Mantoux Skin Testing and Isoniazid Prophylaxis in the Netherlands Army

Improving on Existing Tools

Mantoux Onderzoek en Isoniazid Profylaxe in het Nederlandse Leger

Verbetering van Bestaande Technieken

Proefschrift

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Table of Contents

List of Abbreviations

ALT	Alanine aminotransferase
ARI	annual risk of tuberculosis infection
AST	aspartate aminotransferase
ATS	American Thoracic Society
BCG	Bacille Calmette-Guérin
CBS	Central Bureau of Statistics
CDC	Centres for Disease Control and Prevention
CMH	Central Military Hospital
DHS	Delayed Hypersensitivity
DMGZ	Dienst Militaire Gezondheidzorg
DOT	Directly Observed Therapy
GIT	Gastrointestinal tract
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IPT	Isoniazid Prophylactic Treatment
ITSC	International Tuberculosis Surveillance Centre
IUAT	International Union Against Tuberculosis
IUATLD	International Union Against Tuberculosis and Lung Disease
KNCV	Koninklijke Nederlandse Centrale Vereniging voor de bestrijding van tuberculose
MAC	Mycobacterium avium complex
MDR	Multiple Drug-Resistant
MMR	Mass Miniature Radiography
NTM	Non-Tuberculous Mycobacteria
PPD	Purified Protein Derivative
RIVM	Institute of Public Health and Environment
RNLA	Royal Netherlands Army
TB	Tuberculosis
TNO	Netherlands Organisation for Applied Scientific Research
TU	tuberculin units
ULN	upper limit of normal
USPHS	United States Public Health Service
WHO	World Health Organisation

CHAPTER

1

INTRODUCTION

INTRODUCTION

"If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, ... must rank far behind tuberculosis." Robert Koch (1882) quoted by Waksman (1)

General Introduction

Tuberculosis (TB) is a good example of a disease that is easy to cure with modern chemotherapy but yet continues to ravage entire communities leaving in its wake a trail of human suffering. Since time immemorial, tuberculosis has reaped untold suffering in human society and continues to do so with near impunity in some countries. In the latter part of the nineteenth century, Robert Koch proved that tuberculosis was due to a specific organism, the *Mycobacterium tuberculosis* (2). The introduction of effective anti-tuberculosis drugs, started in the 1940s with the discovery of streptomycin by Selman Waksman (1) in the US, heralded a new optimistic stage in the control of tuberculosis. Brightman and Hilleboe best summed this optimism in 1962 (3):

> *"The white plague, tuberculosis - is retreating ... The decade ahead of us, the sixties, will be decisive. We are determined ... that the retreat of the tubercle bacillus shall inflict as few casualties upon our human resources as possible. Today tuberculosis workers have found it increasingly more difficult to find the persons who have active tuberculosis and control work requires case-finding methods that have the accuracy of high-powered rifles ... If we work hard in the decade ahead, tuberculosis is one disease that we can relegate to a position of minor importance in public health..."*

It is now more than three decades ago since Brightman and Hilleboe wrote and yet tuberculosis remains a major public health problem. Estimates of the global tuberculosis problem portray a gloomy and bleak prospect. According to the World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) one-third of the world's population, that is about 1.7 billion people, is infected with *M. tuberculosis.* These are, therefore, carriers of live bacilli and can reactivate and disseminate it (4). WHO and IUATLD further estimate that:

a) about 20 million of these have active tuberculosis;

b) of these tuberculosis patients at least 2.5 million die every year - making tuberculosis the leading single cause of death world-wide from an infectious disease;

c) every year there are about 8 million new cases of tuberculosis - of which 3 million are contagious (4).

Before 1985 the industrialised nations of the world had experienced a steady decline in tuberculosis, but this changed when the downward trend in the United States was reversed. More countries in the industrialised world began reporting similar findings. From 1985 through to 1991, the United States reported an 18% increase in the number of tuberculosis cases notified (5). This sudden resurgence of tuberculosis in industrialised nations during the era of modern chemotherapy is multifaceted. Dramatic cutbacks in public funding and in facilities to control and treat TB, increasing poverty, homelessness, overcrowded housing, and drug abuse all conspired to rekindle tuberculosis which was a dying epidemic in industrialised countries (6). The human immunodeficiency virus (HIV) infection epidemic has also had a profound effect on the resurgence of tuberculosis (7,8). More ominously is the emergence of multiple-drug-resistant (MDR) *Mycobacterium tuberculosis*. MDR tuberculosis shows resistance to at least isoniazid and rifampicin which are key components of therapeutic regimens in the treatment of tuberculosis. The emergence of MDR tuberculosis has been attributed to a number of factors. Jacobs (9) has best summed them up. He highlighted inadequate training of health care workers in treatment and control of tuberculosis; inadequate knowledge in epidemiology of tuberculosis; unmonitored outpatient tuberculosis treatment; deterioration of infrastructure for public-health-services and the onset of human immunodeficiency virus (HIV) infections.

Tuberculosis control in the Royal Netherlands Army has been a prominent feature of the Army Health Services since the end of World War II. The Army has used over the years different tuberculosis control tools in minimising the TB problem in the Service. Data which have been accumulated by the Army especially on tuberculin skin testing initiated in 1956 is of particular interest. Tuberculin skin testing is to this day the only method available to screen and identify persons infected with *M. tuberculosis* and to assess the risk of tuberculosis in a defined group of persons. Information from the Royal Netherlands Army (RNLA) tuberculin skin testing programme has been used by Styblo to provide insight into the annual risk of infection (ARI) for the Dutch population (10). By calculating the ARI based on this screening method, useful epidemiological information has been generated not only for the military but also for civilian public health. The Army populations used in the tuberculin skin testing programme thus provide a unique insight into epidemiological changes and trends, which reflect the general tuberculosis epidemiology in the country.

The tuberculin skin testing programme is also the basis for isoniazid prophylactic treatment (IPT) of persons infected with *M. tuberculosis*. The tuberculin skin testing, however, is not a straightforward clear-cut qualitative "positive" or "negative"(10). Much attention has been paid to standardising the test and adopting the same methodological approaches while administering the test. Since the beginning of tuberculin skin testing in the Army, for the tuberculin skin test (Mantoux) a concentration of 1 TU of Purified Protein Derivative (PPD) RT 23 has been used as recommended by the World Health Organisation in 1963 (11). To make the results comparable to those from past surveys, the Army has continued to use this dosage of PPD. However PPD is far from a standard to diagnose tuberculosis infections. PPD even in its purest form is a mosaic of multiple antigen (12). These antigens partially cross-react with non-tuberculous mycobacteria (NTM) and therefore do not elicit a monospecific response (13). Most of these NTMs are not or are only facultatively pathogenic for humans. This cross-reactivity might result in NTM infected persons reacting with a positive result in response to a tuberculin skin test. Such persons will therefore be erroneously classified as having tuberculosis infection. This has important implications for individual patient care and for epidemiological studies. Examples are the overestimation of the annual tuberculin index in the general population by including false-positive PPD RT 23 reactions and the unnecessary prescription of isoniazid prophylaxis in Army personnel. The prevalence of NTM sensitivity limits the usefulness of the tuberculin skin test as a diagnostic and epidemiological tool in tuberculosis control. Tuberculosis control programmes dependent on a policy of tuberculin skin testing would need to identify *M. tuberculosis* infected persons with a high degree of specificity. Edwards and Palmer (14) used dual skin testing to separate infections due to *M. tuberculosis* from those resulting from NTM by supposing that subjects with a stronger reaction to tuberculin prepared from *M. tuberculosis* than to sensitin prepared from NTMs could be considered as infected with the tubercle bacilli. Earlier experiments proved that infection with a single mycobacterial species provided a degree of tuberculin sensitivity that was definitely greater to the homologous antigen than to the heterologous mycobacterial antigen (15). During recruitment, the Army performs mandatory tuberculin skin testing on the recruits. The limitation that NTMs might pose on the interpretation of the tuberculin skin testing results are therefore of concern and increasing the specificity of the skin test is of major importance.

Concern about the specificity and sensitivity of the tuberculin skin test lies in the fact that the army recommends isoniazid prophylaxis for persons with a positive test. In the early 60s, the effectiveness of prophylactic isoniazid administration in reduction of tuberculosis morbidity was first reported by Ferebee and Mount (16). In 1967, the American Thoracic Society recommended the use of isoniazid prophylaxis therapy for

all persons with a positive tuberculin skin test (17). Unfortunately since the 1950s and 1960s the use of isoniazid prophylaxis for persons infected with *M. tuberculosis* has been associated with numerous reports of undesirable side-effects, mostly hepatitis (18-21), at a time when the drug gained importance in tuberculosis control. Because these early studies were based on only a limited number of patients who were in most cases also receiving other drugs, it was difficult to implicate isoniazid as cause of the side effects. However Scharer and Smith in 1969 proved that isoniazid was responsible for hepatitis among *M. tuberculosis* infected persons who took the drug for prophylaxis (22). Since then a number of studies have reported many persons with hepatitis that are linked to isoniazid prophylaxis (23-27). Whether or not to use isoniazid prophylaxis, in view of the potential side effects, has become a big question in tuberculosis control programmes in which an IPT strategy is applied. Despite more upbeat reports that have documented an efficiency of 93% in treatment of latent tuberculosis with isoniazid (28, 29), the decision on its use has been marred by much controversy. The use of isoniazid in persons with a positive tuberculin skin reaction with a normal chest x-ray has ended with conflicting opinions for or against its use (26, 27, 30-37). On the other hand persons with untreated healed fibrotic lesions on chest x-rays are given up to 70% protection from reactivation of disease by isoniazid prophylaxis (38, 39). Amidst all these controversies, the Royal Netherlands Army has continued to use isoniazid prophylaxis therapy for Army recruits with a positive tuberculin skin reaction. Recruits into the Army are on average 20 years of age. Studies have demonstrated that in younger age groups, such as those of recruits into the Dutch Army, isoniazid prophylaxis has a clear advantage (27,37). However, age in relationship to isoniazid prophylaxis has not been devoid of conflicting results and opinions. Stead et al. (40) demonstrated that isoniazid prophylaxis had a clear benefit among elderly persons who show evidence of new tuberculosis infection.

In this thesis a historical review of the Royal Netherlands Army tuberculosis control programme is outlined in chapter two. An overview is provided of the tools that have been used by the army to control tuberculosis. Through the years, the changes in trends in tuberculosis have been monitored and this has often resulted in reviewing and adapting control strategy to reflect on the epidemiological situation or level of current scientific knowledge. This historical review discusses issues of policy and practices over the years and their scientific basis.

The Army isoniazid prophylaxis programme in the period 1984-1995 is presented in chapter three. Particular attention is given to the documentation of side effects. The incidence of these side effects therefore forms a basis on which decisions regarding the use of isoniazid prophylaxis in the Army can be made. Different population groups

often respond differently to medicaments and it is therefore of scientific importance to provide firm data on isoniazid prophylaxis as arising in programme conditions.

The prevalence of non-tuberculous mycobacteria sensitivity in the army recruit population through the years is presented in chapter four. This data provides information on the prevalence of NTM in the general Dutch population and - as mentioned earlier - NTM sensitivity does affect the specificity of the tuberculin skin test, which forms the cornerstone of the isoniazid prophylaxis programme in the Royal Netherlands Army.

Taking into consideration the presence of NTM also in the Army population, chapter five presents the results of an investigation that uses a double skin testing procedure to distinguish *M. tuberculosis* from NTM infections. It is the opinion of this investigator that this method minimises the unnecessary administration of isoniazid and is an important method to improve the tools available to control tuberculosis.

In chapter six as an example, a case study on the usefulness of tuberculin skin testing to identify infection with a suspected MDR strain is presented. The army has had increasing international deployments. In recent years, servicemen have been deployed in fields as far apart and diverse as from Cambodia to Eastern Zaire. The Army is increasingly mobile and so is the general population in much of the world. International migration and increased travel have brought persons in areas previously considered relatively at low TB risk in contact with tuberculosis. In the era of MDR tuberculosis, the usefulness of isoniazid - an important tool in the Royal Netherlands Army tuberculosis control - threatens to become obsolete. In chapter six, the need to control the global tuberculosis problem is stressed.

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CHAPTER

2

TUBERCULOSIS CONTROL IN THE ROYAL NETHERLANDS ARMY

Historical Perspective

Tuberculosis Control in the Royal Netherlands Army: Historical Perspective

"Het gevaar van de ziekte wordt nog altijd onderschat en tuberculose is eigenlijk het best te vergelijken met een heidebrand. Het vuur sluimert, maar laait af en toe weer op. En daarin schuilt nu juist het gevaar". HA van Geuns (1)

Tuberculosis continues to be of great concern worldwide inspite of significant positive developments in the last decades in its treatment and control. At the beginning of the 1960s, there was great optimism that eliminating tuberculosis - now defined as a case of one per million population - was a goal that could soon be attained. This up-beat mood resulted from recently proven efficacy of antituberculosis chemotherapy and the prospect of isoniazid prophylaxis therapy (IPT) to prevent the advance of tuberculous infection to disease (2).

Today, the goal of eradicating tuberculosis and achieving "zero tuberculosis" still remains elusive inspite of the giant strides made in elucidating the epidemiology of this ancient scourge. The emergence of multiple-drug-resistant (MDR) *Mycobacterium tuberculosis* and tuberculosis associated with human immunodeficiency virus (HIV) infection threaten or have even reversed the gains achieved in TB control realised in the last decades. The problems in many technologically less advanced countries may be of exploding numbers of sputum positive tuberculosis cases and the burden therein of providing reliable and sustainable control measures (3). In technologically advanced countries there is a come-back of tuberculosis. The first evidence of this reversal in the later occurred in the USA (4). In the Netherlands, the number of notified tuberculosis patients has been rising since 1987 (5). An increase in notifications has indeed been registered in other countries such as Ireland, Italy, Denmark, Norway and Switzerland (6). With the resurgence of tuberculosis, a number of controversial policies that had been ignored or subject to little research, given the declining trends in technologically advanced countries, need to be re-evaluated. Notable among these problems are the use and interpretation of the tuberculin skin test, isoniazid prophylaxis therapy (IPT) and the use of BCG vaccination. Studies investigating the use of IPT among persons who have a positive tuberculin skin reaction with a normal chest radiograph have ended with conflicting opinions on its use (7-10). The use of BCG vaccination on the other hand has shown great variation in protection ranging from 80% in some populations and nil in others (11).

It is over a century ago that Robert Koch announced at the Tenth International Congress of Medicine in Berlin a breakthrough in the treatment of tuberculosis (12). Koch's curative agent was described as a "brownish transparent fluid" and many referred to it as Koch's lymph or Koch's remedy. This fluid was a culture filtrate of *Mycobacterium tuberculosis* to which the name tuberculin was given by Bujwid (13). However the enthusiasm of this curative agent failed the tests of the critical scientific community. Tuberculin was found to lack the curative properties that Koch had claimed and the euphoria of Koch's method of treatment of tuberculosis was soon lost. The end of tuberculin as a mode of treatment however did not spell the end of Koch's "brownish transparent fluid".

Tuberculin found a new use as a diagnostic agent – what Koch himself had observed (14). Koch employed a method of subcutaneous inoculation of tuberculin to make a diagnosis of tuberculosis. Persons with tuberculosis, when inoculated with tuberculin subcutaneously, had a sharp rise in body temperature lasting several hours. This test was not widely used by the medical profession in the early years of this century as it was considered that practically everybody reacted to tuberculin. Veterinarians on the other hand saw the potential of the tuberculin test to control tuberculosis in cattle. The test was used to identify diseased cattle to be disposed of. In the Netherlands, Mouton in 1897 found that tuberculin was useful to control tuberculosis in herds but was dangerous and unreliable in man (15). Thus Mouton was among the first persons in the Netherlands who registered scepticism on the use of the tuberculin test to control tuberculosis in man.

In spite of doubts about the use of the tuberculin test, attempts to improve it for the diagnosis of tuberculosis continued in different countries. In particular new methods of administering tuberculin were developed. Griep, among others, outlined in 1957 the different methods of tuberculin administration (13). These included a percutaneous test (Moro), a conjuctival test (Calmette), a modified Koch subcutaneous test (Hamburger), a cutaneous test (Von Pirquet). Other methods of administering tuberculin have included the Heaf test, Trambutsi test, the patch test of Vollmer and a host of others. In 1908 an intracutaneous test was described independently by three scientists: Mantoux in France, Mendel in Germany and Van Balen in the Netherlands (13). The latter is credited as the first to use adrenaline in an attempt to make the tuberculin reaction better defined. In spite of attempts by proponents of Van Balen, such as Cornelia de Lange (13) to honour this Dutch achievement by referring to the Balen-Mantoux test, the intracutaneous test is now globally known as the Mantoux reaction. In almost all areas of the world, it is the Mantoux test that has survived as the standard means to administer

tuberculin. The primary advantage of the Mantoux test in comparison to all the above tests is its ability to provide a quantitative assessment of the tuberculin response.

In the first half of this century, the Von Pirquet method was popular in the Netherlands. The earliest Dutch records on tuberculin skin testing were between 1925 - 1948 performed by the Amsterdam Municipality clinic. These surveys employed the Von Pirquet method to test children aged up to 14 years and who were not in contact with tuberculosis patients (16). The results demonstrated that there was a steady decline in the prevalence of infection at all ages during the 23 years. In 1954, Duit and Vreeling employed (17) for the first time a tuberculin skin test (Von Pirquet) as an epidemiological tool within the Royal Netherlands Army. They skin-tested 131 soldiers following the detection of a sputum positive tuberculosis case in the army barracks at Assen. Twenty one (21%) percent of the soldiers investigated showed a positive Pirquet test. It is noteworthy that Duit and Vreeling hinted that if they had used the Mantoux method possibly more positives might have been found among the soldiers. One of their conclusions was that the tuberculin skin test was a necessity for the army in her tuberculosis control program, which at the time relied primarily on radiography for screening and diagnostic test. Indeed the following year witnessed the use of the tuberculin skin test on a routine basis with the Mantoux skin test as the standard method for tuberculin administration. The limitations regarding the sensitivity of the tuberculin skin test method as pointed out by Duit and Vreeling in the aforegoing were just one of the several problems that would and have continued to generate controversy with the tuberculin skin test. These shortcomings of the tuberculin skin test are best summarised by Edwards and Edwards who wrote in 1960 (14):

> *"Indeed, the story of the tuberculin test is punctuated with the unexpected, with periods of high hopes broken by periods of doubt and disillusion about its usefulness as a diagnostic test."*

This could also be said about the entire evolution of the tools available to understand the epidemiology of tuberculosis and therefore to institute effective intervention methods. The following methods have been available to control of tuberculosis:

- the chest X-ray
- the tuberculin test
- sputum investigations (such as Ziehl-Neelsen staining and culture)
- chemotherapy
- chemoprophylaxis
- BCG vaccination

It is noteworthy that even before the introduction of the above tools, tuberculosis already seemed to be declining in the Netherlands. This decline has been attributed to general improvements in the socio-economic conditions (18). In the Netherlands, tuberculosis mortality decreased from 146.1 per 100,000 in 1920 to 43.7 per 100,000 in 1940, with the risk of tuberculous infection declining from 6.7% in 1920 to 2.1% in 1940. Styblo (18) has reffered to this as the "natural" decline of tuberculosis. These trends in mortality and the risk of tuberculous infection are shown in figure 1.

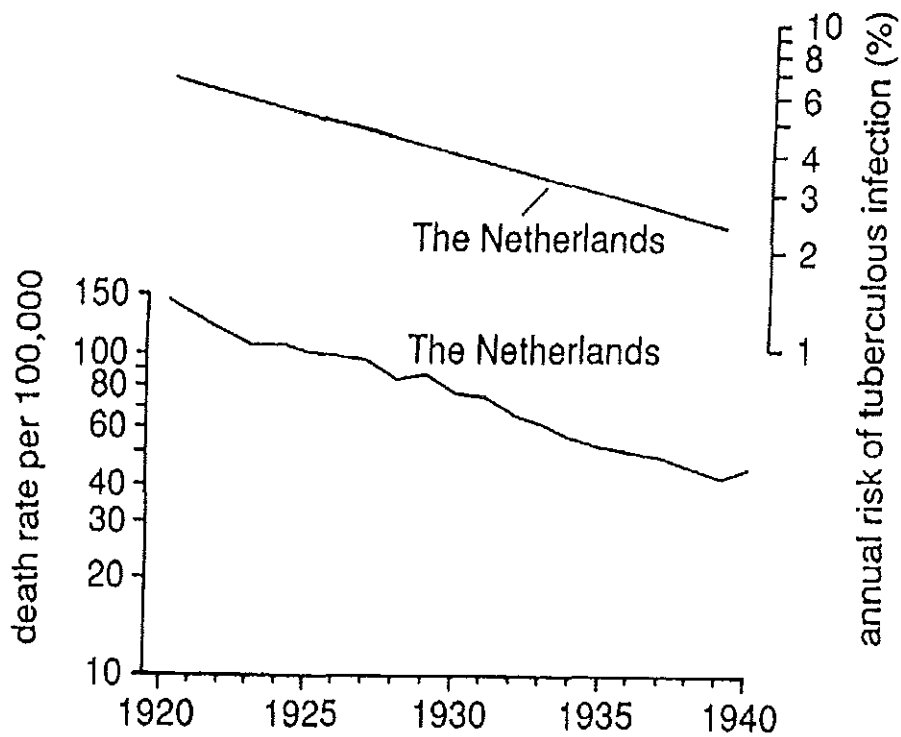

Figure 1. The risk of tuberculos infection in The Netherlands, and death rates in the Netherlands: 1920-1940 (Adapted from Styblo (18))

The crowded living conditions usually found in military barracks are ideal for the spread of infectious respiratory diseases (19). In such crowded settings persons are also at an increased risk of acquiring tuberculosis if there is an infected person in the crowd. Therefore during the immediate post-war period (1945) the army tuberculosis control

program placed emphasis on screening and identifying persons who had been in contact with a known or unknown source of tuberculous infection especially among recruits. Recruits with X-ray evidence of tuberculosis were not enrolled into the army. In this way it was hoped that outbreaks of tuberculosis in barracks' would be minimised.

