door de *Mycobacterium tuberculosis*, die vanuit alle organen ziekteverschijnselen kan geven. Van alle vormen van tuberculose komt longtuberculose het meeste voor. Bij 70% van de patiënten met tuberculose is er sprake van longtuberculose. Longtuberculose is tevens de meest bekende vorm, omdat de patiënt door hoesten besmettelijk kan zijn voor zijn omgeving. Het doel van de behandeling is dat de patiënt geneest in de kortst mogelijke tijd en dat de ziekte later niet recidiveert. De chemotherapeutische behandeling van tuberculose ontwikkelde zich in de periode 1940-1950: streptomycine (1941), PAS (1948), isoniazide (1952), ethambutol (1961), rifampicine (1965) en pyrazinamide (1978). Pyrazinamide werd in de jaren vijftig toegepast in hoge dosering. Dit leidde tot onacceptabele bijwerkingen. Sedert 1978 vond toepassing plaats in therapeutisch adequate dosering. Er bestaat niet één behandeling, die alle tuberkelbacteriën gelijktijdig kan opruimen, omdat de tuberkelbacteriën in een tuberculosepatiënt zich op wisselende niveaus van metabole activiteit bevinden. De duur van de behandeling hangt wel samen met de soort tuberculostatica die men gebruikt. Een 9 maanden durende behandeling met isoniazide en rifampicine gaf een recidiefpercentage van 1%. Na de herintroductie van pyrazinamide in 1978 werd al snel duidelijk dat de 9 maanden durende behandeling met alleen isoniazide en rifampicine verkort kon worden, mits men pyrazinamide gedurende de eerste 2 maanden er bij gaf. Gezien het werkingsmechanisme van de tuberculostatica kan pyrazinamide na 2 maanden gestopt worden, maar de vraag is hoelang vervolgens isoniazide en rifampicine gecontinueerd moeten worden. Een kortere therapie is goedkoper en bovendien beter vol te houden voor de patiënt. In de tachtiger jaren zijn er studies gedaan in landen waar tuberculose endemisch is naar 6 maanden en zelfs korter durende therapieschema's. De AIDS-en resistentieproblematiek speelde toen nog niet. De meeste studies zijn gedaan bij patiënten met longtuberculose. Op basis van deze studies werd eind jaren 80 internationaal geadviseerd om patiënten met longtuberculose 6 maanden te behandelen. Voor de extrapulmonale vormen werd vaak nog een langere behandelduur geadviseerd omdat hierover minder onderzoekgegevens beschikbaar waren. In Nederland bleef men patiënten met longtuberculose gewoon 9 maanden behandelen met isoniazide en rifampicine. Aan deze medicatie werd pyrazinamide gedurende de eerste twee maanden toegevoegd.

Na 1987 werd er wereldwijd een toename gezien van het aantal tuberculosepatiënten, waarbij tuberculose met name gezien werd bij AIDS-patiënten, in landen waar tuberculose al endemisch was. De toename van tuberculose, die in

Nederland gezien werd na 1987 hing rechtstreeks samen met de migratie van personen afkomstig uit voor tuberculose hoogendemische gebieden. In Nederland zijn er jaarlijks ongeveer 1500 nieuw gediagnosticeerde patiënten met tuberculose. De sociaal-culturele verschillen en de grote mobiliteit van met name asielzoekers in Nederland maakt optimale therapiebewaking moeilijk. Op dat moment rees de vraag of ook in Nederland niet overgegaan moest worden op een 6 maanden durende behandeling. Een eenduidig therapiebeleid onder behandelaars op de GGD-en en in de kliniek alsmede een korte therapie zou de kans op therapietrouw vergroten. Het belang van de therapietrouw om resistentie vorming te voorkómen alsmede het feit dat men internationaal al lang 6 maanden behandelde hebben er toe geleid dat besloten is tot een systematisch onderzoek naar de resultaten van een 6 maanden of langer durende behandeling van patiënten met tuberculose, waarbij het behandelschema isoniazide, rifampicine en pyrazinamide moest bevatten. De resultaten van de systematische literatuurstudies worden beschreven in hoofdstuk 2, 3b, 4, 6 en 7. Steeds is dezelfde werkwijze gevolgd. Een uitvoerige literatuursearch werd gedaan via Medline database, waarbij publicaties verschenen na 1978 (introductie van pyrazinamide) in beschouwing werden genomen. Referenties werden nagetrokken. Er was geen restrictie met betrekking tot de taal en op basis van de abstracts zijn artikelen opgevraagd. Omdat een 9 maanden durende behandeling met isoniazide en rifampicine goede behandelresultaten gaf zijn er internationaal geen vergelijkende studies gedaan naar de behandeling van 9 maanden en 6 maanden met isoniazide, rifampicine en pyrazinamide bij patiënten met long-, meningitis-, bot-en niertuberculose. Alleen bij patiënten met lymphadenitis tuberculose werden in één studie de behandelresultaten met elkaar vergeleken van 66 patiënten, die 6 maanden werden behandeld en 70 patiënten, die 9 maanden werden behandeld. Doordat vergelijk van behandelresultaten van 9 en 6 maanden niet mogelijk was op basis van gerandomiseerde gecontroleerde studies is gekozen voor vergelijk van patiëntengroepen, die voldeden aan vooraf opgestelde inclusie –en exclusiecriteria. Het hanteren van een checklist heeft er toe geleid, dat alleen die studies voor analyse in aanmerking zijn gekomen, waarin op zorgvuldige wijze de patiëntenkarakteristieken zijn beschreven alsmede het therapieschema en de behandelresultaten. Een beschrijving en vergelijking van de uitkomsten van de onderzochte patiëntengroepen uit de verschillende studies waren hierdoor mogelijk. Dit noemt men een meta-analyse. Conclusies konden hierdoor getrokken worden als waren alle studies onderdeel van één groot onderzoek. De meeste artikelen, die voor analyse in aanmerking kwamen waren Engelstalig. Alleen voor meningitis tuberculosa zijn de auteurs aangeschreven. Dit is gedaan omdat niet duidelijk