The present chapter gives insight into the different screening methods that have been used by the Netherlands army in the past five decades. Particular reference is made to the chest X-ray and the tuberculin skin test. In the light of changing epidemiological trends, the suitability of these strategies is also discussed.

Tuberculosis problem in the army before World War II

Accurate records on tuberculosis prevalence in the Netherlands army during the beginning of this century are hard to come by. Existing reports indicate that tuberculosis was indeed a problem within the army. A clear indication of the severity of the problem is described in a 1913 letter from the Tuberculosis Commission (*Staatscommissie inzake tuberculose-bestrijding*) addressed to the Minister of War. In this letter the commission was concerned about the high tuberculosis morbidity and mortality within the Dutch military compared to that in the French and German military. In the Netherlands army, the tuberculosis incidence was 4 per 1000 soldiers in 1913. Reacting to this letter, the Surgeon General wrote:

> *"In response to the statement by the Tuberculosis Commission, I wish to clarify that claims to the effect that the Netherlands army has a higher tuberculosis problem than other countries are erroneous and unfounded".*

The Surgeon General pointed to two factors as being responsible for this seemingly high tuberculosis figure within the Dutch military:

1. The short conscription period (82 months). In other European countries, recruits were obliged to serve for longer periods, usually years. Therefore, the Dutch conscription practice meant that about three cohorts of recruits were inducted while other countries were still dealing with one cohort of recruits. The chances of finding new tuberculosis cases was, therefore, much higher in the Netherlands military.
2. Absence of proper record keeping which resulted in many double registries.

With such irregularities taken into account, the Surgeon General argued, the tuberculosis incidence would be 2.86 per 1000 soldiers. This latter figure would then not be much different from what was being observed in Germany and France. According to the Surgeon General, record keeping was an area of immense weakness. It was with this in mind that the Minister of War and the Surgeon General resolved that beginning with

1919, the statistics on health matters would be handled by the Central Bureau of Statistics (CBS), a civil organisation. Statistical data processed by the CBS for the year 1919, 1920 and 1921 showed respectively 121, 83 and 76 army recruits admitted to sanatoria for tuberculosis treatment. In 1919, Heynsius van den Berg, in a report to the Surgeon General (20) called for more measures to treat and control tuberculosis in the army. He justified this to the Ministry of War on a community health perspective and for the well being of the military. He recommended five measures, which laid the foundations of tuberculosis control program in the army:

1. Early diagnosis of tuberculosis
2. Notification of all cases of tuberculosis to the CBS
3. Early treatment in sanatoriums and hospitals
4. Discharge from the army and provision of social support
5. Aftercare and cooperation with civilian organisations working to control tuberculosis.

During this period the only diagnostic test which was used routinely to identify cases of active disease was the bacteriological examination of sputum. Other nonspecific tests included measuring the erythrocyte sedimentation rate - which is usually high in cases of active tuberculosis. These tests were unsuitable to screen large populations such as of recruits. It was, therefore, a giant step forward when chest X-rays could be used as a screening tool.

Beginnings of Röntgenography in the RNLA

In the period before 1955, the Netherlands military relied almost exclusively on physical examination supplemented with X-ray examination of the chest to identify cases of active pulmonary tuberculosis. During this period chest X-ray screening of all recruits into the army became part of the routine medical examination at induction and it was "methode de choix" to detect cases of active and latent disease in this group.

From the time of Röntgen Discovery to World War II

Röntgen rays were discovered in 1895 by Wilhelm Conrad Röntgen (21). A few years later, in 1901, Gillard in France conducted possibly the first chest radiographic investigation in a military setting (22). Another French study conducted in the years 1922 and 1934 by Sieur (22) involved 106070 military servicemen who underwent chest X-ray examination. Active tuberculosis was found in 0.17% of those screened. The value of routine chest X-ray examination to identify recruits with tuberculous was soon

apparent to military establishments in other countries. From a military point of view, the exclusion of tuberculous recruits could provide the following advantages:

- The spread of tuberculosis within the army could be limited by isolating infectious sources.
- The time lost due to disease could be minimised.
- The economic burden of providing care in later years would be minimised, even though prior to World War II this was not the case in the Netherlands. The Dutch army treated all persons found with tuberculosis at induction. This practice was in sharp contrast to the system in other countries where persons with tuberculosis at induction were not recruited but were passed on to civilian organisations for treatment.

In 1931 a compulsory chest X-ray of all members of the armed forces was initiated in in Germany 1931 (22). In that year, out of the 106070 persons examined radiologically, 1.68% had active pulmonary tuberculosis and 1.75% had the inactive form. In the Netherlands it was Burger (23) who recommended that chest X-rays form part of the routine medical check-up of all those enrolling into the RNLA. Burger had at the time completed a mass chest X-ray screening program for employees of the Philips factory in Eindhoven. He was quick to recognise the importance of chest radiology in a military setting. In this period, J.C. Diehl was the Surgeon General and he too appreciated the immense potential of radiology as a tool to identify asymptomatic tuberculosis cases within the army. He encouraged and facilitated efforts to adapt this form of tuberculosis screening for recruits into the RNLA. Subsequently, the first trial with X-ray screening was initiated in 1933. It took nearly four decades after Röntgen's discovery of the X-rays before the RNLA supplemented physical examination and history with radiography in to improve the chances of identifying active pulmonary tuberculosis cases to minimise the induction of tuberculous recruits. This first trial involved 1001 recruits who were reporting for military duty. The results were viewed with gratification since six cases of active tuberculosis were found, which otherwise would not have been identified through physical examination alone (23). Studies elsewhere had also shown that chest X-rays identified some persons with advanced tuberculosis with minimal or no symptoms (24-26). Thus the chest X-ray became an indispensable tool to identify not only early but even extensive tuberculous lesions that could be present without symptoms.

By 1936, S.W. Praag had succeded Diehl as Surgeon General. Just like his predecessor, Praag also was convinced of the value of radiography. In 1936 the RNLA officially incorporated chest radiology as part of the routine screening of recruits. Between March

1936 and June 1937, 86033 recruits to the RNLA underwent chest radiographic examination (23). The yield from this mass chest radiography was 44 cases of open tuberculosis (about 0.5%), 262 cases of "active lung processes" and 16 cases of pleuritis. During the general mobilisation of 1939, X-ray screening was extended beyond the conscripts to include military personnel already in active service.

However the chest X-ray at the time was not devoid of problems. A major bottleneck was the cumbersome radiographic equipment available before 1936. This made it difficult to radiograph every newly inducted conscript on recruitment into the Army. Botenga (27) pointed out that another major frustration with the equipment at the time was its inability to record the fluoroscopic image. To overcome this deficiency, Botenga conducted studies at the Military hospital in Utrecht in collaboration with a private firm - they investigated possibilities to develop a practical way of photographing the fluoroscopic image (22). These attempts were abruptly and prematurely ended when the Germans occupied the Netherlands in 1940. But also by this time (1940) the idea of photographing a fluoroscopic image had already been developed by the Brazilian radiologist Manoel de Abreu in 1936 (28). De Abreu conducted mass X-ray surveys in a number of South American countries. This improvement of the radiographic technique and equipment revolutionised radiography and made it possible to screen hundreds of persons within a short period using Mass radiography (Mass Miniature Radiography - MMR). This approach was considered as the most effective method to detect tuberculosis and the technique was extensively employed in many surveys of military populations. MMR was not a "new" diagnostic technique in the sense of providing better identification of tuberculous cases. It was a faster and efficient screening method well adapted for mass surveys. The switch over to use MMR was looked at with suscipicion in certain circles. Some considered the use of small sized films in the diagnosis of tuberculosis as an oversimplification of case finding and doubted its usefulness in tuberculosis control (29). Eventually the wider appreciation of the advantages of MMR as a screening method prevailed over such criticisms.

In 1938, Germany began using the new techniques of Abreu to conduct chest radiographs of military servicemen (30). In Britain and the United States the first MMRs for examining recruits was started in 1941 by the Royal Navy and US Navy respectively (31-34). The policy of radiographing all new US army recruits followed a year later (35). These new techniques were not to be adapted in the Netherlands until after the end of World War II.

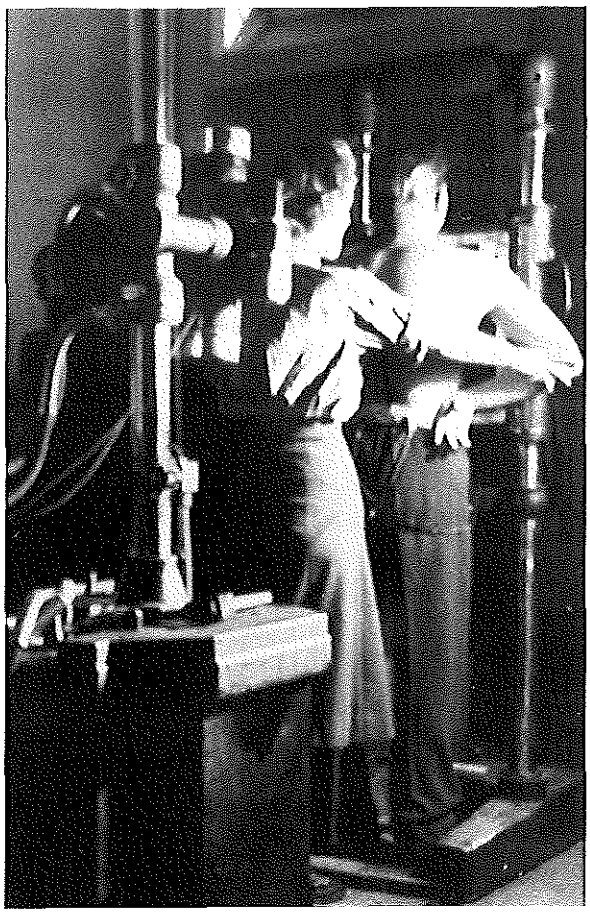

Figure 2. The Watson radiographic equipment used during a chest x-ray session of young military recruits, ca. 1952. (Photograph DMGZ archive)

Tuberculosis control between 1945 - 1955

In the period 1944-1945, just before the liberation, the incidence and mortality due to tuberculosis in the Netherlands was reported to be high (36). War conditions had brought about great deprivations and in the winter of 1944 - 1945, there was famine in large parts of the country. These factors, coupled with the breakdown of social services resulted in increases in tuberculosis cases. It was therefore a necessity to reactivate the tuberculosis control measures crippled during the war. With the end of the war, the recommendations of Burger to carry out routine chest X-ray screening of all army recruits could now be followed. It was S.L Fransman, an army physician who initiated steps to establish the "Dienst Röntgenologisch Borstonderzoek - ROBO " - the military X-ray screening department. It is also due to him that in 1945 the new technology of MMR was used for the first time in the Netherlands (37).

Fransman recognised the importance of identifying cases of tuberculosis through this method to safeguard the health of other recruits during the period of their induction into the military. By August 1945, the first photofluorographic unit, a "Watson", was installed in Amsterdam (27). It was three years later that MMR was used for the indiscriminate screening of the general Dutch population (37). The "Watson" was a major advancement – it facilitated radiographing many recruits and enabled the ROBO to X-ray this group of persons within a short stay in the barracks compared to the pre-war average of three weeks (figure 2 is a picture of an RNLA clinic with the Watson in action). This was an important step forward as the army recruits had to stay in quarters where close contact was inevitable while awaiting medical examinations. In this kind of setting, a conscript with open tuberculosis could be a source of infection to a large group, hence the emphasis on shortening the duration between induction and the first chest X-ray. The average duration of stay of recruits with chest X-ray evidence of tuberculosis from time of first day in the barracks to radiographic investigation in the year 1951 - 1960 was studied by van Alten and his results are reproduced in table 1 (22).

Table 1. The average time interval between first day in barracks and when recruits underwent chest X-ray examination – for recruits who were found to have active disease

Year	Average interval (days)
1951	6.8
1952	5.8
1953	6.9
1954	6.9
1955	6.8
1956	6.8
1957	8.2
1958	5.9
1959	3.7
1960	3.0

These results show a shortening of the interval in 1960 by 56% over the 1951 average of 6.8 days. This was made possible through a policy of having mobile units that X-rayed recruits at different sites of induction. Figure 3 shows a mobile x-ray unit that was used by the army tuberculosis programme. This specially designed bus traversed the country radiographing army recruits at different induction centers. With the development of better technology, it was possible by 1967 to X-ray all recruits on their *first* day at an induction centre (38). Limiting time that recruits took before the chest X-ray examination did not mean that radiography was the ideal means to identify cases of tuberculosis disease. Infact a hitherto unrecognised problem presented itself after World War II in civilian and military populations. This was the finding of variability in the interpretation of chest X-rays even by experienced radiologists (39-41). Discrepancy was also noted in the same radiologist when examining the same films after a short interval of time (intra-observer disagreement). To minimise this problem, Birkelo et al. (39) recommended that all survey films be read by at least two independent persons ("double reading"). In the Netherlands, Griep reviewed over 3,000 films that had earlier been examined and reported upon during a mass survey. In that study, all the films were studied and reported upon by six persons experienced in interpreting chest X-rays. It was found that 27.8% of the films with tuberculous lesions had been misinterpreted in the earlier reading.

Figure 3. The ROBO bus at a military complex, ca. 1959. (Photograph DMGZ archive).

In another investigation, Griep demonstrated that double reading of chest films identified 91% of all films with tuberculous lesions (42, 43). From the results of this Dutch study and of other studies conducted elsewhere, the ROBO department incorporated the policy of double reading in 1953. The ability to conduct chest X-rays in large populations with relative ease set the pace for epidemiological studies of tuberculosis as it occured in the Netherlands Army. In their study which consisted of 123,902 soldiers, Bangma and Aulbers (44) found that there were 22 times more recruits professional soldiers with active tuberculosis. This was surprising especially since barracks' with their close living conditions are considered places in which infectious respiratory diseases could spread easily. They thought it most likely that the difference was related to the extent the two groups interacted with the general population. Professional soldiers were confined to barracks' and only went home on the weekends whereas the recruits were directly coming from the general population where the degree of exposure to tuberculosis was higher. Also, the professional soldiers underwent frequent chest X-ray examinations so persons with active disease could be identified and isolated. Recruits coming directly out of the general population lacked this regular control. In the study by Tuinstra and Van der Linde (19) it was observed, however, that tuberculosis among recruits was 1.3 times higher than among similar age groups in the

general population. Since the films in both groups were not read by the same radiologists, these differences are possibly largely methodological. Tuinstra and van der Linde also observed that the cases of active tuberculosis in the army were showing a downward trend, and that there was a seasonal pattern in the case finding with most active tuberculosis being in spring. This downward trend in the cases of active tuberculosis has continued to be observed within the military to this present day.

The first chest X-ray screening in 1933 was directed at recruits with the intention of preventing tuberculous cases from entering the army. With the formation of ROBO in 1945, the X-ray program was expanded beyond the recruit population to involve professional soldiers and civilians working for the RNLA. The ROBO tuberculosis control program provided the following measures:

1. Recruits into the RNLA had to undergo a chest X-ray as part of the medical examination at induction. Persons found to have an abnormal chest X-ray would therefore not be enrolled into the army, but channeled to the civilian health services for further management. Those found eligible for the army were expected to report for duty in a period of 12 months.
2. Recruits reporting for duty had to undergo a second chest X-ray within a short period after reporting. Cases of tuberculosis missed out between induction and the start of active service were usually found. Such persons were also discharged from the army.
3. Röntgenographic examination of the chest of all recruits after six weeks of stay in the service. This examination at the time was thought to be useful to identify cases of viral pneumonia which were common in such crowded conditions during the first six weeks. An occassional case of tuberculosis was also found during this examination.
4. Annual chest radiological examination of all military personnel and civilians in military service who were 40 years of age or younger.
5. Persons older than 40 years (both civilian and professional soldiers) had to undergo a chest X-ray twice a year. This examination was influenced by the fact that persons in this group had a more increased risk of developing lung malignancies and it was in that period found desirable to screen these at an early stage.
6. All military persons being deployed to foreign countries had to undergo a radiological examination of the chest. Persons found with abnormalities were not deployed.

7. All military personnel being discharged or released from active service also underwent a radiological chest examination.
8. A chest radiograph for all reserve military personnel who report for active military duty.
9. Persons showing abnormalities suspected of tuberculosis were referred to a military pulmonologist for further assessment to verify such a diagnosis.

It is therefore evident that the ROBO not only aimed at controlling tuberculosis but also at a strategy providing comprehensive health care for persons employed by the military. In 1955 the army incorporated the tuberculin skin test (Mantoux) as an extra tool into her armament to fight against tuberculosis.

Tuberculin Skin Testing in the RNLA: 1954-1995

Although it were Duit and Vreeling in 1954 who first employed a tuberculin skin test as an epidemiological tool in the RNLA, the tuberculin skin test was made part of the routine physical examination for military recruits in 1955. This followed the recommendations of a study group "De Adviescommissie T.N.O. inzake het BCG vraagstuk" which was a collabora-tive work between T.N.O and the Military Health Service (22). This study group was originally set up to study the suitability of BCG vaccination in the Netherlands on request of the Health Council (Gezondheids Raad). The army as a group represented a suitable and reliable population for investigations on this subject. Hence the recommendation for tuberculin skin testing in the army was based on the need to:

1. Provide information on the tuberculin sensitivity in the Netherlands of males with an average age of 19 years.
2. Investigate at a later stage the value of BCG in tuberculine negative recruits.

It is important to note here that this study group was the fore-runner of the International Tuberculosis Surveillance Center (ITSC), a collaborative body bringing together tuberculosis experts from the International Union Against Tuberculosis (IUAT), WHO, TNO, KNCV and the Department of Military Health Care (DMGZ).

From 1955, the RNLA tuberculosis program had an additional diagnostic method supplementing the chest X-ray in identifying persons infected with tuberculosis. The late implementation of tuberculin skin testing in the RNLA is in contrast to the policy in other countries. In the United States Navy, routine testing of recruits became a reality in 1948. The recruits were skin tested with intermediate strength purified protein derivative (PPD) by the Mantoux method (45).

The late introduction of the tuberculin test to control tuberculosis in the RNLA is possibly due to the controversies surrounding tuberculin as such and the epidemiological situation in the Netherlands. Before World War II negative tuberculin reactions among persons with radiographic evidence of pulmonary calcifications were observed in the United States (46-49). Then, such calcifications were synonymous with unequivocal evidence of healed tuberculosis. Therefore the findings of these non-reactors led to serious doubts and controversies on the use of tuberculin. A common argument at the time was on the erroneous assumption that tuberculin sensitivity dissappeared with complete healing of the tuberculous focus (14). Later confidence was restored in the tuberculin test when it was found that many of these calcifications were due to histoplasmosis (50, 51). Another factor that influenced the late introduction of skin testing in the army was to be found in the distribution of tuberculin sensitivity in the population. In the early part of this century, the usefulness of the tuberculin test was limited as a large percentage of the Netherlands population was infected with *Mycobacterium tuberculosis* or *Mycobacterium bovis.* The presence of infection with *M. bovis* therefore would result in a large population of persons with positive results to the tuberculin skin test. In 1946 Green (52) published his classic chart (reproduced here in table 2). The chart indicated existence of cross-reactions with all six PPDs. Only small differences existed in the specificity of the human, bovine and BCG PPDs. As a result, the tuberculin skin test would not have been a helpful tool to identify cases of active tuberculosis then since many persons were believed to harbour *M. bovis* infection. However in the 1950s the incidence of *M. bovis* infections had substantially decreased after bovine tuberculosis had been eliminated in 1956. It is only then that the epidemiological potential of tuberculin became apparent.

Table 2 Specificity factors of PPD antigens prepared from different organisms, and used to test guinea pigs sensitized by infection with the homologous and heterologous organisms (52).*

Type of Sensitization	Type of PPD Antigen					
	human	bovine	BCG	johne	avium	phlei
human	1	2	2	30	20	150
bovine	1	1	2	30	40	150
BCG	1	2	1	30	20	150
johne	10	10	10	1	3	50
avium	20	40	40	3	1	100
phlei	150	150	150	50	100	1

* The number of weight units of heterologous PPD required to elicit the same intensity of skin reaction as one unit of homologous PPD.

Before the work of Florence Seibert of the Henry Phipps Institute, Philadelphia, in the 1930s (53), there had been little attempt to standardise tuberculin – then not a simple unit but a complex substance. Green (54) has referred to this old tuberculin (O.T) as:

> *".... any witches' brew derived by evaporation of any unspecified fluid medium in which any unspecified strain of mammalian. M. tuberculosis had been grown, provided its potency matched that of another witches' brew kept in Copenhagen and called international standard, or any allegedly equivalent sub-standard thereof, when tested on an unspecified number of guinea-pigs without worrying too much about statistical analysis of results."*

Florence Seibert prepared precipitates of O.T. which she called purified protein derivative (PPD). In 1941, Seibert and Glenn made a single large lot for deposit as the standard reference material in the United States (55). This lot known as PPD-S (the "S" after Seibert) was established as the International Standard for Purified Protein

Derivative of Mammalian Tuberculin by the WHO Expert Committee on Biological Standardization in 1951 (56). In addition, it remained unclear what dosage of PPD would be suitable for use. The practice of using a series of skin tests with graduated doses of tuberculin was clearly inappropriate for large groups of persons. It was Furcolow and collaborators in 1941 (57) who showed that 5 TU of PPD tuberculin was the limit dosage that would detect tuberculous infected persons and minimised the number of nonspecific reactions. Palmer et al (58) and Goddard et al (59) later found that in the USA, 5 TU dose of PPD-S was highly efficient in identifying persons with pulmonary infilitrates and calcifications who did not react to histoplasmin.

It was also known even before 1955, that most of the strong-dose tuberculin sensitivity was not caused by tuberculous infection and doubts also began emerging about the small reactions to 5 TU (14). It is now generally believed that these reactions are caused by sensitisation with nontuberculous mycobacteria (NTM) (18). Through such cross-reactions as a result of shared antigens between PPD and NTMs, false positive results would be common in geographical areas with a high prevalence of NTM. This kind of sensitivity to tuberculin as a result of cross-reactions with NTM has been referred to as "aspecific" or NTM sensitivity. In his study of school children in different countries published in 1967 and 1968, Bleiker found that the Netherlands with a prevalence of 4 percent was among the countries with a high prevalence of NTM sensitivity (60,61).

From 1955 to 1958, recruits were skin tested using the Mantoux technique with 5 tuberculin units (TU) of PPD RT 22 (Staten Serum institut, Copenhagen, Denmark) following the TNO recommendations (22). Before 1955, 10 TU of PPD-S was in regular use in most countries but was observed to cause many untoward reactions such as blistering at the injection site, fever, joint pains. In addition a dose of 10 TU elicited nonspecific reactions. The TNO BCG work group collected information on recruits inducted in the years 1955 and 1956 and an attempt made to find if a regional difference in the prevalence of tuberculin sensitivity existed (13). Figure 4 presents this distribution by districts of the tuberculosis control program in the Dutch population.

This figure showed that the tuberculin sensitivity ranged from 14 to 30%. The lowest percentage of tuberculin sensitive persons were observed in the northern provinces. The most important factor influencing this distribution was the rate at which bovine tuberculosis had been controlled in the south and north. The northern part eradicated tuberculosis in herds long before the same results were realised in the south. These regional differences in controlling tuberculosis in herds was influenced largely by economic reasons. After the World War II United States troops stationed in western Germany made a decision to buy their beef and milk supplies from the northern parts of the Netherlands. However beef would only be accepted if the meat was free from bovine

tuberculosis. This led to increased efforts to control tuberculosis in the northern herds (Bleiker, personal communication). It has also been suggested that the population density had an influence on this distribution, as the northern parts are less populated in comparison to the south: therefore the chance of coming into contact with an infectious case of tuberculosis was greater in the south (13).

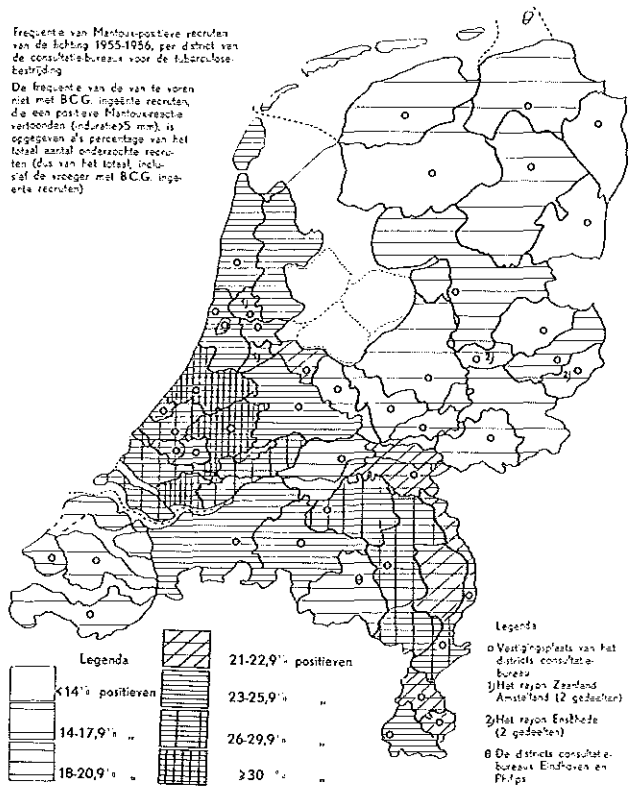

Figure 4: The percentage frequency tuberculin sensitivity among recruits 1955 – 1956 based on their places of origin in the Netherlands.

A Search for the Best Tuberculin Concentration

In 1956 Guld and colleagues observed that PPD was unstable, and that this instability affected the potency of the tuberculin (62). This instability was observed with tuberculins RT 19,20, and 21. They did not observe this effect with other tuberculin concentrations. The possibility that tuberculin was being adsorbed on the glass ampoules was suggested. Since the army was using PPD RT 22, there was concern as to whether this preparation was subject to the same effect as that seen by Guld and collaborators. Studies by Bleiker and the Tuberculosis Research Office in Copenhagen

showed a similar instability which resulted from the adsorption of PPD RT 22 on the glasswalls of the ampoules (63). The Tuberculosis Research Office in Copenhagen solved the problem by adding a small quanty of a detergent called Tween 80. This product stabilised PPD and its addition made it possible to diminish the strength of the tuberculin test liquid to 1 unit. From January 1959, recruits into the army were skin tested with 1 TU of PPD RT 23 + Tween 80 by the Mantoux method. Bleiker showed that 5TU PPD RT 22 and 1 TU of PPD RT 23 + Tween 80 had a similar biological activity (64). Thus the tuberculin sensitivity results of the period 1955 to end of 1958 could be fairly compared with those that would be found using the new concentration of 1 TU. By 1963, the World Health Organization (WHO) had adapted 1 TU of PPD RT 23 as the recommended dosage for the tuberculin test (65).

To coordinate the activities of tuberculosis control within the army, a special "Mantoux" group, combined RNLA/TNO teams, was established in 1958. Nurses were trained how to properly apply the Mantoux skin test. To obtain comparable results it was essential that attention was paid to how the technique was performed. The ROBO and the Mantoux group were finally brought under one organization, the Department of Military Health Care (Dienst Militaire Gezondheidszorg - DMGZ) under Branger. The DMGZ emphasised preventive health care and a close collaboration was established with other institutes designing strategies to reduce disease burden through prevention. These included The TNO, present RIVM and NIPG. These civil organisations co-operated with the army in conducting a number of disease preventive measures such as inoculations against smallpox, tetanus, polio, diphtheria, and BCG vaccination (when indicated). This relationship between these organisations and the military has flourished till this day. The ROBO and the Mantoux departments of the DMGZ embarked on a large scale program of screening the military population for tuberculosis. The results from these activities were used to give an insight into the changing epidemiology of tuberculosis in the Netherlands in general.

In spite of all these reorganisations, there was still room for improvement. In the period between the end of the war and 1960, Van Alten (22) assisted in shaping policy on tuberculosis control. He extensively used the Mantoux skin test in contact tracing of recruits in barracks'. His work underscored the importance of using tuberculin skin testing in conjuction with the chest X-ray in order to arrive at optimal tuberculosis control. He recommended the following measures to minimise the risk of recruits with infectious tuberculosis spreading the infection in a barracks setting:

1. Apart from the obligatory dual reading of chest X-rays of recruits, a third reading is necessary for those with a positive tuberculin skin reaction at entry into the military service.

2. Recruits with a positive skin reaction or those with a positive history of tuberculosis in their immediate family should regularly be controlled by a chest physician.
3. All recruits with a positive skin test should undergo a chest radiograph at three months interval during their stay in the Army.
4. A central administrative and supervisory body is indispensable in maintaining a registry on tuberculosis control activities.
5. Persons entering the military service should undergo a chest X-ray on the very day of enrollement and this should under no circumstances be postponed.
6. If the number of Mantoux conversions amounts to over 10 per cent in case of contact tracing in a group of exposed persons, the scope of the contact examination should be broadened.

These recommendations were to a large extent incorporated into the tuberculosis control policy of the army. Although appreciated, some were found difficult to implement. A third chest X-ray reading of all those with a positive Mantoux and the three monthly chest X-ray proved a difficult organizational problem. The latter measure was modified to twice yearly chest radiography but was later abandoned because of the small number of recruits found with active tuberculosis during such subsequent chest X-rays. In his fourth recommendation, Van Alten recognised the importance of a tuberculosis registry in keeping track of the epidemiological trends of disease. Over the years this registry has provided a unique set of data on tuberculosis control. Sutherland and collaborators (66) stated the following in regard to this unique set of tuberculosis control data:

> *"The series of tuberculin surveys of male army recruits in the Netherlands, ... is almost certainly the best and most informative material of this type."*

Walig (67) examined the change in the tuberculin sensitivity (prevalence of *M. tuberculosis* infection) patterns of army recruits during the period 1956 to 1969. His results showed a downward trend in prevalence. Indeed this downward trend has continued to be observed since the start of the Mantoux skin testing. Figure 5 shows this downward trend among army recruits over a span of 4 decades.

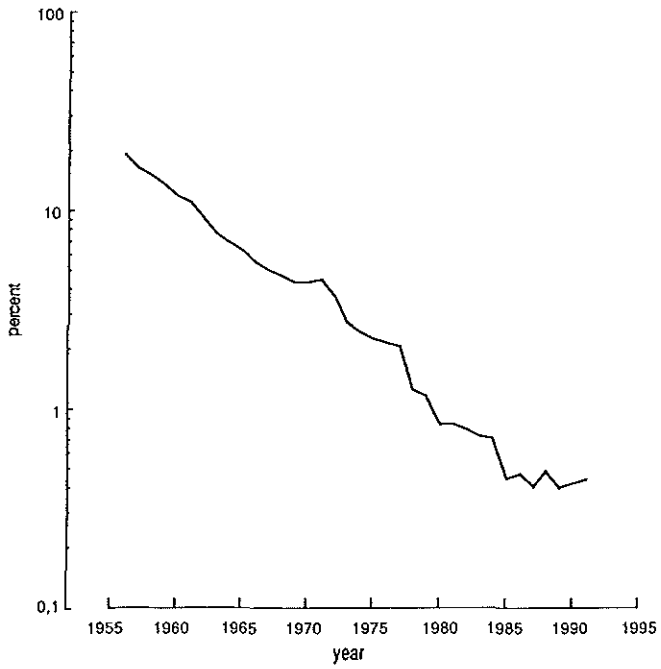

Figure 5. Prevalence of tuberculous infection among army recruits 1956 - 1995 (the y-axis is a semilog scale).

During the period 1956 to 1969, the percentage of recruits reacting with a positive Mantoux, that is more than 9mm diameter, decreased from 19.2% to 4.4%. In 1995, the percentage of recruits with a positive Mantoux test was 0.42. The downward trend in the prevalence of tuberculosis infection among recruits reflected the declining trend within the general Dutch population from which the group of recruits is drawn. Unlike in the general population, in the army active tuberculosis cases have consistently continued to decline. In the general population, tuberculosis cases showed a decline from 145 cases per 100,000 persons in 1950 to 10 per 100,000 persons in 1980 with the lowest number of registered cases being in 1987 (68). Since then, the number of tuberculosis cases has increased as pointed out earlier. Figure 6 shows the trend of active tuberculosis cases within the army in a period of 40 years.

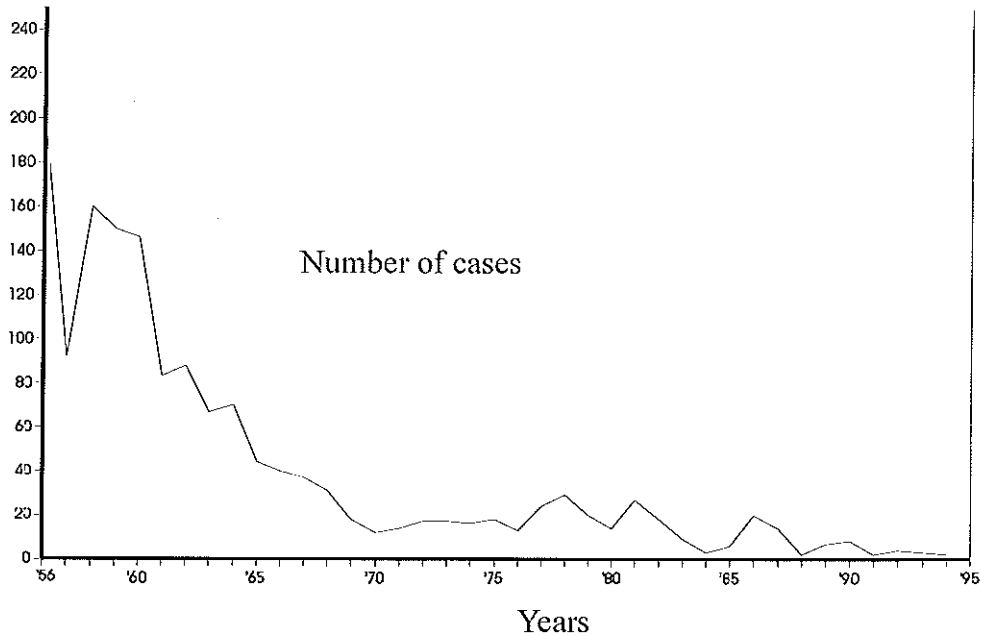

Figure 6. Notifications of all forms of tuberculosis in the army, 1955 -1995.

The increase in tuberculosis in the general population has been attributed to risk factors such as:

- immigration from countries where tuberculosis is widespread
- drug addiction and or other associated social problems such as homelessness
- HIV infection.

Whereas these factors are notable in the general population, they are not prominent in the Dutch army. Their insignificance in the army may therefore explain the observed downward trend of active tuberculosis within the military. For example in 1995, foreign-born persons accounted for only about 0.02% of the conscript population. To what extent these factors will be of importance within the military will depend largely on the interaction between the military and these risk groups on the one hand and the intensity and effectiveness of the civil tuberculosis control efforts on the other.

Recruits into the army account annually for about 50% of each male population cohort in the Netherlands, therefore information gathered from tuberculin testing provides a rare chance to examine the epidemiological trends of tuberculosis over time. Using this Army data, Bleiker has applied Styblo's calculations to give an insight into the age

prevalence of tuberculosis infection in the indigenous population of the Netherlands for the year 1945, 1975, and 2005 (69). These are illustrated in figure 7.

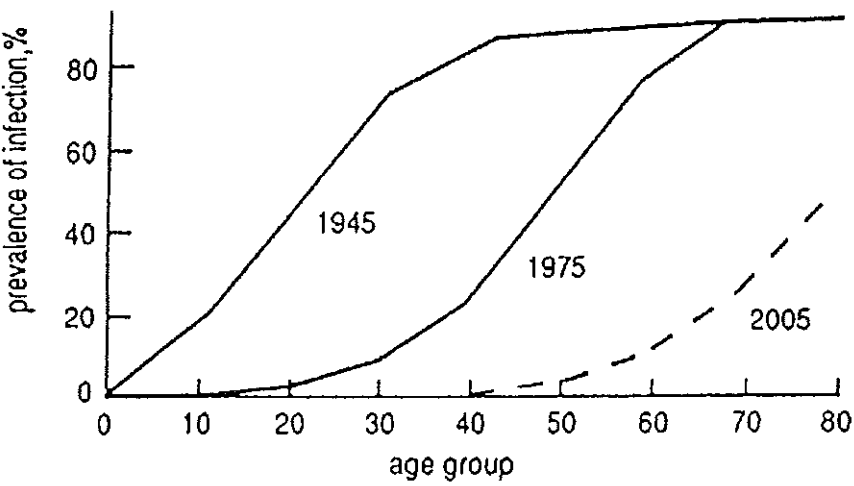

Figure 7. Estimated prevalence of tuberculous infection by age: The Netherlands, 1945, 1975, 2005 (Bleiker, 1984)

Another important measure of the epidemiology of tuberculosis is the annual rate of infection with tubercle bacilli, also known as the annual risk of infection (ARI). This is defined as the percentage of the population that is infected or reinfected during a calendar year. The ARI is the best single indicator for evaluating the tuberculosis problem and its trend in both developed and developing countries. The data from army recruits has been of extreme value to calculate the ARI for the Netherlands population. Styblo (18) has pointed out that the ARI, unlike disease notification rates, is not linked directly to the case-finding and treatment measures of the tuberculosis program. The rates of the ARI have been derived since 1956 from the data on recruits. The decrease in the ARI was 13.7% annually between 1956 and 1965, 10.4% annually between 1966 and 1979 (66) and about 8% between 1980 and 1990 (70). The changing ARI is shown in Figure 8.

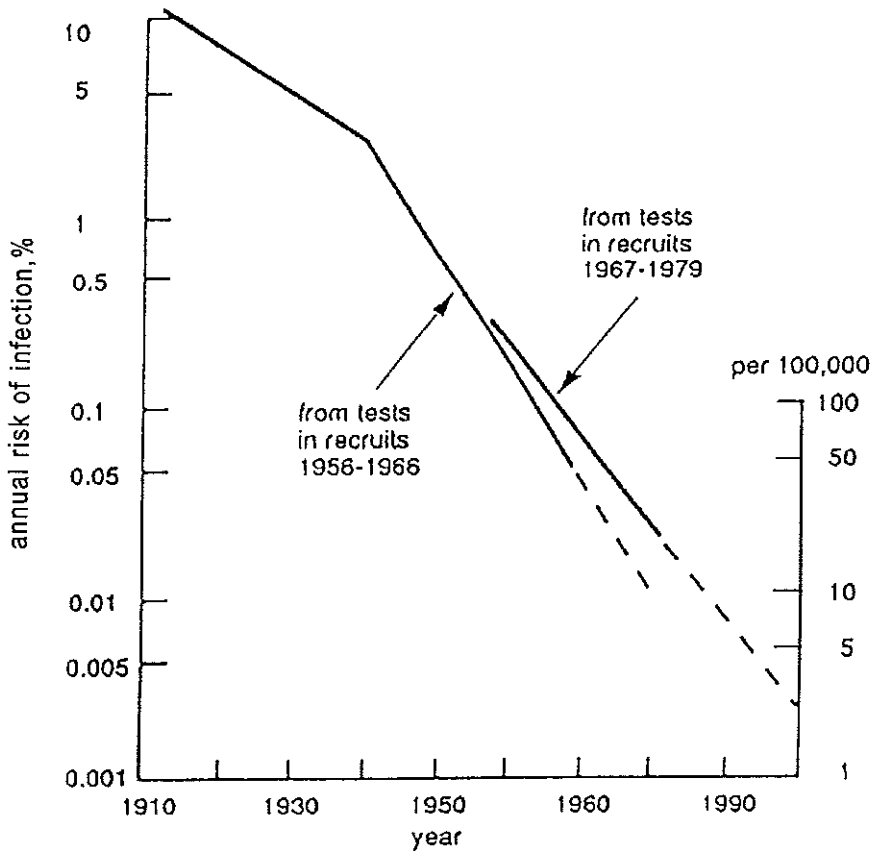

Figure 8. Annual risk of tuberculous infection: The Netherlands 1910 -1979 (From Sutherland (66)

Policy on BCG Vaccination

In the early 1900s, Calmette and Guérin working at the Pasteur Institute in Lille, France, during many years attenuated a strain of *M. bovis* (BCG). The first administration of the vaccine in humans took place in Paris in 1921. Since then, BCG has become one the worlds most used and also most controversial vaccines. A worldwide assessment of its protective value has indicated greatly divergent results - from 0 to 80% (11). These conflicting issues regarding BCG are underscored best by Rouillon and Waaler (71):

> *"When and where is it indicated to undertake, to pursue or to discontinue BCG vaccination? This is the question which today ... gives rise to burning controversies, often strongly loaded with emotion, as is the whole story of BCG."*

A look at different practices in other national Armies clearly show these confusing aspects of BCG. In France, it has been compulsory for all soldiers to undergo a BCG vaccination since 1952, if this was not given in childhood. The overlap between national public health policy and military health care meant that all incoming recruits in some countries are already vaccinated and if not, BCG is administered. One of the largest study to examine the prophylactic effects of BCG in a military population was the series of over 60,000 Swedish national servicemen conducted by Dahlström and Difs (72) during1941-1946. This Swedish retrospective study found that BCG appeared to confer protection against primary tuberculosis only after two months from vaccination, or against other forms of tuberculosis only after six months. In the Netherlands, Bergsma studied the potential protective effect of BCG against primary tuberculosis by studying a group of student nurses working in the sanatorium "Sonnevanck". His findings confirmed the observations of Dahlström and Difs (22). Muller and Edens had similar findings (22). Other studies using oral BCG in children did not find much optimism. This study conducted in the cities of Hilversum and Schiedam registered a high incidence of otitis media complicating oral BCG vaccination (Bleiker, personal communication). Such complications, some directly linked to BCG, discouarage the use of this vaccine.

Within the military, there were people who advocated for a policy of BCG vaccination as a result of these studies. For example, Duit and Vreeling (17) in 1955 wrote:

> *"Naar aanleiding van de tuberculose-epidemie in de Noordelijke garnizoenen komen wij tot de conclusie, dat tengevolge van het grote aantal anergischen onder de militairen de mogelijkheid geschapen was, dat één soldaat met open tuberculose een epidemie deed ontstaan, die ons inziens voorkomen had kunnen worden door algehele BCG vaccinatie van het leger"*

The above argument by Duit and Vreeling advocating BCG vaccination for the entire army was expressed in financial terms by Tuinstra and Van der Linde (19). Using data based on the number of active tuberculosis cases seen in the army during 1951-1955. They applied the findings of Dahlström and Difs to calculate the number of tuberculosis cases that would have been prevented by early BCG vaccination. Their findings showed that during the five years period, the BCG protective effect would have saved the

military over five million Dutch guilders in treatment costs. However as early as 1952, the Health Committee advised the Minister of Health to *limit* the use of BCG to the following groups (22).

a) Persons exposed to a known infectious case of pulmonary tuberculosis.

b) Persons for whom it was unclear if there had been any exposure to a given infectious case of tuberculosis, or persons who through their nature of work or circumstances are at increased risk of exposure to tuberculosis.

Subsequently, BCG has not been used on a large scale in the Netherlands and has only been limited to selected groups. Despite all the arguments for its use within the Dutch army, the positive tuberculin reaction caused by BCG vaccination was considered a major drawback in the use of the tuberculin test as an epidemiological and clinical tool. However the use of BCG was not summarily rejected by the military. By 1956, its use was confined to the following groups (22):

a) All military health-care workers (including the sub-department "Milva" which consisted almost entirely of females working in the military Health sector).

b) Military personnel exposed to a known infectious case of tuberculosis.