werd uit de studies op basis waarvan men een langer dan 6 maanden behandeling adviseerde.
Als maat voor de effectiviteit van behandeling werd gekeken naar het aantal patiënten, dat een recidief tuberculose kreeg nadat de patiënten tenminste 12 maanden na het beëindigen van een succesvolle therapie gevolgd waren. Het recidiefpercentage alsmede het 95%-betrouwbaarheidsinterval werd berekend. Een absolute norm voor een recidiefpercentage is er niet. In de studies waren zowel kinderen als volwassenen opgenomen, maar bij longtuberculose en niertuberculose betrof het uitsluitend volwassenen. Er waren geen HIV-positieve patiënten, voor zover daarop getest was. Bij long-en niertuberculose konden patiëntengroepen met elkaar vergeleken worden, bij wie de diagnose bij alle patiënten bacteriologisch bewezen was en kon het resultaat van de behandeling bacteriologisch geëvalueerd worden. Bij patiënten met lymphadenitis tuberculosa, meningitis- en bottuberculose was de diagnose bacteriologisch bewezen bij respectievelijk 50%, 28% en 31%. Er waren geen resistente stammen voor zover bepaald. Indien geen bacteriologisch bewijs voor handen was werd de diagnose gesteld op basis van histologische, epidemiologische, klinische, laboratoria en radiologische gegevens.
Een recidief tuberculose na een 6 maanden behandeling kregen 116/4833 (2,4%; 95% C.I. 2,0-2,8) van de patiënten met longtuberculose, 13/422 (3,3%; 95% C.I. 1,7-5,5) van de patiënten met halskliertuberculose, 2/131 (1,5%; 95% C.I. 0,2-5,5) van de patiënten met meningitis tuberculosa, 0/56 (0%; 95% C.I. 0,0-6,4) van de patiënten met bottuberculose en 1/170 (0,6%; 95% C.I. 0,0-3,2) van de patiënten met niertuberculose. In de onderzoeken van de patiënten met longtuberculose met een controleperiode van 18-36 maanden na het beëindigen van de therapie trad 75% van de recidieven op in het eerste jaar na het stoppen van de medicatie. Bij geen van de patiëntengroepen met tuberculose, ongeacht de hoofddiagnose was het behandelresultaat na 6 maanden therapie slechter in vergelijk met de resultaten van de groep patiënten, die langer dan 6 maanden was behandeld. In alle studies werd het belang van een bacteriologisch bewijs onderstreept. Na definitieve typering kan bepaald worden of de tuberkelbacterie normaal gevoelig is voor de gebruikelijke tuberculostatica. Bij de patiënten met een recidief tuberculose werd voor zover bepaald steeds weer een normaal gevoelige tuberkelbacterie gevonden.
De meeste studies zijn gedaan in landen waar tuberculose hoogendemisch is en waar de laboratoriumfaciliteiten niet te vergelijken zijn met de mogelijkheden in Nederland. Desalniettemin was het voor het stellen van de diagnose ook in die landen het allerbelangrijkste dat men tuberculose hoog in de differentiaaldiagnose had staan, waarbij de bevinding van een granulomateuze ontsteking