BCG would only be administered if persons in any of the above groups were found who had a negative tuberculin reaction and the chest X-ray results showed no evidence of tuberculosis. With the observation in 1959, that the decline in tuberculosis morbidity among military persons was not as rapid as that seen in the general population (table 3), the Ministry of Health and Soical Affairs recommended BCG vaccination on a voluntary basis within the military. This came into force within the military in 1960.

Table 3. A comparison of tuberculosis morbidity among recruits and the general population (13)

Year	Recruits per 10,000	General population per 10,000
1951	24.4	25.7
1952	25.1	23.1
1953	20.9	19.5
1954	18.4	15.6
1955	15.6	12.7
1956	13.8	10.3
1957	7.9	9.5
1958	10.3	6.5
1959	16.4	4.9

There are no exact figures on the number of persons who underwent BCG vaccination voluntarily following the above recommendations. Tuinstra and Van der Linde (19) in 1955 had already shown that tuberculosis in the group of recruits was much higher than in the general population. The difference between military personnel (by and large recruits) and the general population regarding tuberculosis morbidity might be a result of increased risk to infection and disease within the confines of a military barracks. This argument however directly contradicts the findings of Bangsma and Aulbers (44) who showed that professional soldiers had less tuberculosis than recruits, suggesting that the argument of living conditions within the close confines of a military barracks was not a big factor, at least in the Netherlands. It should however be pointed out that the living conditions of professional soldiers were relatively much better than those of recruits and that this might have strongly influenced the results of Bangsma and Aulbers. It is also possible that through its intensive tuberculosis program the army could detect more cases of tuberculosis than their counterparts in the civil tuberculosis program. This would therefore be reflected in higher numbers of tuberculosis being recorded in the army tuberculosis register.

In 1966, the military broadened the group of persons to be vaccinated with BCG. This included persons being deployed to areas considered as with a high risk of tuberculosis infection. Military personnel deployed as part of a United Nations unit in areas of conflict were also to have a BCG vaccination. These recommendations were similar to those already in civil practice. The number of persons coming into the army with a history of BCG vaccination has continued to decline. In 1956, 11.7% of the recruits already had BCG before joining the army. This percentage was 0.4% in 1993 and 0.017% in 1995. With the dynamic nature of the Dutch society, more army recruits who immigrated from countries with a policy of childhood BCG are being enrolled in the army. In 1995, the Mantoux department registered a total of 306 recruits with evidence of past BCG vaccination of whom 74% were foreign born.

Isoniazid Prophylactic Therapy (IPT)

Ferebee and Palmer set the pace for isoniazid chemoprophylaxis following their experiments with animals (73). In 1956, Debré (74) described the use of isoniazid to prevent the development of progressive tuberculous disease in cases of primary tuberculosis. In 1960, the army started with the isoniazid prophylactic therapy (IPT) program for persons showing a conversion of the Mantoux reaction. This was referred to as secondary INH chemoprophy-laxis. In his study begun in 1960, Hölscher (75) investigated the protective effect of INH in Dutch marines showing a positive Mantoux reaction. This was a double-blind study involving 261 with a positive Mantoux. Of

these persons, 133 received INH and 128 were given placebo. The results showed that after seven years of follow-up, 9.5% of the persons treated on placebo developed pulmonary lesions suspicious of tuberculosis compared with only 0.8% in the INH group. However, as Walig (67) pointed out, the application of secondary INH prophylaxis was difficult in many cases – as symptoms of disease were already present when the positive Mantoux reaction was detected. For more effective interventions Walig recommended the use of the primary INH prophylaxis which was defined as giving INH to possibly very recently infected persons with a still negative Mantoux reaction. INH as an intervention tool in the army tuberculosis control program is presented in chapter three.

Epidemiology and Changes in Control Measures

The policies of the army tuberculosis program have changed over time. As results there are many important changes affecting the tools used to control tuberculosis over the years. Many of these changes are mainly results of the declining importance of tuberculosis within the army and the general population.

It has already been pointed out that the number of tuberculosis cases and the prevalence of positive tuberculin sensitivity has consistently shown a downward trend in the military. Subsequently the screening methods, largely the chest X-ray were increasingly not identifying tuberculous cases at a rate that would justify their application. Many other disease conditions over time had gained more importance and therefore are being paid more attention than a "search" for tuberculosis. At induction, the medical examination is aimed at detecting persons with health impairements that would pose limitations on their military service and or who might be a source of health risk for others. In the period after the war, tuberculosis was an important factor for not enrolling persons into the military service. Walig (67) studied the number of persons who were not inducted into the service between 1956 to 1969. He showed that persons not inducted as a result of tuberculosis declined from 8.9% in 1956 to 0.4% in 1969. Other diseases such as sarcoidosis were becoming more important than tuberculosis. In 1956, 1.4% persons were not inducted due to sarcoidosis, and this percentage was 1.1% in 1969. Hence the interest in tuberculosis as an important disease began declining - a direct result of the changing epidemiological pattern.

Nearly twenty years after the establishement of ROBO, the military in 1964 began examining whether the returns from the chest X-ray justified the cost. Other aspects that were seriously considered were the risks of radiographic screening. Subsequently, in 1964, the annual chest X-ray for all conscripts was discontinued. These changes in the ROBO program are shown in chronological order in table 4.

Table 4 The chronology of events in the ROBO policy

1964	Annual chest X-ray among conscripts discontinued
1971	Chest X-ray at 6 weeks after recruits have reported for active service is discontinued. The effect of overcrowding which had been responsible for the viral pneumonias during this period had been overcome by establishing more recruitment centers
1973	Half yearly chest X-rays for those above the age of 40 was no longer compulsory
1974	The chest X-ray as a routine medical examination for recruits at induction is discontinued.
1983	Annual chest X-rays for professional soldiers was discontinued as was the chest X-ray at demobilisation.
1986	Chest radiology for reservists reporting for active service discontinued
1988	Chest X-ray for recruits reporting for active service discontinued
1989	All compulsory chest X-rays discontinued

The army ROBO department definitely contributed to the decline of tuberculosis in the army.

Currently the tuberculin skin test is the only method available for diagnosing tuberculosis infection in recruits. However the sensitivity of the test is limited, especially with a lessening of tuberculosis prevalence. The tuberculin antigen is not a single protein but consists of multiple antigens. Partial cross-reactivity of purified protein derivative (PPD) products with non-tuberculous mycobacteria means that a monospecific response that separates *M. tuberculosis* infected from non-infected persons is precluded. This has implications for recommending isoniazid chemoprophylaxis in view of a positive Mantoux test and may result in an overestimate of the annual tuberculin index. The future use of the Mantoux skin test in the military will therefore have to reckon with the NTM factor. Perhaps advances in molecular biology will result in the possibility of using molecularly defined tuberculins based on antigens which are predominantly or exclusively expressed by the tubercle bacilli and not by NTMs. Such a development would remove many of the uncertainities of using the tuberculin skin test in a low prevalence country.

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CHAPTER

3

THE ISONIAZID PROHYLAXIS PROGRAMME IN THE ROYAL NETHERLANDS ARMY: 1984-1995

THE ISONIAZID PROPHYLAXIS PROGRAMME IN THE ROYAL NETHERLANDS ARMY: 1984 - 1995.

Introduction

To effectively control tuberculosis the following aspects have to be addressed:

- *Prevention of tuberculous infection* by:

  a) case-finding and treatment of sputum positive patients. Sputum examination and the chest X-ray are the important tools in this aspect.

  b) isolation of infectious tuberculous patients. Isolation in sanatoriums was a popular tool before the advent of effective chemotherapy. With modern chemotherapy, this practice is no longer necessary as long as persons are not infected with multiple drug resistant tuberculosis.

  c) minimising the opportunities of infection from an unknown case of open tuberculosis through better ventilation and avoidance of overcrowding at home, at work, places of entertainment and public transport such as aeroplanes. There is increasingly more information documenting infections acquired in such circumstances especially in the aircraft environments (1, 2).

- *Increasing host defences* through:

  a) increasing the standard of living. This creates an environment not conducive to infectious diseases that might weaken host immunity.

  b) specific vaccination. BCG has been used extensively in many countries for this purpose.- *Prevention of disease in infected persons:* an important tool in identifying this group of persons is the tuberculin skin test. Persons classified as reacting positively to this test can be given isoniazid prophylaxis.

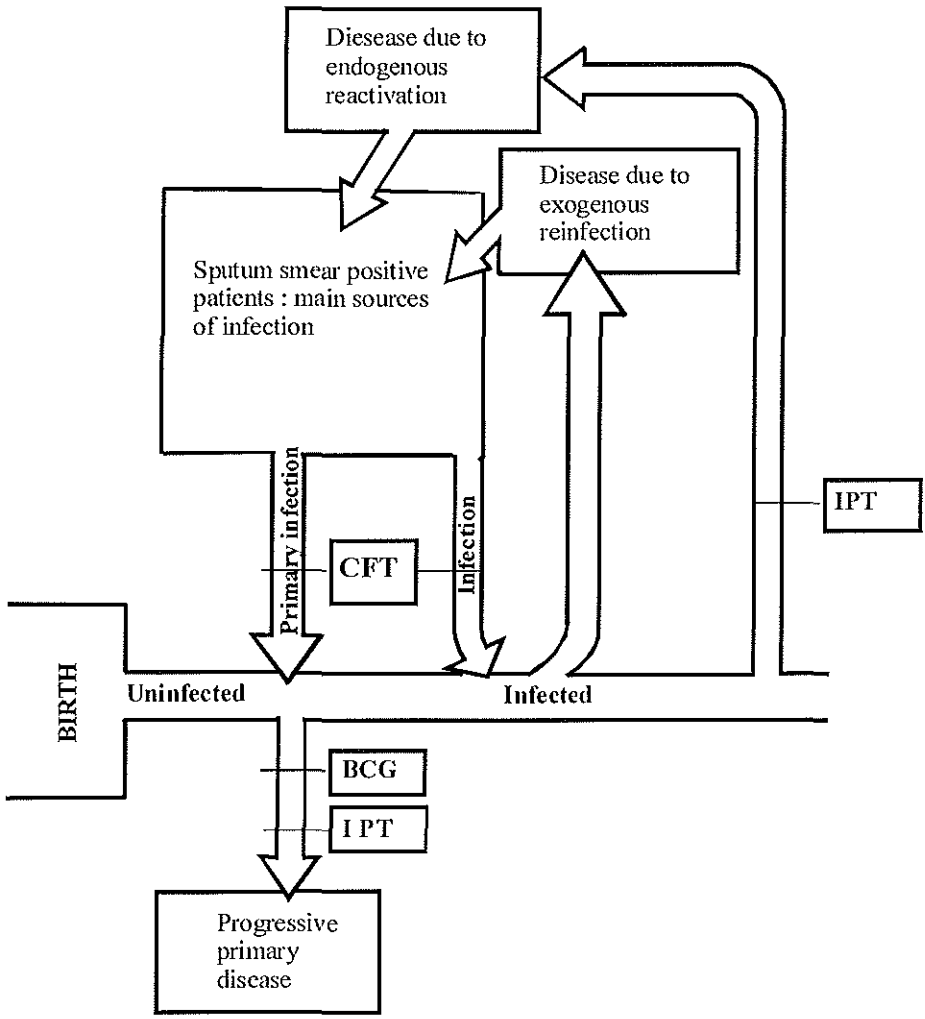

Figure 1. Interrupting the chain of tuberculosis transmission.

These measures if appropriately applied will interrupt the chain of transmission of tuberculous disease among persons. figure 1 (adapted from reference 3) illustrates the points at which the various intervention tools can be applied to interrupt the chain of tuberculosis transmission in man. This model is based on our understanding of the progression of tuberculosis from the time of infection. Prevention of disease in infected persons is by administering isonicotinic acid hydrazine (INH) commonly referred to as isoniazid. Isoniazid is an important bactericidal drug in the treatment of active tuberculosis. Its use as a prophylactic medicament in preventing tuberculosis followed the elaborate animal experiments of Ferebee and Palmer conducted in the 1950s (4). The

use of drug prophylaxis in preventing development of progressive tuberculous disease in cases of primary tuberculosis was subsequently demonstrated by Debre in 1956 (5). Since then isoniazid prophylaxis has found a place as an intergral component in tuberculosis control, albeit the conflicting medical opinions (6). The efficacy of isoniazid prophylaxis in preventing tuberculosis reactivation has been shown to range from 60 - 80 % (7). The rationale of isoniazid prophylaxis for persons without active disease was stated by Ferebee and Mount (8) as: "for the recently infected, to prevent progression to clinical disease; for those with dormant infections, to prevent future activation of diseases. Among persons with subclinical tuberculosis infection mycobacteria are present in small numbers and can easily be reduced using isoniazid (6). The small number of bacteria in subclinically infected persons permits the use of monotherapy without being limited by concerns about development of isoniazid resistance. However as early as 1966, a case report on the development of drug resistant tubercle bacilli in a person with inactive disease in an isoniazid prophylactic program was reported (9). Therefore the exclusion of active disease before iniation of isoniazid prophylaxis becomes of paramount importance. This is mainly done by taking a chest X-ray before initiation of therapy and if found abnormal, a sputum specimen is collected and both Ziehl-Nielsen staining and culture performed.

Initiating isoniazid prophylaxis for infected persons has been mainly hampered by reports of its untoward effects, more especially hepatitis, sometimes fatal, in persons older than 35 years of age. The largest study to monitor the effects of isoniazid prophylaxis conducted by the US Public Health Service (USPHS) indicated that death rates in those older than 35 years and receiving isoniazid was 0.1% (10). Salpeter has re-evaluated the USPHS study and concluded that many of the deaths that occurred would have been prevented if current guidelines, such as excluding patients with acute liver disease and detecting early signs of toxicity with routine laboratory monitoring had been practiced (11). Given its apparent effectiveness in preventing active clinical disease on one hand and the potential of fatal hepatitis on the other, many studies have been conducted to establish the cost-effectiveness of this intervention. The results of these studies have come to conflicting results (12-21). These studies of isoniazid intervention to control tuberculosis have not been conducted by the Royal Netherlands Army.

Only few of the persons who are infected only develop clinically active tuberculosis. Progression from infection to active disease depends largely on cell-mediated immunocom-petence. It is estimated that progression from infection to disease is approximately 10 per cent over a lifetime for a newly infected immunocompetent child (22). However half of this 10 per cent lifetime risk occurs in the first 2 years following infection (23). Persons with a normal chest x-ray whose tuberculin reaction has been positive for an unknown duration of time are generally believed to have a risk of 0.08%

per year for progression to disease (20). A very potent factor influencing the shift from tuberculosis infection to disease is infection with the human immunodeficiency virus (HIV). The cumulative incidence of tuberculosis in persons infected with HIV and having concomitant tuberculosis is estimated at 2 per cent year, for a relative risk of 100 to 500 times average (24,25). The incidence of active tuberculosis is also increased by as much as 5 per cent among persons with a chest X-ray consistent with old healed tuberculosis (26). Therefore certain factors clearly increase the risk of developing tuberculosis among the infected.

The tuberculin skin test is the only tool for detecting subclinical infection with *M. tuberculosis*. Infected persons show a "positive test" which is produced by a delayed hypersensitivity (DHS) reaction characterised by an induration which is read at 48 or 72 hours after tuberculin administration. The interpretation of the test has very important implications especially in decisions to give isoniazid. In the United States, the Centers for Disease Control and Prevention (CDC) has re-defined a diagnostic criteria for a positive reaction aimed at maximising the predictive value of the tuberculin skin test (23). These guidelines have been prompted by an increase in the incidence of new cases of active tuberculosis especially among immunocompromised patients. Table 1 shows the CDC criteria of determining the need for preventive therapy for persons with positive tuberculin reactions by category. The size of the tuberculin induration that eventually influences choice of chemoprophylaxis not only varies with risk category, but also takes into account the age of patients. Although isoniazid preventive therapy is recommended for all ages in patients with risk factors, some are not keen on prescribing isoniazid for those older than 35 years due to fears of isoniazid-induced hepatitis in this age group (14). Because of the current resurgence of tuberculosis, the ATS recommends that persons with previous BCG vaccination should be screened and treated as if they were never vaccinated (27).

In spite of these recommendations, isoniazid prophylaxis therapy is still an issue that is marred by controversy and conflicting opinion. Some authors have stopped short of calling a total-ban on IPT accusing the practice as being dangerous and unrewarding (28). In a study of patients receiving chemoprophylaxis at a US Air Force Medical Center, Byrd and collaborators showed that routine clinical and liver function evaluation of patients should avoid serious liver damage (29). In their series of 1,000 patients, none of the persons died of hepatitis although 6.4% of the group on isoniazid had therapy discontinued due to abnormal liver functions. It might be argued that routine liver function monitoring might be impracticable in some IPT programmes due to financial and organizational constraints. However if an equilbrium in the controversial isoniazid prophylaxis equation is to be sought, there is a strong temptation to opt for an approach of frequent liver function monitoring to avoid a possible fatal outcome. Although the

Table 1. Risk groups for which various-sized indurations on tuberculin skin testing are considered as a positive result.

Induration of 5 mm or more
- Persons with known or suspected HIV infection
- Persons who have had close contact with someone with infectious tuberculosis
- Persons with a chest radiography showing fibrotic lesions likely to represent healed tuberculosis
- Intravenous drug abusers with unknown HIV status

Induration of 10 mm or more
- Persons with medical conditions or undergoing therapies known to substantially increase the risk of tuberculosis
- Silicosis
- Diabetes mellitus
- Haematologic or reticuloendothelial disease
- End-stage renal disease
- Chronic malabsorption syndrome
- Carcinoma of the oropharynx or upper gastrointestinal tract
- Body weight 10% or more below ideal
- Dialysis
- History of intestinal bypass surgery
- History of gastrectomy
- Prolonged immunosuppressive therapy
- Prolonged corticosteroid therapy
- Foreign-born persons from areas where prevalence of tuberculosis is high (eg, Asia, Africa, Latin America)
- Medically underserved, low-income populations, including high-risk minorities (blacks, Hispanics, native Americans)
- Persons who are alcoholic, homeless, or intravenous drug abusers and are HIV-negative
- Residents of long-term-care facilities (eg, correctional institutions, nursing homes)
- Healthcare workers

Induration of 15 mm or more
- Persons with no risk factors (ie, all others)

Adapted from reference (31)

Although the American Thoracic Society guidelines of 1983 recommended obtaining baseline and periodic liver function tests for persons older than 35 years and discontinuing treatment if aminotransferase levels exceeded three to five times normal

(30), these recommenda-tions were not extended to younger age-groups as the risk of isoniazid-induced hepatotoxicity was less in these younger age-groups (26).

Isoniazid prophylactic therapy (IPT) for treating tuberculous infection has been extensively used in the Dutch army since the inception of the programe in 1960. The army policy has been to administer isoniazid to all personnel who reacted with a positive Mantoux induration to tuberculin. This study describes the army isoniazid chemoprophylaxis in the period 1984 - 1995. The characteristics of persons enrolling into the IPT programme are presented including the frequency of side-effects that were possibly isoniazid-associated. The usefulness of isoniazid prophylaxis within the Dutch army and regular assessment of liver functions are discussed.

Materials and Methods

The Dutch army tuberculosis screening programme in the period 1984 -1995 conducted tuberculin skin tests on all persons recruited into the army as part of a routine medical evaluation aimed at identifying candidates for isoniazid prophylaxis. Besides the routine skin testing of army recruits, tuberculin skin testing of army personnel was carried out in the event of contact with a known case of tuberculosis or when personnel returned from overseas deployement in areas designated as highly endemic for tuberculosis.

Screening of servicemen for tuberculosis infection is perfomed by nurses of the Department of Military Health Care (DMGZ). A Mantoux skin test with 1 TU of PPD RT 23 + Tween 80 is administered and the amount of induration determined after 72 hours. Persons with a positive skin test were defined as having an induration diameter of at least 10 mm to 1 TU of PPD. Since 1989, all persons reacting with an induration diameter of 10 - 15 mm to PPD undergo a second test with an *M. scrofulaceum* sensitin (32). This means that persons reacting with an induration in this range are considered as infected with tuberculosis when the indurations to PPD surpass those by M. scrofulaceum sensitin by at least 3 mm.

All persons with a positive skin test are then referred to the Chest Clinic of the Central Military Hospital (CMH), Utrecht, where a chest X-ray is performed to exclude the presence of active tuberculosis. In addition a detailed history to establish if persons have risk factors for tuberculosis activation is conducted. Chest physicians at the CMH make the decision of placing tuberculin positive persons on isoniazid prophylaxis. Isoniazid is administered as an adult dose of 300 mg daily for a period of 6 months. The 6 months regimen has been preferred over the more beneficial 12-months isoniazid regimen because it gives better compliance (33). Vitamin B_6 or pyridoxine (10 mg/day) is also prescribed along with the isoniazid. Pyridoxine has been shown to prevent occurrence of peripheral neuropathy which might happen among persons taking isoniazid (26). Persons placed on isoniazid are informed of the possibility of untoward

side-effects that might develop while on the drug. In the event of such a side-effect happening, they are advised to report immediately to their doctor. The doctor asesses their condition and only refers them to the Chest Clinic if his findings suggest that the untoward symptoms could be associated with isoniazid therapy.

Before initiation of isoniazid chemoprophylaxis, baseline liver function tests are performed at the CMH laboratories. The levels of ASAT (normal range 10-34 IU/l), ALAT (normal range 6-37 IU/l) are measured in addition to total bilirubin (normal range 1-17 rmol/l). Subsequent follow-up after initiation of isoniazid is done through the Chest Clinic of the CMH. After the initial visit, patients are seen after six weeks during which period liver function tests are performed. Thereafter persons are seen every two months at the CMH where the chest physicians question patients on any unusual symptoms that might be attributed to the medicaments being used. During these visits, the pretreatment liver function tests are repeated. In between visits to the Chest Clinic, persons can also consult their doctor in case of problems with isoniazid. In the event of such cases, the patient is referrred to the Chest Clinic and a decision to continue or discontinue with the drug is made by the chest physician. Persons with complaints attributed to isoniazid but in whom the chest physicians find no reason to discontinue the drug are then seen at more frequent intervals. If there is evidence of liver damage during follow-up persons undergo additional tests which include serology for hepatitis B (HbsAg and anti Hbc) and heterophile antibodies for Epstein-Barr infections.

Records on all persons on isoniazid and the progress of their treatment are submitted to the Department of Military Health Care (DMGZ) for entry into a data-base specifically kept for monitoring the tuberculin screening programme of the army. This information provides the following:

1. Patients demographic characteristics – name, military registration number, sex, age.
2. Risk factors for tuberculosis - these are classified as;
   1) contact with an infectious case of tuberculosis.
   b) recent conversion of Mantoux - defined as a 10 mm increase within two years.
   c) fibrotic lesions on chest X-ray
   d) foreign-born
   e) positive mantoux of unknown duration (low-risk tuberculin reactors) - these are reactors in whom time of infection is not known and lacking any established risk factor for tuberculosis activation.
3. History of travel to areas designated as having a serious tuberculosis problem.
4. BCG vaccination status.
5. Date of start of treatment.

6. Presence, nature and severity of sideeffects - the severity of sideeffects is defined as severe when such untoward symptomatology or signs lead to discontinue treatment. In addition when these sideeffects appeared is also noted.

A study number was given to each person on isoniazid prophylaxis, by arranging all the military registration numbers in ascending order which meant that the person with the earliest birthday was given study number 1 and the one with the latest birthday was given the last study number.

Statistical Analysis

All data were entered in a computerised database and analysed using statistical software in public domain (Epi info Version 5, CDC, Atlanta). Students t test and Fisher's 2-tailed exact test were used for univariate analysis of the significance of association. The Mantel-Haenszel test was used for stratified analysis.

Results

Between January 1984 to December 1995, a total of 739 persons were enrolled into the army isoniazid prophylaxis programme, being followed up until completion of treatment or until therapy was discontinued. The mean age of the population was 22 years (range 18 to 54 years) with only 11 (1.5%) persons being above the age of 35. Most of the group (98.8%) was male. Evidence of BCG vaccination through a positive history of childhood immunisation or presence of a characteristic scar was obtained only in three male patients. In these three cases, the Mantoux induration diameter was >15mm. One of the persons was foreign-born and the other two persons did not have any history or evidence of factors associated with tuberculosis activation.

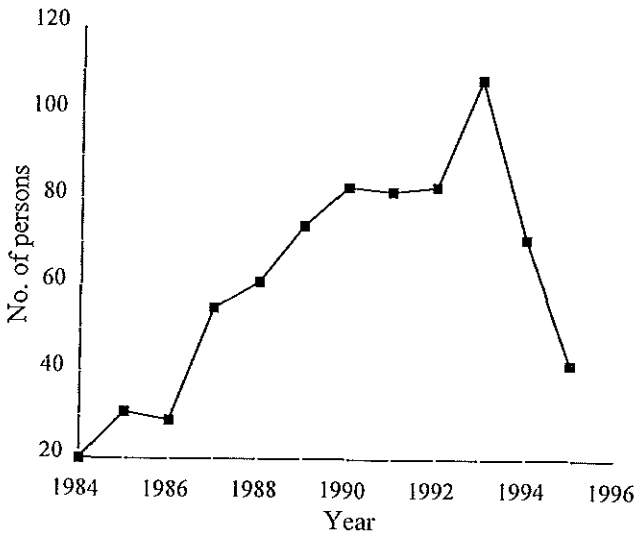

Figure 2. Number of persons on isoniazid prophylaxis, 1984 - 1995.

The trend in the number of persons placed on isoniazid chemoprophylactic therapy from 1984 to 1995 is shown in figure 2. In 1984, 20 persons were placed on isoniazid chemotherapy and this number did not fluctuate considerably till 1987, when the number more than doubled to 55 persons. This represents an increase of 175% over the 1984 figure. This increase continued to show a moderate rise in the subsequent years peaking to 108 persons on isoniazid in 1993. After 1993, the number of persons on isoniazid took on a downward trend, with only 42 persons placed on chemoprophylaxis during 1995.

Tuberculin Test Results

The Mantoux skin induration (mm) was recorded in 729 out of 739 persons. Ten persons were recorded "positive". The mean Mantoux induration in the 729 persons was 16.7 mm (95% CI; 16.4-17.0). There were 239 (32.8%) persons (out of 729) with induration diameter <15mm. The mean induration diameters in the different age groups are shown in table 2. These means are not statistically different. Two persons with an induration diameter of 8 mm and 9 mm respectively were placed on isoniazid chemoprophylaxis. These two persons had risk factors for activation of tuberculosis. In one, there was a history of contact with an infectious case of tuberculosis and the other with an induration diameter of 8 mm showed a Mantoux conversion in 6 months.

Table 2. Mean Mantoux indurations and age

Age group	No. of persons	Mean Induration (mm)	95% CI for mean
#19	158	16.3	15.7-16.8
20-24	468	17.1	16.6-17.5
25-29	79	15.8	14.8-16.7
30-34	11	18.6	14.7-22.4
≥35	13	14.5	12.1-17.0
Total	729*	16.7	16.4-17.1

* Excluding 10 persons whose Mantoux result was only indicated as "positive".

Risk-factors of Tuberculosis Activation

Most of the persons receiving isoniazid chemoprophylaxis in the period 1984-1995 had no recognizable risk factor for tuberculosis activation. These low-risk tuberculin reactors (Mantoux of unknown duration) formed 72.7% of the population on isoniazid. Among the remaining 202 persons in whom a risk factor was identified, most (47%) were classified as recent tuberculin converters. Persons with a positive Mantoux and having been in contact with an infectious tuberculous case accounted for 25.2% while 15.8% were foreign-born. Fibrotic lesions on chest x-ray were seen in only 24 persons, representing 11.9% of persons in the group with a known risk factor. Table 3 shows the mean Mantoux indurations classified according to risk factors. The mean indurations were only significantly lower in persons with recent Mantoux conversion when compared to those who were foreign-born (p=0.044).

Table 3. Mean Mantoux indurations in different risk groups for TB activation.

Risk factor for TB activation	Mean Mantoux induration (mm)	No. of persons	95% CI
Unknown	16.9	529	16.5-17.2
Foreign-born	18.1	32	16.4-19.7
Fibrotic lesion on chest x-ray	17.0	24	15.1-19.0
Contact with infectious TB	16.6	49	15.2-17.9
Recent Mantoux conversion	15.6	95	14.7-16.5

*Excludes the 10 persons whose Mantoux result were only indicated as "positive".

Between 1984-1986, out of the 80 persons placed on isoniazid chemoprophylaxis, 63.8% had an identifiable risk factor for tuberculosis activation. From 1987-1995, there was a reversal in the relationship between those on isoniazid with a known risk factor and the low-risk tuberculin converter. In that period, persons with a known risk factor accounted for 22.9% of those placed on isoniazid. This is a significant difference when compared to the period 1984 –1986 ($p < 0.005$).

Figure 3. shows the number of persons on isoniazid according to presence or absence of a known risk factor for tuberculosis activation. It is shown that the absolute numbers of persons with a known risk factor who were placed on isoniazid did not show great fluctuations over the years. In contrast among the low risk tuberculin converters, a steep rise was registered in 1986 peaking in 1993. Low risk tuberculin converters accounted for much of the increase in the number of persons on isoniazid chemoprophylaxis from 1986 to 1995. This increase was remarkable in those with a Mantoux induration greater than 15 mm (figure 3). Overall, a total of 490 (66%) persons with an induration diameter ≥15 mm were placed on isoniazid during the entire study period.

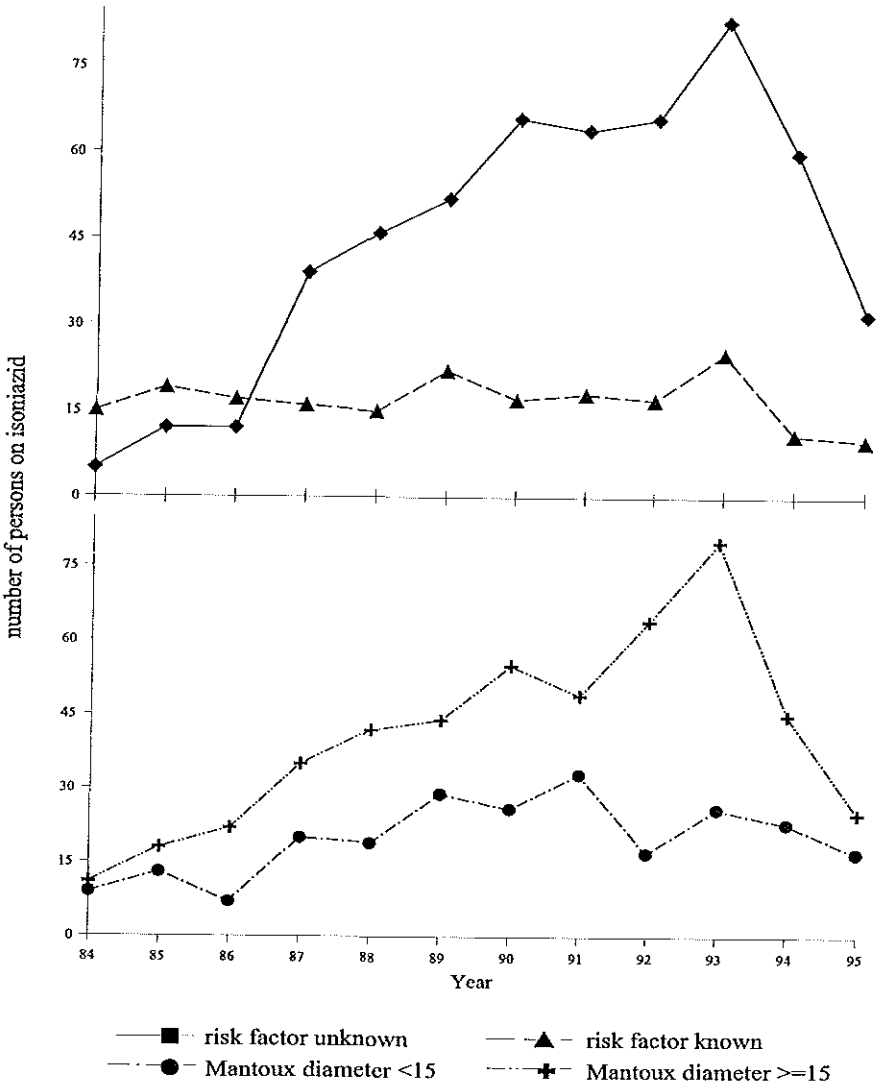

Figure 3. Number of persons on isoniazid by risk factor and Mantoux diameter

The general trend in isoniazid prescription over the entire period 1984-1986 in relationship to the presence of the different risk factors for tuberculosis activation are shown in figure 4. The figure shows a steep rise in the number of low risk tuberculin reactors – those prescribed isoniazid over the years – with the peak in 1993.

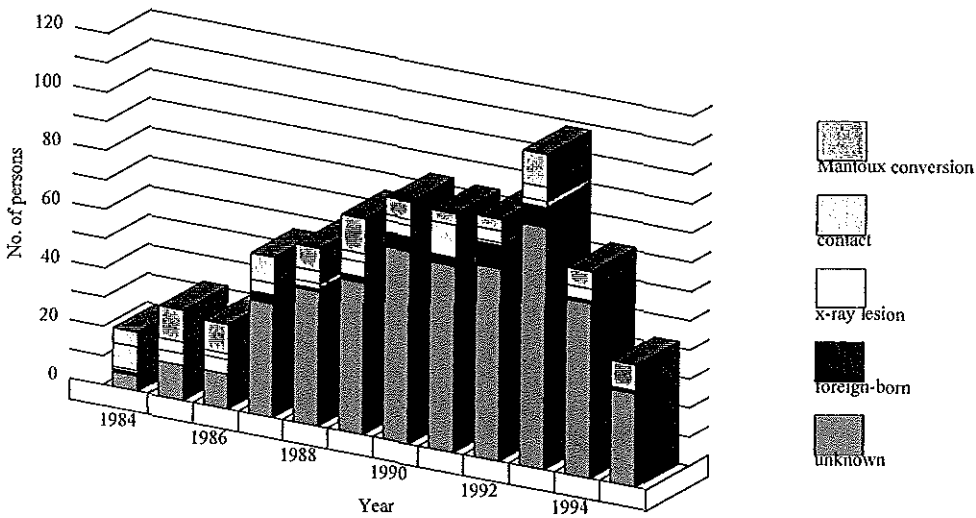

Figure 4. Risk factors for enrollment into the isoniazid programme, 1984-1995.

Side-effects in study group

Table 4 shows the frequency of adverse reactions reported during 1984-1995. In this period 79 (10.6%) out of 739 persons on IPT had adverse effects suspected to result from isoniazid chemoprophylaxis. The most frequently encountered adverse reaction was an abnormal liver function test (elevated AST or ALT) which was recorded in 40 persons. If liver injury is defined by the international standard of an increase in AST of > two times the upper limit of normal (ULN) (34), then of these persons only 10 (25%) developed AST levels of > 2 times ULN. Only one person had an AST level greater than 5x ULN. Among the 10 persons with liver damage, 6 (60%) were low risk tuberculin converters (three with a Mantoux < 15 mm and two with a Mantoux of ≥ 15 mm) and the rest had a known risk factor for tuberculosis activation. Mantoux indurations of < 15 mm were recorded in four of these persons and the other six had induration diameters of ≥ 15 mm. Two persons had elevated transminase levels that were explained by other factors that were more likely to have caused the liver injury than isoniazid. One of these patients had an infection with Epstein-Barr virus (Pfeiffer disease) at the time of liver function test elevations (AST > 3.6 X ULN) while the other was on paracetamol (self-prescribed following a festive evening) to which he had reacted with cutaneous symptoms. In the latter transaminase levels were the highest recorded in this study (14 X ULN). In both cases isoniazid prophylaxis was

discontinued. Remarkable in all these cases of elevation in the liver function tests was the absence of clinical hepatitis.

Six persons were found to have mild transaminase elevations before initiation of isoniazid therapy. One of these persons had an increase in the transaminase levels during treatment, although the AST remained less than two times ULN. Three persons in this group developed sideeffects that were isoniazid-associated. Treatment was not discontinued in any of the six persons. It is remarkable that four persons with initial elevated transaminase levels developed sideeffects to isoniazid. However given the small numbers no conclusions can be drawn from this observation.

In the one person who developed neurological symptoms these were characterised by a tingling sensation in the face with a feeling of numbness in the left half of his body. He noticed these symptoms four days after commencement of INH therapy. The symptoms got worse with continued INH use, forcing discontinuation after one week of treatment.

Seventy-seven per cent of the adverse effects were registered within the first three months of isoniazid therapy. Isoniazid adverse reactions were deemed serious and leading to discontinuation of therapy in 19 persons. This represented 24% of all those persons who developed adverse reactions attributed to isoniazid therapy. Reasons for discontinuing isoniazid chemoprophylaxis are shown in table 5. Nine persons with elevated transaminase levels had treatment discontinued with all but one being asymptomatic. One person with elevated liver function tests also reported fatigue.

Table 4. Frequency of suspected INH-related side effects

Adverse Reaction	No.
Abnormal LFTs	40
Fatigue	31
Dizziness	10
GIT symptoms	9
Loss of concentration	3
Headache	3
Depression	1
Neurological	1

To association between the risk, diameter of induration or age and the development of isoniazid-related side effects were assessed using univariate analyses. Among the 537 persons in whom the risk of tuberculous activation was unknown, sideeffects were reported by 56. This compares with 23 persons out of a total of 202 in the group with known risk factors for tuberculous activation. The differences between these two groups are not significant (OR= 0.91; 95% CI= 0.53 - 1.57).

Fifty persons with an induration of at least 15 mm developed side effects compared to 27 with an induration diameter of less than 15 mm (these differences are not significant OR=1.12; 95%CI= 0.66 - 1.89). Similarly age (older than 35 years or 35 years and younger) was not associated with occurrence of side effects, although these data are not conclusive given that only 13 people were at least 35 years. However side effects were reported by 76 persons out of a total of 726 persons younger than 35 years, while 3 out of the 13 persons who were at least 35 years of age reported side effects (OR=0.39; 95%CI= 0.10 - 2.26).

In the 56 persons developing isoniazid-associated side effects but in whom the risk of tuberculous activation is unknown, 38 (67.9%) had an induration of at least 15 mm and 17 (30.4%) had an induration of less than 15 mm. In one person, the Mantoux result was recorded as "positive".

Table 5. Adverse reactions among persons in whom IPT was discontinued

Age	Sex	GIT	Neuro-logical	Rash	Fatigue	Dizziness	Loss of Concentra-tion	Head-ache	ALAT	AST	Onset*
46	M				yes						2
35	M								92	39	5
27	M	yes	Yes		yes						1
26	M						yes				1
24	M								140	103	3
25	M				yes				265	97	2
22	M			yes							2
22	M								253	160	3
24	M	yes			yes	yes	yes				2
23	M								172	50	4
24	M								214	107	2
21	M					yes					3
23	M								236	93	2
23	M				yes						1
22	M								234	81	1
23	M								224	185	2
21	F	yes			yes						1
19	M					yes					2
20	M			yes							1

* months of therapy before onset of symptoms

Other Findings

One person was found with an elevated bilirubin level (25.3 µmol/l Total) before iniation of isoniazid therapy. Isoniazid was administered and a rise in total bilirubin to

32.3 μmol/l happened during month 5 of treatment. The levels went back to near pretreatment bilirubin at end of treatment. This person did not develop any rise in transaminase levels.

Discussion

The adequate control of tuberculosis involves treatment of active disease and provision of isoniazid prophylaxis to the pool of infected persons. Over a 12-year period, 739 persons infected with tuberculosis, mostly young males with a mean age of 22 years, were enrolled into the army isoniazid prophylaxis programme. This study found that isoniazid-associated adverse effects were present in 10.6% of the study population. In a univariate analysis, the development of isoniazid-related side effects were not related to risk factors for activation of tuberculosis. There was also no association between the indurations and development of side effects when a cut-off point of 15 mm was considered. Therefore these two factors (presence of risk factors or size of induration) could not be used to predict the risk of side effects.

Isoniazid has been associated with a number of sideeffects, most of which are mild. Byrd et al. described 11 different symptoms occurring among 120 subjects at a United States Airforce Medical facility who were placed on isoniazid prophylactic therapy (35). However these symptoms did not occur at a significantly increased frequency among isoniazid recepients when compared to subjects taking placebo. In the current study persons presented with eight adverse effects which were attributed to isoniazid intake (see table 4). Of all adverse effects associated with isoniazid intake, liver damage is the most feared. In a few persons on isoniazid, toxic hepatitis may result in a fatal outcome (36). Experimental evidence in the early 1950s had shown that lethal doses of isoniazid resulted in liver damage (37). It was Randolph and Joseph who in 1953 reported the first case of possible isoniazid-associated hepatitis in clinical practice (38). However their patient had also reacted adversely to p-aminosalicylic acid and was also receiving streptomycin. A liver biopsy of the patient showed a moderate degree of cirrhosis which could not be explained by the short period of isoniazid intake. It was thus not possible to entirely attribute the liver abnormalities to isoniazid as other potentially hepatotoxic drugs were being given. More isolated case reports of hepatitis possibly resulting from isoniazid therapy continue to appear in the medical literature (39- 43).

In spite of all these reports, it was not until 1969 when Scharer and Smith convincingly demonstrated the role of isoniazid as a hepatotoxic agent (44). In that study 90 persons were placed on isoniazid chemoprophylaxis and elevations in transaminase levels were seen in 12.2 percent with the majority being asymptomatic. In the current study, elevated transaminase levels were seen in 5.4 per cent of the study group with evidence of hepatic damage according to international definition (34) being found in 1.4%.

Hepatic damage being defined as an increase in AST of greater than two times upper limit of normal. The majority of the transaminase level elevations were less than two times ULN. It is estimated that approximately 15 percent of persons on isoniazid have minor asymptomatic elevations in serum aspartate aminotransferase which normalise spontaneously even with continued treatment (45). In the United States Air Force study, Byrd et al (29) found a much higher percentage of 22% who developed elevated transaminase levels while on isoniazid prophylaxis. They give no independent data on number of persons with transaminase levels greater than two times ULN. The reasons for the wide discrepancy between the findings of Scharer and Smith (44), and Byrd et al (29) on the one hand and this study on the other hand is possibly related to the age of the patients. In the isoniazid prophylaxis study described by Scharer and Smith the mean age of the group was 29 years, while 72% of persons enrolled into the Byrd et al study were at least 30 years. The persons in the current study were generally much younger with 96.8% younger than 30 years of age and a mean age of 22 years. Isoniazid hepatotoxicity has been shown to occur with increased incidence with increasing age (35). The current study could not conclusively evaluate if those aged $\geq$ 35 years were at increased risk of developing hepatitis due to the small numbers. However the data seemed to show no particular risk for those aged $\geq$35 years in comparison to those less than 35 years (OR=0.39; 95% CI=0.10 - 2.26). In the USPHS study the risk for hepatitis was approximately three times greater among patients aged $\geq$ 35 years than among those aged $<$ 35 years (10). These findings led to recommendations that limited the use of isoniazid to reactors at high-risk of developing active tuberculosis and those under 35 years of age and recommended monthly monitoring for adverse effects (46).