met verkazende necrose in het punctaat of de biopsie altijd leidde tot het starten van de tuberculostatische therapie. Uitstel van de behandeling, in afwachting van de kweek geeft progressie van het ziektebeeld waarbij irreversibele orgaanschade kan optreden. Het langer doorgeven van tuberculostatica nadat men te laat gestart is kan nooit meer deze schade ongedaan maken. Dit heeft ertoe geleid dat in hoofdstuk 3a ook voor de Nederlandse situatie op het belang van de macroscopische en histologische bevindingen van het punctaat of de biopsie wordt gewezen.
De medicamenteuze behandeling is bij alle vormen van tuberculose obligatoir, maar ernstige restschade kan chirurgisch ingrijpen bij met name bot-en niertuberculose noodzakelijk maken. Dit is waarschijnlijk de verklaring voor het feit dat in de artikelen over bottuberculose de nadruk met name ligt op de techniek van de chirurgische interventie. Onzekerheid of de tuberculostatica de infectiehaard wel bereiken heeft er toe geleid dat per orgaan de behandelresultaten in kaart zijn gebracht. Diezelfde onzekerheid is een verklaring voor het feit dat men met name bij meningitis tuberculose de medicatie in een hogere dosering werd gegeven dan bij andere vormen van tuberculose. Uit de in hoofdstuk 5 beschreven behandelresultaten van Nederlandse kinderen met tuberculose blijkt dat een isoniazide dosering van 4-8 mg/kg lichaamsgewicht volstaat. De resultaten van de studies geven weliswaar geen antwoord op de vraag waarom de behandeling effectief is, maar wel óf hij effectief is.
De studies zijn gedaan in landen waar tuberculose veel voorkomt. Dit betekent, dat de kans bestaat, dat een patiënt na een succesvolle behandeling opnieuw aangehoest wordt en een actieve tuberculose ontwikkelt, die dan ten onrechte geduid wordt als een recidief tuberculose, een falen van de eerdere behandeling. Met DNA fingerprint techniek, zoals in hoofdstuk 9b beschreven is het tegenwoordig mogelijk na te gaan of patiënten met dezelfde tuberkelbacterie geïnfecteerd zijn. Onderscheid tussen een recidief tuberculose tengevolge van een endogene reactivatie of exogene reïnfectie is op deze wijze mogelijk. Bovendien geeft het inzicht in de import en verspreiding van tuberkelbacteriën in Nederland. Dit is niet alleen een kwaliteitsmaat voor de effectiviteit van de behandeling van tuberculosepatiënten, maar toont ook verbanden aan tussen patiënten, die niet door het traditionele bron-en contactonderzoek van de GGD zijn gelegd. Het traditionele bron-en contactonderzoek is beschreven in hoofdstuk 9a. Het onderzoek vond plaats rond een asielzoeker, bij wie bij binnenkomst een longtuberculose werd vastgesteld. De volstrekt inadequate opvang in slecht ventilerende ruimtes van de groep asielzoekers, waartoe deze patiënt behoorde heeft er toe geleid dat medeasielzoekers en Nederlandse hulpverleners geïnfecteerd zijn. Zeker gezien de kans heden ten dage op import van

resistente tuberkelbacteriën is een dergelijk opvangbeleid onverantwoord. Naast het individuele belang van de patiënt speelt bij tuberculose ook het algemene volksgezondheidsbelang. Dit is dan ook de reden dat elke tuberculosepatiënt in Nederland gemeld moet worden bij de GGD, van waaruit bron- en contactonderzoek gestart wordt. Bovendien wordt de patiënt mede begeleid door de GGD tijdens de duur van de therapie. In de geanalyseerde studies over de behandelresultaten van patiënten met tuberculose werd de medicatie meestal niet onder volledige supervisie gegeven. Wel was de voorlichting aan en de begeleiding van de patiënten heel intensief.

In hoofdstuk 8 wordt beschreven hoe uit de gegevens van de Nederlandse Tuberculose Registratie (NTR) in vergelijk met de gegevens van het Geneesmiddelen Informatie Project van het College voor zorgverzekeringen bleek dat er een grote overeenkomst was tussen het aantal dagen geregistreerd pyrazinamide gebruik in de NTR en de afgeleverde dagelijks dosering pyrazinamide door de apothekers. Hieruit werd geconcludeerd dat de patiënten met tuberculose in Nederland ook daadwerkelijk gemeld worden en bekend zijn bij de GGD. Overleg tussen de klinisch werkzame artsen en artsen en sociaalverpleegkundige werkzaam op een GGD vindt dus plaats. In hoofdstuk 10 wordt beschreven welke factoren mogelijk een rol hebben gespeeld bij de implementatie van het advies om de behandeling van longtuberculose in Nederland met 3 maanden te verkorten. Algemene factoren, die altijd spelen bij een veranderingsproces speelden ook hier; factoren zoals de omvang van het probleem, onbekendheid met de materie, niet overtuigd zijn van de noodzaak, alsmede het feit dat behandelaars van tuberculose tot verschillende organisaties behoren, nl. een GGD, de KNCV en de ziekenhuizen. Het ligt in de lijn der verwachting, dat door inzicht in deze factoren en inzicht op basis waarvan een behandeladvies tot stand is gekomen alsmede door de wettelijk kwaliteit eis die tegenwoordig aan behandelaars wordt gesteld de implementatie van het behandeladvies voor de extrapulmonale vormen van tuberculose snel tot stand komt.