The Dutch army isoniazid prophylaxis program prescribes isoniazid for persons found to have a positive Mantoux induration defined as $\geq$ 10 mm. Most of these persons are seen at conscription into the army with the result that isoniazid will be prescribed to mainly young male adults. However the last years have seen an increasing role of the army in peacekeeping and disaster relief operations overseas. These overseas deployments have led the army to pursue a policy of tuberculin testing servicemen upon return from deployments especially in areas of high tuberculosis endemicity. This might explain the increase in the number of persons on isoniazid which began showing a rise in 1987 as more persons were being tuberculin tested. However this is unlikely to be the entire reason. Another explanation for the increase might be related to the general trend of tuberculosis infection in the Netherlands. This trend which had been showing a decline witnessed a reversal after 1987 (47). Factors that have been attributed for this increase after 1987 have included an increase in the number of persons immigrating from high endemic countries. However in this present study, the number of foreign-born persons on isoniazid prophylaxis accounted for only 4.3% of the study population. It should be noted that before 1987 more emphasis was placed on the side effects of

isoniazid as had appeared in the literature (10) and hence a more selective approach based on giving isoniazid to persons with a known risk factor. However with the increase in tuberculosis cases being notified in the Netherlands after 1987, emphasis in the army tuberculosis programme focused on the need to prevent tuberculosis re-surgence, hence a rise in the number of persons with low-risk for tuberculosis activation being enrolled for isoniazid. The majority of persons (71.6%) on isoniazid in this study were young males, < 35 years, with a positive Mantoux and without a known risk for tuberculosis activation. If the practices of isoniazid prescription in the army are therefore compared to guidelines from CDC (table 1) with age and risk-factor being taken into account, then isoniazid therapy would be indicated in 70 % of those with no known risk factors for tuberculosis activation. The remaining 30 % would not be given isoniazid prophylaxis because of concerns for hepatitis. Among persons with evidence of liver damage while on isoniazid, 33% were persons with no known risk factor for tuberculosis activation and an induration diameter of less than 15 mm. If the CDC guidelines were to be followed, hepatic damage would be avoided in these three persons. However the hepatic damage was not deemed of a serious nature to lead to discontinuation of therapy in two out of the three persons in this group. In the entire group of persons developing isoniazid-associated adverse effects, treatment was discontinued in 2.6% of all persons who were started on isoniazid. Much attention has been given to the hepatic-related adverse effects of isoniazid since these are the ones likely to result in a fatal outcome, however other intolerances do occur. In this study among persons in whom isoniazid was discontinued just over one-half were due to reasons related to hepatic damage occurring either alone (asymptomatic) or in combination with other symptoms. Stead et al. reported that other types of isoniazid intolerance such as nausea without any significant change in liver functions, anxiety, headache, somnolence, fever, and skin rashes occurred often than hepatitis (14).

It is generally recommended that patients on isoniazid should be advised to stop treatment at the onset of symptoms that are suggestive of incipient hepatitis, such as nausea, loss of appetite, and dull mid-abdominal pain (45). In this study among those persons in whom treatment was discontinued eight out of the nine patients with an elevated transaminase level had the isoniazid stopped on basis of a rise in the hepatic enzyme levels alone. This supports evidence from other studies which showed that symptoms alone are not a sensitive method to detect liver function abnormalities (29).

Whereas the threshold to initiate isoniazid prophylaxis was low in the army programme, therapy was discontinued at much lower levels of transaminase elevation in comparison to other studies. In a recent Danish study on liver injury during anti-tuberculosis treatment, Døssing et al did not discontinue treatment even at transaminase elevations of

four times ULN (48). Byrd et al (29) used a transaminase elevation of five times normal as a cutoff level to discontinue isoniazid therapy.

The highest transaminase level associated with isoniazid therapy in this study was 5.4 times ULN. Much higher transaminase levels associated with isoniazid therapy have been recorded. In the series reported by Døssing et al (48), three cases had an AST level exceeding 20 times ULN. However these patients were taking also other antituberculous drugs. Remarkable in this study is the very high transaminase levels of 14 times ULN in a patient who reacted to paracetamol while on isoniazid therapy. The part played by concomittant medications in persons taking isoniazid prophylaxis needs further investigation. It is known for instance that in 29 percents of isoniazid recipients, combined isoniazid and rifampicin therapy predisposes to elevated plasma hepatic enzymes (35). Phenytoin is hepatotoxic and its toxic effects are potentiated by isoniazid (35). Paracetamol is also known to cause liver damage when taken in higher doses, and doses higher than 6 grams can lead to irreversible liver damage (49). However the patient who reacted to paracetamol in this study was not taking high doses of this drug. It is possible that paracetamol and isoniazid potentiated each other resulting in more extensive liver damage as witnessed by a very high transaminase level. A history of medicaments is thus important before initiating isoniazid therapy. It is recommended from this case that caution with isoniazid be exercised if persons are already taking medicaments that by themselves are known to have a hepatotoxic effect. Similarly persons with elevated hepatic enzyme levels should be investigated for other possible causes of liver injury, such as viral infections. In this study, one of the patients with hepatic enzyme elevations had Pfeiffer disease. Epstein-Barr virus can probably cause hepatic damage and in the case of this patient, isoniazid could not be entirely responsible for the transaminase elevations that were registered.

Merritt et al. reported in 1959 the first possible isoniazid-associated fatality in a 38 year old female who developed massive bleeding from oesophageal varices complicating liver destruction following isoniazid administration (40). No patients in the current study population died of hepatitis or an isoniazid-related adverse effect. This might be attributed to the close clinical and hepatic enzyme monitoring programme for all those on isoniazid. The risk of fatal hepatotoxicity is reduced when patients on isoniazid are regularly monitored (11). While reviewing the risk of fatal hepatitis among recipients of isoniazid who had been monitored routinely, Salpeter found that the rate of fatal hepatoxicity was equivalent to the rate in the general population of death from acute hepatitis and acute liver necrosis from any other cause, that is, 0.001% (11). The unusually high fatal hepatotoxicity rate (0.1% in those 35 years plus) observed in the USPHS study was perhaps due to other reasons. Seven of the eight deaths in that study happened in one state where the fatality rate for cirrhosis that year was significantly higher than in the rest of the United States (11). However fatalities due to isoniazid

continue to be reported. Moulding reported 20 isoniazid-induced hepatitis deaths in California (50). In 1993, a report from New York described 10 cases of severe hepatitis attributed to isoniazid of which 4 resulted in death (51).

Three persons in this study had a history of past BCG vaccination. To assess these persons for isoniazid prophylaxis, risk factors other than a positive induration diameter were taken into account. This avoided indiscriminate isoniazid prophylaxis to all persons who had a post vaccination BCG-induced tuberculin reactivity. Persons with a history of BCG vaccination are known to react to tuberculin with indurations ranging from zero to an induration of 19 mm (52). Hence the presence of a positive tuberculin reaction is not a factor to determine whether persons are infected with *M. tuberculosis*. The United States Advisory Council for the Elimination of Tuberculosis statement recommends that a diagnosis of tuberculosis and the use of isoniazid prophylaxis should be considered if the tuberculin reaction in BCG vaccinated persons is $\geq$ 10 mm in the presence of the following circumstances:

a) the vaccinated person is in contact with an infectious case, particularly if the case has transmitted tuberculosis to others

b) birth in a country with a high tuberculosis prevalence

c) exposure of vaccinated persons to populations with a high tuberculosis prevalence, such as, volunteers at homeless shelters (52).

It is noteworthy that in two persons with a Mantoux induration less than the cut-off point of 10 mm (defining the lower induration limit for infection in the army programme) were given isoniazid. Consideration in these two cases took into account the presence of other risk factors that were likely to support the view that these persons were infected inspite of an induration diameter less than 10 mm.

Out of the 6 persons with an initial elevated transaminase level, 67% developed side effects while on isoniazid therapy. Although treatment was not discontinued in any of these persons, they should be closely and more frequently followed.

Much controversy regarding the use of isoniazid has mainly centered on low-risk, young adult tuberculin reactors (46) - a group that formed 71.6% of the study population in the current series. The results of this study show that there is no difference in the frequency of side effects between young adult low-risk tuberculin reactors and those in the same group with a known risk factor for tuberculosis activation. This suggests that when assessing the suitability of isoniazid prophylaxis in the young adult with a low-risk for tuberculosis activation, it should be borne in mind that they are not at an unduly increased risk of developing side effects.

In conclusion, clinical monitoring and hepatic enzyme monitoring even for younger persons on isoniazid prophylaxis will minimise the chances of severe hepatitis. Such

monitoring should at least take place during the first 3 months of therapy. This study shows that 77% of these adverse effects happened during this period. However side effects happened throughout the study period. Although the prevalence of isoniazid-associated side effects in this study were much lower than in many other studies, guidelines should be devised to even minimise these further. The American Thoracic Society guidelines for selecting persons into the isoniazid programme could be adapted. Of course the other factor that needs addressing is the extent to which cross-reactions with nontuberculous mycobacteria contribute to the rate of false Mantoux positives. This will be the subject of the next chapter which will be exploring a strategy of using isoniazid in a more rational manner.

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CHAPTER

4

SKIN SENSITIVITY TO MYCOBACTERIA OTHER THAN MYCOBACTERIUM TUBERCULOSIS IN THE ROYAL NETHERLANDS ARMY

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Introduction

Mycobacteria not assigned to the *Mycobacterium tuberculosis* complex or *M. leprae* have been referred to variously as "atypical mycobacteria", "mycobacteria other than tubercle bacilli - MOTT", "environmental mycobacteria", "anonymous", "chromogenic", "achromogenic" and "non-tuberculous mycobacteria – NTM". In this text the term non-tuberculous mycobacteria (NTM) will be used in referring to these organisms. In 1959 Runyon (1) suggested a classification of these bacteria into four groups: photochromogens; scotochromogens; nonchromogens and, rapid growers. This classification was based on cultural characteristics such as morphology, presence of pigment and rate of growth. Non-tuberculous mycobacteria are ubiquitous and have been isolated from a wide range of environmental sources. Falkinham et al.. in 1980 reported on isolates of NTMs that were recovered from 33% of the water samples collected from various acquatic environments (marine and fresh waters) in the southeastern United States (2). Tuffley and Holbeche in 1980 described the isolation of various NTM organisms from rainwater tanks used to conserve water in parts of Australia (3). Katila and colleagues (4) in Finland found evidence of NTMs in surface waters. The high frequency of NTMs in water sources has often accounted for small epidemics. In 1987 Stine and associates (5) reported on a pseudoepidemic of non-tuberculous mycobacteria which affected 22 patients following infection from a contaminated hospital water supply. NTMs have been isolated from fish, dust and soils. Brooks and colleagues investigated the relationship between soil characteristics and presence of NTMs (6). However, Brook's study did not show any strong correlation between the different soil characteristics, such as, acidity, conductivity, moisture, and the frequency of NTMs. Other sources of potential infection of NTMs to man include domestic and wild animals and birds.

With the advent of the AIDS epidemic, infections with some of these mycobacteria, e.g. *Mycobacterium avium* complex, are increasingly important health problems. For instance, in the United States, in addition to *Mycobacterium tuberculosis*, the non-tuberculous *Mycobacterium avium* complex (MAC) is a common cause of clinical disease due to mycobacteria mostly in AIDS patients (7). However, most non-tuberculous mycobacteria are not or are facultatively pathogenic in immunocompetent hosts. NTMs can produce pulmonary and cutaneous disease, lymphadenitis and

disseminated infection (8, 9, 10). When pathology occurs, there is a wide range of diseases. Disseminated disease has been described in both immunocompetent and immunodeficient persons (11, 12). Non-tuberculous *mycobacterial lymphadenitis* is one of the well recognized clinical entities especially in paediatric practice. Wright provided an extensive review in 1996 of non-tuberculous mycobacterial lymphadenitis in New South Wales province of Australia covering a period of over 30 years (13). Joshi et al.. in 1989 reported on eighty-six children with NTM lymphadenitis in Victoria province of Australia (14). In 1995 Wolinsky reported on the results of a prospective study spanning 32 years in which NTM lymphadenitis among children seen in Ohio state , United States, was described (15).

In the Netherlands, the role of non-tuberculous mycobacteria as pathogens in human disease was first recognized as early as 1935 by Dinger and Ruys (16). In 1943, Bekker reported to have isolated from the urine of a patient sufferring from renal tuberculosis an acid-fast strain which was apparently differrent from the then known acid-fast bacteria (16). In 1967 Van Joost and associates (16) conducted an investigation aimed at establishing the occurrence of infections with non-tuberculous mycobacteria disease in the Dutch population. In that study it was found that *M. kansasii* accounted for more than 60 percent of the cases with pulmonary lesions resembling tuberculosis. Cervical lymphadenitis was found to be caused by both *M. scrofulaceum* and *M. battey* organisms. The nature of the non-tuberculous mycobacteria isolated in relation to the lesions they evidently or probably caused is shown in table 1.

In tuberculosis control, the ubiquitousness of NTMs is of fundamental significance. For example, some workers have suggested that immunologically effective contact with NTM has a profound influence on the way an individual responds to infection by *M. tuberculosis* or other pathogenic mycobacterial species (16,17). In 1981, Stanford and associates postulated that a positive tuberculin test is a result of two mechanisms of cell mediated response to mycobacteria (18). These mechanisms were referred to as the Listeria-type and the Koch-type responses. It was postulated that depending on the species of NTM, contact with these bacteria would either result in a Listeria-type reaction (which enhanced the protective effect of BCG) or a Koch-type reaction which makes BCG ineffectual. NTMs are also capable of affecting the interpretation of the tuberculin skin test (Mantoux) by causing nonspecific tuberculin sensitivity. The most classical study that investigated the prevalence of nonspecific tuberculin sensitivity is that which was reported in 1955 by Edwards and Palmer (19). The tuberculin skin test (Mantoux) is the only means available to identify persons with subclinical *M. tuberculosis* infection. A positive reaction is considered indicative of previous infection with *M. tuberculosis*. However, if the size of reactions to PPD in the general population are plotted against the frequency, it is found that a large number of persons have small

reactions, a relatively small number have intemediate reactions and then the rest having larger reactions. The conclusion from these observations is that there are two sorts of reactions to tuberculin - specific (reflecting previous tuberculosis infection) and nonspecific (which are manifested by a smaller response to tuberculin). Nonspecific reactions have been attributed to infections with non-tuberculous mycobacteria. Each mycobacterial species has a mosaic of protein antigens. Some of these antigens are specific for a given species, but many others are shared by all mycobacteria. The PPD used in the Mantoux test is a mixture of different mycobacterial antigens which partially cross-react to species of non-tuberculous mycobacteria which are common sensitisers of the human population (20). Such cross-reactions to PPD among persons infected with non-tuberculous mycobacteria hinder the interpretation of a Mantoux test. The extent to which NTMs are distributed in a given geographical region on the one hand, and the extent of the tuberculois problem on the other, will ultimately affect the usefulness of the tuberculin test in epidemiological or clinical investigations.

During a routine skin testing procedure in the 1980s following military exercises in West Germany, it was found that a suspiciously large number of Dutch troops had a positive Mantoux in the range 10 - 15 mm (unpublished report). There was no history of these persons being in contact with a known tuberculosis source. It was therefore unlikely that these results represented a new tuberculosis infection acquired while on deployment in West Germany. This led the Army tuberculosis programme to look at the potential role that NTMs were playing in this group of persons. Indeed many were found to have large indurations to M. scrofulaceum sensitin in comparison to PPD RT 23 reactions. It was concluded that these reactions had been caused by NTM infections. On the basis of these findings, it became pertinent to study the frequency of NTM infections in the Army as this has important bearings on the interpretation of the Mantoux skin test and the ultimate enrollement of persons into the isoniazid prophylaxis programme. The results of a study that investigated the frequency of NTM sensitivity in the population of Dutch army recruits are presented in this chapter.

Table 1. 122 strains of atypical mycobacteria according to underlying disease (adapted from reference 16).

Underlying disease	M. Kansasii	M. Scro-fulaceum	Other scoto-chromogens	M. battey	M. avium	Rapid Growers	Total
Pulmonary process resembling tuberculosis	42	-	2	9	-	3	56
Silicotuberculosis	11	-	-	-	-	-	11
Pulmonary and arthritic lesion	1	-	-	-	-	-	1
Pulmonary and genitourinary lesion	1	-	-	-	-	-	1
Pleural exudate	-	1	-	-	-	-	1
Lymphadenitis	-	13	-	10	1	-	24
Not mentioned	12	-	-	-	-	-	12
Total	67	14	2	19	1	3	106

Materials and Methods

The study was conducted between January 1986 and December 1988. In the study 37755 clinically healthy army recruits without previous BCG vaccination were enrolled. All were male recruits with a mean age of 22 years. The study participants were drawn from all over the country. Each of the recruits was tested with two different intradermal injections given simultaneously one on each arm.

Skin testing

Injections and readings were done at the Department of Military Health Care (DMGZ), Utrecht, by a tuberculin testing team. The first skin test was made with 0.1 ml of PPD RT 23 + Tween 80 obtained from Statens Seruminstitut (SSI) in Copenhagen, Denmark. The second test was made with 0.1 ml of *Mycobacterium scrofulaceum* sensitin + Tween 80 RS95 also obtained from Statens Seruminstitut (SSI), Denmark.

The administration and reading of the PPD RT 23 and *M. scrofulaceum* sensitin was in accordance with the World Health Organization (WHO) protocol for standard WHO tuberculin test. All tests were read 72 hours later and the diameter of the induration recorded in millimeters.

In this report a skin test is defined as positive (subject infected with either *M. tuberculosis* or non-tuberculous mycobacteria) if the induration to either antigens is more than 9 mm. Only the results of readings following the administration of *M. scrofulaceum* sensitin will be presented in this chapter.

Results

Out of the 37755 recruits tested, 31130 (82%) showed complete anergy to *the M. scrofulaceum* sensitin. Induration diameters 10 mm and greater were recorded in 7.76% of the study group. However there was considerable fluctuation over the three year study period in the frequency of persons reacting with ≥10 mm induration. In 1986, this percentage was 6.9 and the following year witnessed a moderate rise to 9.7%. During 1988, the percentage had showed a moderate decline to 6.5% (table 2).

Table 2. Induration diameters to M. scrofulaceum *sensitin in period 1986-88*

Year	Total no. of persons studied	Induration ≥ 6 mm		Induration ≥ 10 mm	
		no. persons	%	no. persons	%
1986	13353	1556	11.65	925	6.93
1987	12380	1870	15.11	1206	9.74
1988	12222	1330	10.88	799	6.54
Total	37755	4739	12.55	2930	7.76

Geographical distribution

The current address of the participants during the time of the study was recorded. Therefore it is possible that in some of the subjects this address did not correspond with birthplace or areas where participants have spent a greater part of their lives. The frequency of persons with induration diameters > 5 mm were examined according to province of residence. The results are in table 3.

Table 3. Geographical distribution of sensitivity to M. scrofulaceum *sensitin per province.*

Province	Total no. tested	Diameter of induration			
		> 5 mm		> 9 mm	
		No.	%	No.	%
Friesland (rural)	1309	155	11.8	97	7.4
Groningen (rural)	1364	167	12.2	111	8.1
Drenthe (rural)	945	105	11.1	59	6.2
Overijssel (rural)	2840	340	12.0	211	7.4
Gelderland (rural)	4911	578	11.8	351	7.2
Flevoland (rural)	346	54	15.6	36	10.4
Limburg (urban)	2870	317	11.1	177	6.2
Brabant (rural)	7274	834	11.5	490	6.7
Noord-Holland (urban)	4848	617	12.7	382	7.9
Zuid-Holland (urban)	7643	1137	14.9	744	9.7
Utrecht (urban)	2230	302	13.5	185	8.3
Zeeland (rural)	1175	133	11.3	87	7.4
Total	37755	4739	12.6	2930	7.8

Within the Netherlands, provinces can be looked as either rural (mainly farming) and urban, or as coastal versus inland. The results did not show any geographical variations in frequency of indurations to *M. scrofulaceum* antigen. However, among indurations > 9 mm, the rural province of Flevoland scored the highest (10.4%) with the lowest frequency of indurations being registered in persons from Limburg and Drenthe (6.2%). Details are presented in table 3.

Discussion

Infections with non-tuberculous mycobacteria sensitises persons to tuberculin (20,21,22). These cross-reactions are attributed to shared antigens among mycobacterial species. It was during studies conducted to investigate the nature, as well as variations in prevelance of the tuberculin sensitivity interpreted as cross-reactions among

apparently normal, healthy populations that evidence about the role of non-tuberculous mycobacteria in causing this phenomenon came to light (22). The usefulness of the tuberculin skin test is a trade-off between the prevalence of the infection with *M. tuberculosis* and the relative prevalence of cross-reactions to non-tuberculous mycobacteria (21). The prevalence of non-tuberculous mycobacteria sensitivity in a given area will therefore determine the usefulness of the Mantoux test as an epidemiological or diagnostic tool.

In this study recruits were tested with *M. scrofulaceum* sensitin. This sensitin was chosen because it cross-reacts more broadly with all other non-tuberculous mycobacteria (23). In the current study it was found that the prevalence of NTM sensitivity (7.8%) in a group of 37755 army recruits seen in a period of three years was high. However this percentage is less than that found by Bleiker among Dutch school children in Delft (24). In the Delft study, begun in 1966 and repeated every five years, the prevalence of non-tuberculous mycobacteria reactions > 9 mm were found to be 12.9% in 1985. The Delft area is in the Zuid-Holland province and when the frequency of non-tuberculous mycobacteria sensitivity in only those recruits from Zuid-Holland is considered, a higher frequency of 9.7% is noted. This is second only to Flevoland province which at a prevalence of 10.4% represented the highest frequencyof NTM in this army study.

There is a varying frequency of non-tuberculous mycobacteria sensitivity in different parts of the world. Different studies have employed varying types of mycobacterial sensitins to test for the frequency of non-tuberculous infections in populations. During the 1950s and 1960s, Edwards, Palmer and associates in the United States performed studies on the sensitivity of populations to non-tuberculous mycobacteria (19,25). These large USA studies were conducted among army recruits and it was found that a high percentage of 33% reacted to *Mycobacterium intracellulare* (Battey) sensitin. It was remarkable that only 4% of these recruits reacted to tuberculin (PPD-S). In Sweden Lind et al.. (26) found a high degree of reactions to sensitin among school children. A total of 25% of these reacted with > 5 mm induration diameters to *M. avium* sensitin, whilst 32% reacted to *M. scrofulaceum* sensitin.

Dascalopoulos and associates studied non-tuberculous mycobacteria sensitivity in Greek army recruits. They found rates of over 8% in segments of their study population (27). Svandovæa et al.. using a cutoff-point of > 5 mm to define sensitization, found high prevalences to *M. scrofulaceum* sensitivity (over 20%) in some areas of Chechoslovakia (28). In 1995 Kwamanga and colleagues in Nairobi, Kenya, tested school children using *M. scrofulaceum* sensitin (29). In that study, 22.7% of the school children reacted to the sensitin with diameters of at least 9 mm. Although these studies have used different

sensitins and different cutoff points (>5 mm or > 9 mm), the fact that the sensitivity of populations to non-tuberculous mycobacteria is often high remains unobscured.

Van Joost and associates described in 1967 the distribution of infections with non-tuberculous mycobacteria within the Netherlands (16). They found that disease due to *M. avium* were more common in the provinces of Limburg and in North Holland. The province South Holland had the highest incidence of disease due to *M. scrofulaceum* as well as disease due to *M. battey*. The high incidence of *M. kansasii* in the provinces of Limburg and North Holland it was speculated, was related to the prominence of these areas in the coal and steel industry. In this study no clear geographical patterns to *M. scrofulaceum* sensitin sensitivity within the country were noted. However, it should be pointed out that some provinces contributed fewer persons to the study. This is the case with the provinces of Flevoland and Drenthe. On the other hand, some provinces were over-represented eg. Brabant with over 7000 persons. This uneveness in distribution of numbers is because during the study period more recruits came from the Brabant area and fewer were from Flevoland. Although this study attempted to classify the provinces according to the dominant form of commercial activity (industrial/rural), this classification is rather unsatisfactory. The Netherlands is a small country that is heavily industrialised and a strict distinction between the provinces based on this criteria does not entirely reflect the actual situation. Persons coming from relatively rural provinces might originate from what is rather urban setting. It would therefore be misleading view them as representatives of a rural agricultural population.

Studies elsewhere have demonstrated that the prevalence of non-tuberculous sensitivity varies geographically within the same country. Studies done in the United States during the 1950s and 1960s showed that non-tuberculous mycobacteria sensitivity showed a high frequency in the southeastern states (19,25). Recent studies have also supported the predominance of these non-tuberculous mycobacteria in the southeastern United States. Falkinham et al.. sampled various aquatic environments in the southeastern United States and found a correlation with the frequency of persons reacting to non-tuberculous mycobacteria sensitins demonstrated in earlier studies (2). Codias and Reinhardt in 1979 studying cultures of *Mycobacterium avium-intracellulare-scrofulaceum* (MAIS) isolated in residents of Georgia, United States, also found a correlation with the studies of Edwards and associates indicating that the largest reactors to non-tuberculous mycobacteria sensitins resided in coastal regions (30). Dascalopoulos et al.. in Greece found a higher frequency of non-tuberculous sensitivity among persons residing along seaside areas and those living near big rivers compared to those from mountainous regions (27). This Greek study supports the theory that living in the neighbourhood of large bodies of water are an important source of infection with non-tuberculous mycobacteria. Lind et al.. (26) attempted in their study of school children to examine

reactions in relationship to presence of various pets. They found that the presence of birds, dogs and cats in homes was associated with an increased frequency of children reacting to the sensitins used. Many studies have demonstrated that pets (animals and birds) can be infected by non-tuberculous mycobacteria and could be an important reservoir of infection to human populations (31, 32, 33). For example inhalation of dust from the litter in bird cages is one way in which human hosts become infected (26). In this current Dutch army study the association between domestic pets and sensitivity to non-tuberculous mycobacteria was not investigated. Although the study examined the possible association between non-tuberculous mycobacteria and aquatic environments by classifying provinces as inland versus coastal, this approach too, for a country such as the Netherlands which is traversed by many water sources, does not allow for such a distinct classification.

The frequency of non-tuberculous mycobacteria disease among certain populations has been shown to be increasing over the years. Isaac-Renton and associates were able to demonstrate that over a 10 year period in British Columbia, Canada, the absolute and relative numbers of non-tuberculous mycobacteria increased (34). Bleiker and associates (24) also found that non-tuberculous sensitivity among school children in Delft was showing an increase over time. In 1975 this prevalence was 9.5% increasing to 13.3% in 1980. Thereafter this frequency remained relatively stable and by 1991 it was 14.4%. In the current army study, the observation period of three years was too short to allow an observation in the trend of non-tuberculous mycobacteria sensitivity. However over the three year period sensitivity to *M. scrofulaceum* sensitin showed great fluctuations. A long term follow-up of *M. scrofulaceum* sensitivity in the army would have provided a clear insight into the trends of non-tuberculous mycobacteria infections in the Dutch population. The increase in the frequency of non-tuberculous mycobacteria over the years remains remains unclear. Johnston et al.. in 1965 suggested that most NTM came from the soil (35). Consequently, they argued, there would be no reason for a decline in the infection or reinfection rate with these mycobacteria in a specific geographic area, even when there was a dramatic reduction in new primary infections.

This study have shown that non-tuberculous mycobacteria sensitivity may interfere with the interpretation of the Mantoux skin test. The Mantoux skin test might be of limited value in regions such as the Netherlands with a high prevalence of non-tuberculous mycobacteria sensitivity and a low prevalence of tuberculin sensitivity. Separating reactions to the Mantoux test due to *M. tuberculosis* infection from those due to non-tuberculous mycobacteria is therefore of major clinical and epidemiological importance. Persons with positive Mantoux skin reaction are prescribed isoniazid chemoprophylaxis, which is not infrequently free of serious side-effects (see chapter three). Being able to identify persons who are actually infected with tuberculosis on the basis of skin tests

alone would greatly reduce the unnecessary prescription of isoniazid to those infected with non-tuberculous mycobacteria but who due to cross reactions, react with a positive skin test to the Mantoux test. The following chapter (chapet five) contributes to improve existing models to classify different indurations so that only persons infected with *M. tuberculosis* are enrolled into the isoniazid prophylaxis programme.

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CHAPTER

5

CONSEQUENCE OF THE PREVALENCE OF NON-SPECIFIC TUBERCULINE SENSITIVITY FOR INH-PROPHYLAXIS IN THE ROYAL NETHERLANDS ARMY

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Introduction

The WHO-standard Mantoux test with 1 TU PPD RT 23 + Tween 80 (1,2) forms part of the medical examination of all RNLA conscripts. The percentage of recruits that react with indurations of 10 mm and more to PPD RT 23 has gradually decreased from 19.2% in 1955 to 0.48% in 1991 (3). As chest x-ray examination on entering the Army in active service was abandoned in 1987, the tuberculin test became the only tool to check for infection with *Mycobacterium tuberculosis* in army recruits.

Persons who have not previously had BCG-vaccination but after Tuberculin tests develop indurations greater than 10 mm are considered to be infected with *M. tuberculosis*. Such persons are given isoniazid (INH) chemoprophylaxis 300 mg/day for six months irrespective of contact or family history.

As side effects to INH chemoprophylaxis are likely in some cases (4-6) the specificity of the induration is very important – especially the development of isoniazid-associated hepatitis. Kopanoff et al. estimated this condition to occur at a case rate of 3 per 1,000 persons in the age group 20 to 34 years and 1 per 1,000 persons in persons less than 20 years of age (4). It is known that infections with nontuberculous mycobacteria (NTM) may cause tuberculin sensitivity through cross reactivity. In the Netherlands an increase in the percentage of NTM infections has been shown (7) and the existence of clinical infections with *Mycobacterium scrofulaceum* documented (8-10).

Recruits infected with NTM could show indurations <10 mm in standard tuberculin test and accordingly would be given, needlessly, INH chemoprophylaxis. To avoid this it is desirable to separate infections with *M. tuberculosis* from those due to NTM.

Double Mantoux skin testing

The use of two skin tests in tuberculosis control to differentiate between skin reactions which are a result of infections due to non-tuberculous mycobacteria *vis a vis* tuberculous infections was a well established procedure in veterinary practice since the early 1930s (11) - long before similar attempts in human medicine. At the time non-tuberculosus mycobacteria which could confuse the significance of the Mantoux test were considered so rare that little attention was paid to the specificity issue of the skin test. In veterinary practice veterinarians had long known that infection of cattle with non-tuberculous mycobacteria was widespread. In particular it was recognized that

cattle were infected with *M. avian* and *M. johnei* organisms which did not matter from an economic point of view but which would interfere with the interpreatation of the tuberculin skin test when screening herds for evidence of infection with *M. bovis*. Differentiation between the tuberculous and non-tuberculous mycobacteria was achieved through a so-called "Single Intradermal Comparative test" (12). This procedure involved the use of two tuberculins, mammalian and avian, injected simulataneously a few inches apart in the animals neck in an attempt to sort out cattle with non-tuberculous mycobacterial infections from bovine tuberculosis.

In human medicine no attempts were made to address the specificity of the tuberculin skin test in terms of the possible effect of underlying non-tuberculous mycobacteria infections in the populations in spite of studies conducted in the 1930s by Mariette and Fenger which pointed to the fact that sensitivity to avian tuberculin in Minnesota, United States, was high (13). As already pointed out above, medical opinion in those days considered the issue of no major practical significance in human medicine although veterinarians of considerable experience in these issues were urging their collageues in human medicine to investigate the subject. A most notable appeal having been made by Green of the Weybridge Laboratories, England. In his opening paper in the Proceedings of the Royal Society of Medicine (1951) Green wrote (12):

> *"Whether the point, or indeed the whole question of "specificity" of tuberculins is or is not of importance in medical usage it would seem at least of scientific interest to explore the possibility of using specificprotein derivatives to identify a Mantoux positive as arising from a hominis infection or from an infection with one or other of the recently described "skin tuberculosis" types, such as the Bairnsadale bacillus Mycobacterium ulcerans."*

Although major opinion in human medicine at the time considered the issue of tuberculin "specificity" unimportant, two skin test procedures employing different skin antigens were already in practice - but for a different reason. In the 1930s studies which cast doubts on the specificity of tuberculin began emerging in the US. It was found that pulmonary calcifications - whose presence at the time were considered the *sine qua non* of tuberculosis - were present in a large number of persons who reacted negatively to the tuberculin skin test (13). It became clear to some that tuberculosis alone could not attest for all the calcifications which were being observed, hence a focus on non-tuberculous origins of the calcificatory chest X-ray lesions.

In 1942 Aronson et al. used tuberculin and coccidioidin skin tests in Indians in the Southwest of the United States to show that coccidioidomycosis was responsible in the localities studied for a considerable amount of calcifications which were being seen on chest x-rays (14). In their classical comprehensive study began in the fall of 1943, Goddard et al. (15) in the US investigated the phenomenon with the help of tuberculin

and histoplasmin skin tests. Their study showed that 82 percent of student nurses studied and with calcifications reacted to histoplasmin and 27 percent to tuberculin. It was therefore concluded that calcifications on chest x-ray seen in some patients with negative tuberculin skin reactions are due possibly to a mild subclinical infection with *Histoplasma capsulatum* or a closely related organism. Having made this discovery another more subtle problem of specificity with the tuberculin skin test was to arise. This was the phenomenon of cross reactions between *M. tuberculosis* and related mycobacterial species (nontuberculous mycobacteria). It had been suspected for some time that the so-called "strong-dose" tuberculin sensitivity were not a result of tuberculous infection and that many of the small reactions to the standard 5-TU test might also be due to other factors. Defining the cause of these cross reactions pre-occupied tuberculosis research in the 1950s. In 1955 tuberculosis researchers at the World Health Organization and two years later Edwards and Krohn were able to demonstrate that avian tuberculins appeared to be effective in identifying persons whose reactions to human tuberculin were considered to be cross reactions (13). However Edwards and Edwards pointed out in 1960 that infection with the avian tubercle bacilli cannot be incrimated as the sole or perhaps even the most frequent cause of cross reactions to human tuberculin for the reason that antigens prepared from a variety of other mycobacteria are equally effective in identifying persons with that kind of infection. Rigorous comparative skin testing by Edwards and Krohn (16) using different mycobacterial antigens in residents of India and the Philippines concluded that:

> *"the low- grade tuberculin sensitivity consisting of small indurations* ***ranging from 3 to 12 mm diameter to 5 TU*** *[*authors emphasis*] to purified human tuberculin seem to reflect a response to an antigenic factor common to various types of acid-fast organisms and not a specific factor in human tuberculin, whereas the higher degrees of* ***sensitivity with induration diameters at least 12 mm*** [authors emphasis*] to purified tuberculin appear to represent a specific response to tuberculous infection."*

In essence the Edward and Krohn (16) study had demonstrated that if infection with other nontuberculous mycobacteria results in low grade sensitivity, then comparative tests with appropriate antigens should provide an opportunity to distinguish *M. tuberculosis* infection from cross reactions. Experimental work by Edwards and her associates, Bjerkedal, and Johnson and Smith provided evidence that infection with a single mycobacterial species provided a degree of tuberculin sensitivity which is definitely greater to the homologous antigen than to the heterologous mycobacterial antigens (17). Edwards and Edwards reported on a United States Navy comparative skin testing study which involved 46,000 Navy recruits each receiving both PPD-S (mammalian) and antigens from the Battey mycobacterium (PPD-B). To arrive at a

practical way of distinguishing the different possibilities when interpreting results, they categorized the recruits into three groups according to induration diameters following administration of the the two antigens:

- those whose reactions to PPD-B was larger than to PPD-S. These persons were designated as having cross reactions to PPD-S and not infected with *M. tuberculosis*.
- those whose reactions to the two antigens were the same size or within 1 mm of each other. No speculations were made regarding this group, perhaps illustrating that a golden standard in addressing the specificity of tuberculin was far from being found even when employing dual skin tests.
- those whose reaction to PPD-S was larger than to PPD-B. These were considered as having true tuberculous infection.

Sensitivity to PPD-B is a reflection of infection with any of a number of species of nontuberculous mycobacteria. The choice as to which nontuberculous mycobacteria antigen ought to be used in a double Mantoux skin test is ultimately dependent upon the strains of nontuberculous mycobacteria prevalent in a particular geographical area. Even in the United States where much of the earlier work on nontuberculous mycobacteria was done, there was considerable variation in the distribution of these bacteria in the population. In the Netherlands a double Mantoux skin test was employed in an investigation of 6532 school pupils (11). In that study, PPD RT 23 + Tween 80 was used to elicit evidence of infection with *M. tuberculosis*, while evidence of infection with nontuberculous mycobacteria was demonstrated in about half the study subjects using PPD avium and the other half with PPD scrofulaceum. Subsequent surveys investigating sensitivity to NTM organisms within the Netherlands showed that tuberculins prepared from *M. scrofulaceum* appeared to offer the best means of identifying persons whose reactions to human tuberculin were considered to be cross reactions. Therefore in this current study, NTM sensitivity has been studied using *M. scrofulaceum* sensitins.

In the present study of *M. tuberculosis* and NTM sensitivity in the Royal Netherlands Army recruits a double Mantoux test is introduced. The current methods to separate infections with *M. tuberculosis* from that with NTM are based on classifying persons using their reactions. Those with stronger reactions to tuberculin prepared from *M. tuberculosis* than to sensitin prepared from NTM can be classified as infected with *M. tuberculosis* and vise-versa (18,19). Attempts have been made to improve on existing models for classifying the different indurations to increase the likelihood that only persons infected with *M. tuberculosis* are prescribed INH chemoprophylaxis.

Populations and Methods

Study Population

The first part of the study, conducted from 1986 - 1988 comprised 37755 army recruits without previous BCG vaccination. Two skin tests - one test on each forearm - were applied simultaneously. One test was made with 1 TU PPD RT 23 + Tween 80 followed by a second test employing *M. scrofulaceum* sensitin + Tween 80. Both tests were read after 72 hours.

The second part of the study was conducted from 1989 - 1993 and consisted of 199 937 recruits without previous BCG vaccination. In this group all received 1 TU PPD RT 23 and the reading was done after 72 hours. In those who showed an induration in the range of 10 - 15 mm a second skin test with *M. scrofulaceum* sensitin was given on the second forearm and results read after 72 hours.

The test was performed and read according to the WHO protocol for standard WHO tuberculin test (20). Both study populations consisted of clinically healthy army recruits, born in the Netherlands, with a mean age of 22 years. For this study the population was not tested for infection with the human immunodefieciency virus (HIV) as this is not routinely indicated.

Methods

The criteria for infection with either *M. tuberculosis* or NTM was set at an induration of at least 10 mm (21). To distiguish between persons infected with *M. tuberculosis* and those infected with NTM, a model based on the one proposed by the International Tuberculosis Surveillance Centre (ITSC) was used (19). Briefly the ITSC model shows four distinct areas:

1. an area that represents the noninfected;
2. a region showing those infected with *M. tuberculosis* with an induration diameter to PPD ≥17 mm);
3. in between these two, a diagonal line separates those infected with NTM from those infected with *M. tuberculosis* but reacting with an induration diameter < 17 mm;
4. further, those whose indurations lie on this diagonal line are equally divided into those with *M. tuberculosis* infection and those with NTM.

In this study an additional criterion was made in such a way that positive indurations to *M. scrofulaceum* sensitin have to surpass indurations to PPD RT 23 by at least 3 mm to be classified as NTM infections and vice-versa. The diagramatic presentation of this model is shown in Figure 1. Area (A) represents non-infected persons; area (D) are persons directly classified as infected with *M. tuberculosis*; area (B) represents the *M.*

tuberculosis infected based on the 3 mm criteria. Area (C') are those infected with NTM, while area (C'') represents those infected with NTM who were classified as giving a false positive induration to PPD RT 23.

Results

During the period 1986 - 1988, 37,755 recruits were tested using two simultaneously applied skin tests with PPD RT 23 and *M. scrofulaceum* sensitin. The distribution of both PPD RT 23 and *M. scrofulaceum* sensitin is shown in Figure 2. Distribution to PPD RT 23 shows neither mode nor antimode, whilst the distribution to *M. scrofulaceum* sensitin shows a bimodal pattern. The antimode is found at 5 mm with the second mode at 9 mm. A total of 30 626 (81%) persons had zero reaction to either PPD RT 23 or *M. scrofulaceum* sensitin; zero reactions to PPD RT 23 were more frequent with 97% (36 643/37 755) compared to 82% (31 130/37 755) for *M. scrofulaceum* sensitin. Induration diameters of 1 - 9 mm occured in 2.6% (967/37 755) with PPD RT 23 and in 9.7% (3688/37 755) with *M. scrofulaceum* sensitin. Indurations ≥10 mm to *M. scrofulaceum* sensitin fluctuated over the three years - averaging prevalence of 7.76%. Throughout the study i.e.1986 - 1993, induration diameters ≥10 mm to PPD RT 23 were registered in about of 0.45% persons; this remained fairly constant throughout the years.

Table 1 shows the percentage of persons reacting with induration diameters ≥10 mm to PPD RT 23 in the period 1986 - 1993 and to *M. scrofulaceum* sensitin in the years 1986-1988. The mean diameter for those reacting to *M. scrofulaceum* sensitin with an induration ≥ 10 mm is 13.5 mm (SD ≥ 3.07), compared with 15.4 mm (SD ≥ 3.85) to PPD RT 23.

Table 1. Percentage of recruits reacting to PPD RT 23 and M. scrofulaceum *sensitin.*

Year	Persons tested	PPD RT 23 ≥10 mm (%)	*M. scrofulaceum* sensitin ≥10 mm (%)
1986	13353	0.47	5.1
1987	12380	0.41	7.9
1988	12022	0.48	5.4
1989	43801	0.46	-
1990	41040	0.44	-
1991	39956	0.49	-
1992	39555	0.39	-
1993	35585	0.48	-

The exclusion percentage using the criteria of 3 mm (Figure 1)

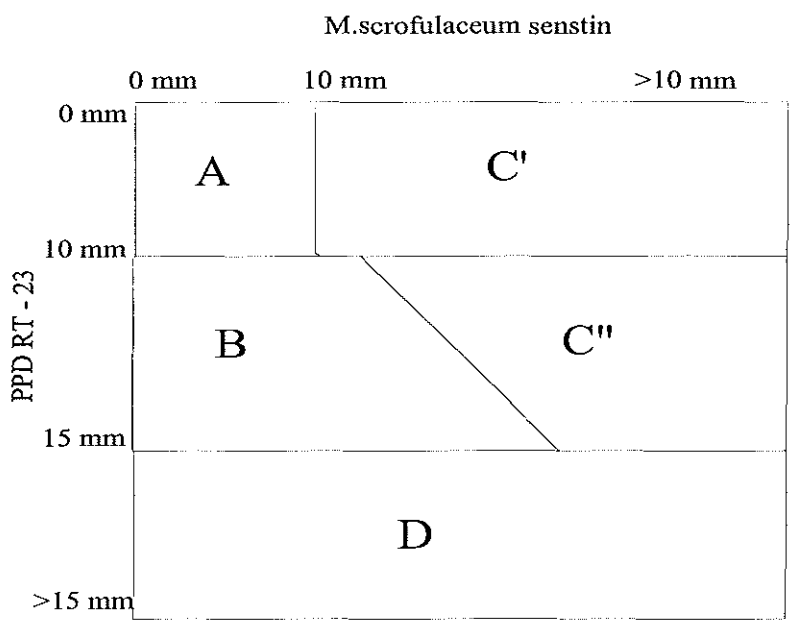

Figure 1. Graphical presentation of model classifying dually skin tested recruits: 1986-1988.