Abbreviations

ATS	American Thoracic Society
BTS	British Thoracic Society
COA	the agency for the reception of asylum seekers (Centraal Orgaan opvang Asielzoekers)
CPT	National Tuberculosis Policy Committee (Commissie voor Praktische Tuberculosebestrijding)
CRL	Commissie Richtlijnen Longziekten
CVZ	Health Care Insurrance Board (College voor zorgverzekeringen)
DDD	Defined Daily Dose
DOT	Direct Observed Treatment
GIP	Dutch Drug Information Project
IUATLD	International Union Against Tuberculosis and Lung Disease
KNCV	Royal Netherlands Tuberculosis Association (Koninklijke Nederlandse Centrale Vereniging tot bestrijding der tuberculose)
MHS	Municipal Health Service (GGD)
NTR	Netherlands Tuberculosis Register
NVALT	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose
RIVM	National Institute of Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu)
WHO	World Health Organisation
H	isoniazid
R	rifampicin
Z	pyrazinamide
E	ethambutol
S	streptomycin
$_2$HRZE/$_4$H$_2$R$_2$	Treatment Regimen: numbers before a group of letters represent the number of months on that type of drug, numbers after a letter or group of letters represent the number of doses of the drug(s) per week,
2HRZE/4HR	and if a letter or group of letters is not followed by any numbers then the drug(s) were given daily

Dankwoord

Tuberculose is een infectieziekte met een levenslange incubatietijd. Zo lang heeft het tot stand komen van dit proefschrift gelukkig niet geduurd, maar de snelheid waarmee de hoofdstukken tot stand zijn gekomen zijn te vergelijken met de wisselende niveaus van metabole activiteit van de tuberkelbacteriën. De laatste 18 maanden was er duidelijk sprake van een groeispurt dank zij de ruimte die mij door de medewerkers van de GGD Regio Nijmegen werd gegeven. De inzet van Annemieke Sintenie-Hendriks voor het maken van de tabellen in hoofdstuk 2 was enorm.
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Curriculum vitae

De auteur van dit proefschrift werd geboren op 2 augustus 1952 te Helmond. Na het behalen van het diploma Gymnasium B aan het Carolus Borromeus College te Helmond in 1970, studeerde zij Geneeskunde aan de Katholieke Universiteit te Nijmegen. Het artsexamen werd behaald in 1978. In 1979 werd begonnen met de opleiding tot internist in het Canisius Wilhelmina Ziekenhuis (hoofd: Dr. J.H.J. Enneking). In 1982 werd de opleiding voortgezet in het Universitair Medisch Centrum St. Radboud (hoofd: Prof. Dr. A. van 't Laar), waarna in september 1983 begonnen werd met de specialisatie longziekten in het Universitair Longcentrum Medisch Centrum Dekkerswald / Dr. van Spanjekliniek / UMC St. Radboud. (hoofd Prof. C.M.Jongerius en in 1987 Prof. Dr. C.L.A. van Herwaarden). Na de registratie tot longarts in december 1986 werd tot maart 1988 parttime gewerkt als longarts in het UMC St.Radboud. Vanaf augustus 1987 tot mei 1988 werd als tuberculosearts gewerkt op de GGD Utrecht, daarna op de GGD Haarlem, Gooi-en Vechtstreek en Flevoland en vanaf januari 1990 tot heden op de GGD Regio Nijmegen. Sedert september 2001 ook werkzaam op de GGD Rivierenland in Tiel. In 1990 werd begonnen met de opleiding Sociale Geneeskunde, tak Algemene Gezondheidszorg en met de module infectieziekten (opleider J.van Steenbergen) te Utrecht, Stichting voor Sociale Gezondheidszorg. In oktober 1993 vond de inschrijving in het specialistenregister Sociaal Geneeskundigen, tak Algemene Gezondheidszorg plaats.
Zij is gehuwd met Jos van Loenhout. Samen hebben zij een zoon Marijn.