Using the 3 mm criterion among persons with indurations to PPD RT in the range 10-15 mm, 46% of the recruits investigated during 1986-1988 were classified as infected with NTM {C''/(B+C'')}. In this same period 20% of the total group of persons who reacted with a diameter ≥10 mm to PPD RT 23 {C''/(B+C''+D)} were excluded.

Table 2. Induration diameters to PPD RT 23 between 10mm - 15 mm and percentage of presumed false positives, 1986 - 1993.

Year	persons tested	No. with induration diameter ≥ 10 mm and ≤ 15 mm	Presumed false positive (%)
1986	13353	23	10 (43)
1987	12380	21	8 (38)
1988	12022	21	12 (57)
1989	43801	59	27 (46)
1990	41040	58	24 (41)
1991	39956	46	14 (30)
1992	39555	55	39 (71)
1993	35585	72	38 (53)
Total	237692	355	172 (48)

Referring to the positive exclusion percentages found in 1986-1988, a second investigation was done from 1989-1993. Only those with induration diameters between 10-15 mm to PPD RT 23, a total of 290 recruits, were tested with *M. scrofulaceum* sensitin. The 3mm criteria was then applied and a distinction made as to whether the reaction represented infection with *M. tuberculosis* or infection with NTM. Those classified as infected with NTM were then excluded from INH chemoprophylaxis. Table 2 shows the percentages of persons who reacted to PPD RT 23 with diameters ≥10 mm and ≤ 15 mm who were excluded from INH chemoprophylaxis using the criteria described above.

The percentage that was excluded (exclusion percentage) from INH chemoprophylaxis fluctuated over the study years, with a strong peak in 1992. The average exclusion percentage over the seven-year period was 48% and 16% for indurations to PPD RT 23 in the range 10 - 15 mm and ≥10 mm respectively.

Discussion

Between 1986 and 1988 the sensitivity to PPD RT 23 and *M. scrofulaceum* sensitin among recruits in the Royal Netherlands Army was investigated. The prevalence of indurations ≥10 mm to PPD RT 23 in these three years was low (0.45%) compared to a high prevalence of 7.76% to *M. scrofulaceum* sensitin. A similar high prevalence of NTM sensitivity was found among Dutch school children in the city of Delft during a 1964 study (11). This high prevalence to *M. scrofulaceum* sensitin in the current study fluctuated over the three-year period, with no clear pattern of nontuberculous

mycobacterial (NTM) infections. Response to *M. scrofulaceum* sensitin in this study was not necessarily an indication of infection with *M. scrofulaceum* but a reflection of the prevalence of NTM in the study population. Therefore the fluctuating pattern to *M. scrofulaceum* sensitin could be the result of shifts in sensitivity to different NTM. The distribution of indurations to PPD RT 23 in the histogram (Fig 2) shows no clear-cut unimodal distribution. This is in contrast to the normal distribution seen in other populations in whom tuberculin test results in a low rate of false positives. In such populations the tuberculin test is highly specific (21). On the other hand, in populations such as in the present study with a low prevalence to tuberculosis and a relatively high NTM prevalence, the utility of the tuberculin test might be limited.

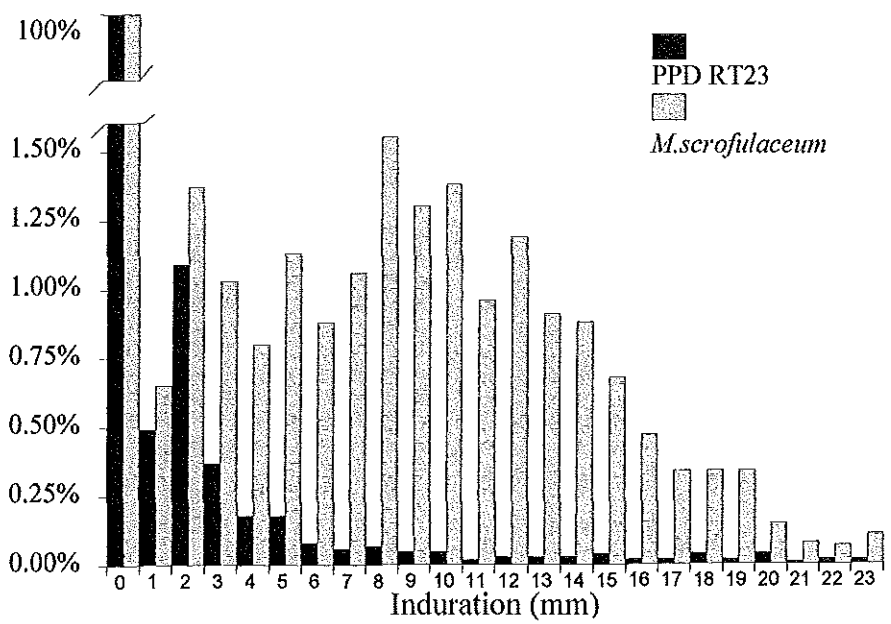

Figure 2. Reactivity to PDD RT 23 and M. scroufulaceum

In the Royal Netherlands Army a cut-off point of ≥ 10 mm in response to PPD is used to define a positive test among non-BCG vaccinated persons; all those with a positive test to PPD are then prescribed isoniazid chemoprophylaxis for six months. However, since mycobacterium species share many common antigens, healthy persons infected with NTM might respond to PPD RT with a positive induration. Attempts should therefore be made at differentiating infections due to *M. tuberculosis* and those due to NTM

among persons reacting with a positive induration to PPD RT, so that isoniazid chemoprophylaxis can be limited to those where it is indicated.

In regions where the distribution of PPD in the population neither shows an antimode nor a mode, both may be obscured by a high frequency of reactions to NTM. When two skin tests are used to each subject (one with tuberculin and the other with sensitin prepared from NTM) this might separate infections due to *M. tuberculosis* from those due to NTM (22). By introducing a model based on this double Mantoux, this present study has attempted to separate responses due to *M. tuberculosis* infection from responses to NTM. The exclusion rate was the percentage of persons who reacted with an induration diameter between 10 mm and 15 mm to PPD RT 23 but with a stronger response on second testing with *M. scrofulaceum* sensitin. Response to *M. scrofulaceum* sensitin had to exceed that due to PPD RT by at least 3 mm. This 3 mm criteria was first proposed as reasonable by Carruthers in 1970 (23). In that study Carruthers studied the difference in size between comparative Mantoux reactions which could be considered outside the limits of observer variation. The study found that it was reasonable to accept differences of 3 mm or more between simultaneous comparative Mantoux test readings as indicating differences in reactions to sensitins used. More recently a dual skin testing procedure using a 3 mm criterion to distinguish between persons with *M. tuberculosis* infection and those infected with *Mycobacterium Avium Complex* (MAC) has been employed by von Reyn et al. (24). They designated skin reactions into *M. avium*-dominant or *M. tuberculosis*-dominant, using a 3 mm criteria.

In the current study, from 1986 to 1988 the percentage of persons reacting to PPD RT with a positive induration between 10 mm to 15 mm and classified as false positive was 45%. The exclusion rate for all persons with indurations ≥0 mm was 20% during that study period. During the second part of the study a second test with *M. scrofulaceum* sensitin was given only to those reacting with an induration diameter of between 10 mm to 15 mm. The exclusion rates fluctuated over the years. On average, the exclusion rate for those reacting with indurations 10 mm to 15 mm was 48% throughout the study period. This means that almost half of the persons with indurations to PPD in the range 10 mm to 15 mm are showing sensitivity as a result of infection with NTM. In the group of persons with indurations to PPD ≥ 10 mm this percentage is 16%. These persons are therefore excluded from INH chemoprophylaxis, and the potential side effects due to INH are eliminated in this group. During this second phase of the study the skin tests were not given simultaneously, which could have introduced a potential flaw in the methodology. A second skin test even with a different sensitin may give a response which is a non specific reflection of all other mycobacterium sensitisation. To overcome this effect both PPD RT and NTM sensitins could be given at the repeat skin testing in the group of persons reacting with induration diameters 10 mm to 15 mm. The assumption here being that persons with induration diameters greater than 15 mm to

PPD RT are statistically more likely to be infected with *M. tuberculosis*. This assumption is based on earlier observations that indurations exceeding 15 mm are statistically more likely to be caused by an infection with *M. tuberculosis* (17).

The cross reactivity between *M. tuberculosis* and NTM also has important implications for using the tuberculin test as an epidemiological tool in calculating the risk of tuberculosis infection. The yearly tuberculin index could be overestimated in situations where the rate of NTM infections in the population are high.

This study proposes a long term standardisation of the double Mantoux test outside the Royal Netherlands Army, in particular in contact surveys, to avoid the unnecessary use of INH chemoprophylaxis. To evaluate this approach an investigation has to be undertaken to ensure that persons excluded from INH chemoprophylaxis using this criteria do not develop tuberculosis. Such a study is yet to be undertaken by the Army.

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CHAPTER

6

HOTEL-ACQUIRED MDR TUBERCULOSIS INFECTION IN 10 DUTCH SERVICEMEN

HOTEL-ACQUIRED MDR TUBERCULOSIS INFECTION IN 10 DUTCH SERVICEMEN

Introduction

Infection with tuberculosis following contact with a case of tuberculosis during travel is well documented, and such contact has even been suggested to happen within the comforts of modern commercial aircrafts (Driver et al., 1994; Kenyon et al., 1996; Miller et al. 1996). These findings might offer little solace to persons from low endemic countries who perhaps perceive that their risk of acquiring tuberculosis is infinitesimally minimal. In the Royal Netherlands Forces, post-deployment screening for tuberculosis has taken on an even more important dimension in the last years given the global increase in the number of tuberculosis cases. With the emergence of multipledrug-resistant tuberculosis (MDR-TB) in several countries, this risk, though small as it may seem, takes on an ominious twist. The account that follows in this article will re-emphasise the importance of travel as a possible risk-factor for tuberculosis infection and that countries such as The Netherlands with a successful tuberculosis control programme cannot entirely be free from this disease as long as the TB problem exists elsewhere. The globe has shrunk and we are increasingly getting interconnected as millions of people can now traverse long distances around the globe in a few hours. Travel amplifies the chance of bringing and acquiring infections from one point of the globe to another.

In 1991 a Royal Netherlands Air Force unit was based in Turkey as part of a multi-national force during "Operation Desert Storm". The unit stayed in Turkey for three months, returning home end of March. As part of routine medical examination after overseas deployment, the servicemen were screened for tuberculosis infection.

Methods and Results

In June 1991, a total of 397 servicemen who had been based in Turkey were contacted and requested to come for a tuberculin test (Mantoux) and or a chest X-ray. Chest X-rays were performed in 127 persons and a Mantoux skin test administered to 270. The Mantoux skin testing identified 10 persons with induration diameters greater than 10 mm, and hence considered to have a positive Mantoux test (some of their characteristics are shown in the tabel). All persons were started on isoniazid prophylaxis therapy.

Further analysis of these persons revealed that they were part of a group of 69 who had been accomodated in the same hotel at Diyarbakir, Turkey. The rest of the group had stayed in other hotels and none of these had a positive Mantoux. According to the servicemen, these other hotels offered better living quarters compared to the hotel which

accomodated those with positive Mantoux tests. Interestingly, these persons reported that there was a hotel guest, probably a local, who constantly coughed although there were no reports suggesting close contact with the said person. There was also no information on whether this particular hotel guest had tuberculosis.

Table 1. Characteristics of servicemen with a positive Mantoux skin test

Pat. No	Age	Sex	Mantoux (mm) before Turkey	BCG (Yes/No)	Year last known Mantoux	Mantoux induration Post Turkey
1*	24	M	0	N	1987	16
2	19	M	0	N	1990	12
3	31	M	0	N	1981	15
4	33	M	0	N	1977	20
5**	33	M	4	Y	1970	20
6	29	M	0	N	1980	12
7	26	M	0	N	1983	23
8	37	M	0	N	1971	12
9	34	M	0	N	1977	17
10	31	M	4	N	1991	16

* This patient developed MDR tuberculosis

** This servicemen had a BCG in childhood. There is no policy of BCG vaccination within the Royal Netherlands Army.

Four months later, one of the 10 (a 24 year old male) developed tuberculosis with positive cultures for *M. tuberculosis*. Drug susceptibility testing done at the Institute of Public Health and Environment (RIVM) showed resistance to rifampicin, isoniazid and streptomycin. The tubercle bacilli were sensitive to ethambutol, pyrazinamide and ofloxacin. His treatment consisted of ethambutol (1200 mg), isoniazid (300 mg), pyrazinamide (2000 mg) and ofloxacin (800 mg). This patient was successfully treated for one year and subsequent follow-up has shown no evidence of relapse. In the rest of the group on INH prophylaxis, treatment was discontinued basing the decision on the likelihood that these persons had been exposed to the same source of infection.

DNA fingerprinting (Restricted Fragment Length Polymorphism) was performed at the RIVM and results indicated that this strain of *M. tuberculosis* was closely associated with two strains that had been identified among persons of Turkish origin residing in the Netherlands.

The remaining 9 persons with positive Mantoux test have been followed routinely with none developing tuberculosis by January 1997. These persons were seen once every three months at the Pulmonary Unit of the Central Military Hospital and chest X-rays done at six months intervals for two years. In January 1997 all persons were contacted by telephone and interviewed for presence of any pulmonary symptoms. All persons reported to be well.

Discussion

Multipledrug-resistant Mycobacterium tuberculosis disease (MDR-TB) defined as resistance to at least isoniazid and rifampicin has emerged as a major public-health threat. Rifampicin and isoniazid are key components of therapeutic regimens that are used in the treatment of tuberculosis. In the late 1980s and early 1990s MDR-TB outbreaks in the United States helped to re-focus public-health measures against tuberculosis. Many of the outbreaks however, have been reported among persons co-infected with the human immunodeficiency virus (HIV). The problem of MDR-TB is not only confined to one particular country. A recent WHO/IUATLD report provides an idea into the burden of MDR-TB in different geographical localities (Bustreo et al., 1996). High prevalence rates of greater than 30% MDR-TB were reported in Nepal (48%), parts of India (33.8%), and New York City, USA (30.1%). Most surveillance-based or hospital-based MDR-TB rates for European countries have shown prevalence rates lower than 2%. In The Netherlands this rate was 0.8% in 1993. In a hospital-based study conducted in 1992 in Turkey, the prevalence of multipledrug-resistance was at 9.2%, a rate much higher than that reported for Western Europe (Tahaolu et al., 1994).

The investigation presented in this article represents the first report of MDR-TB among Dutch servicemen that appears to have a direct bearing to overseas deployment. The last few years have witnessed an increasing number of deployments of servicemen to out-of-area theaters. With such increasing travel it is inevitable that some persons will acquire disease directly related to deployment in these areas. In fact this increase in travel is not only confined to the military population.

In this investigation there is circumstantial evidence to show that the 10 servicemen seemingly acquired infection with MDR tuberculosis while staying at a Turkish hotel. Fingerprinting results identified the strain of *M. tuberculosis* that developed in patient no. 1 as being related to strains isolated in persons closely linked with Turkey. This report also raises a number of issues that have a direct bearing on the future direction of tuberculosis control within the army. Firstly, the pre-deployment Mantoux results in the majority of persons with a positive value were obtained many years before deployment to Turkey. Patient number 5 had under-gone BCG vaccination. It might also be argued that the positive result in this patient following tuberculin testing is a boosted

immunologic response from BCG vaccination in spite of the 4 mm that was registered 20 years earlier. We can therefore not state with 100% certainity that these persons had converted to a positive Mantoux result following the Turkey contact. It might have been useful if a Mantoux test had been done just prior to deployment. Future deployments will have to reckon with this important prerequisite if concrete information on the risk of acquiring tuberculosis in overseas theaters is to be assessed. Likewise, travel clinics should also consider pre-travel skin testing of persons without a recent Mantoux result before such persons embark on a journey to tuberculosis endemic areas. Post-travel screening will therefore be important to establish incidences of tuberculosis infection during travel.

Patient no. 1 was started on treatment with at least three agents to which the organism was found to be susceptible. Although this patient was not placed on Directly Observed Therapy (DOT), he remained compliant until cure was effected one year after initiation of treatment. We would however recommend that in managing MDR-TB, directly observed therapy should be the rule. DOTS is already becoming increasingly favoured within The Netherlands and a number of very successful and innovative DOTS strategies have been described in the cities of Rotterdam and Amsterdam (van Galen and Breemer, 1996; Horsman and Lopes Dias, 1996).

Following the discovery of the MDR-TB case, isoniazid chemoprophylaxis was discontinued in the nine persons with a positive Mantoux reading. There is no suitable chemoprophylactic regimen that these persons (presumed to be infected with MDR-TB) could be given. This therefore begs the question as to how long such persons need to be followed-up. The use of DNA fingerprinting in this case and comparing it with strains that were from persons closely associated with Turkey represents a new and fascinating approach in epidemiology. However, since the routine use of such molecular biology techniques is not well developed in many countries, it makes it difficult even at this time of exciting molecular biology advances, to compare the different strains isolated and try to compare them with strains from other countries. Probably more work will be done in this direction thus enabling molecular epidemiologist to exactly pin-down the source of a patients disease.

That tuberculosis developed among a group of servicemen who were accomodated in a hotel illustrates just how ubiquitous this organism can be. For the traveller who takes solace in staying in luxurious quarters this report may sound alarmist. Although the risk of acquiring tuberculosis within The Netherlands is minimal in comparison to other areas, the truth should not evade us. The truth is that with increasing travel and deployments (for military personnel), persons from tuberculosis non-endemic areas will still run a real risk of acquiring tuberculosis infection. All that travellers require is exposure to a source of infection which in this case is suspected to have been someone

in the hotel. MDR tuberculosis is rare in The Netherlands but this case shows that travel brings persons in contact with diseases that might be rare in their home countries.To control and contain (MDR) tuberculosis therefore requires concerted global efforts since travel that brings persons in contact with environments where the disease might be a problem will not slow but increase in the coming years.

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General Discussion and Summary

Tuberculosis control in the Royal Netherlands Army has always been a prominent element of the Army Health Services ever since the end of World war II. The basic principles of tuberculosis control over the decades have centered around interrupting the chain of trans-mission in Army populations often living and working in congregate settings. Tracing and treating persons infected with tuberculosis but with no active disease has not been a straight forward issue. This thesis traces the evolution of these basic control methods within the Royal Netherlands Army and highlights important bottle-necks inherent in applying the different control techniques. Particular emphasis is placed on MMR and the shortcomings of the tuberculin test. Novel methodologies aimed at increasing the efficiency and specificity of this test are presented.

Chapter two describes the Army tuberculosis program since its inception and how it has evolved over the last 5 decades. Although the basic principles of tuberculosis control have by and large remained unchanged since Robert Koch described *M. tuberculosis* as the causative organism of tuberculosis, the diagnosis and treatment of the condition have made impressive strides. Initially reliance was placed almost exclusively on physical examination to make a diagnosis, but this was later supplemented with X-ray of the chest. Röntgenography was adapted in the Royal Netherlands Army as a tuberculosis screening tool in 1933. In that year, 1001 recruits reporting for military duty underwent a chest X-ray. The Army had clearly found a tool that offerred tremendous advantages as time and manpower lost to the disease could be decreased and spreading of tuberculosis within the service could be limited by identifying infectious cases, which otherwise could escape identification during physical examination alone and thus human suffering could be prevented. Subsequent improvements in X-ray techniques were also adapted through the years. During 1945, photofluorographic equipment , "Watsons", became operational and it was possible for the first time to screen faster and more efficiently. Screening was thus extended to even larger groups using this new technique of Mass Miniature Radiography (MMR). Remarkable was the shortening of the screening interval among Army recruits entering the Army and screening procedures to undergo an X-ray. For instance this shortened in 1960 by 56% over the 1951 average of 6.8 days. By 1967 better technology made it possible to X-ray all recruits on their first day at an induction centre.

The X-ray policy as a screening tool was continuously evaluated to see if the returns from the application of this tool justified the cost. In 1989, there was evidence indicating that compul-sory chest X-ray screening added little to the identification of tuberculosis infected persons.

Other tools were more attractive as a means of identifying these persons. The tool that was relied on was the Mantoux skin test. This test came into usage in the Army in 1955. Between 1955 and 1956, a study was conducted among Army recruits to find out if there was a regional differrence in sensitivity to tuberculin. The study found that the tuberculin sensitivity ranged from 14 to 30% with the lowest percentage being observed in the northern provinces of the Netherlands in comparison to the southern provinces. This phenomenon has faded out over the years. By the decreasing infection-index the percentages in north and south became equal by 1975. Apart from demonstrating such important regional differences, the tuberculin skin testing program of the Army maintained a tuberculosis registry in which the annual prevalence of tuberculin sensitivity among recruits were entered. This registry has provided over the years a unique set of data that gives an insight into the temporal trends of tuberculosis infection among young Dutch males. During the period 1956 to 1969, the percentage of recruits reacting with a positive Mantoux declined from 19.2% to 4.4%. By 1995, tuberculin sensitivity among recruits had drastically declined to a prevalence of 0.42%.

This decline occurred in absence of a BCG vaccination policy in the Army. BCG has never been used on a wide scale even among the general Dutch population. However with increasing mobility of the population in modern times, the Army- just like in the general population- is witnessing an increase in the number of recruits from countries where a policy of BCG vaccination is widely practiced. In 1995, of the 306 recruits with a BCG vaccination, 74% were foreign born. Mantoux skin testing among such persons is unlikely to be a useful tool in identifying tuberculosis infections. Therefore, a Mantoux skin test in this group of persons will be of limited value. Apart from providing useful information on prevalence of tuberculosis infection among Army recruits, the Mantoux skin testing has been extensively used as a means of selecting canditates for isoniazid prophylaxis therapy (IPT).

Isoniazid prophylaxis in the Army was initiated in 1960. Recruits reacting to a Mantoux skin test with an induration of at least 10 mm are recommended for IPT. However, the decision to give IPT is based on assessed risks and benefits of isoniazid treatment. One clear advantage from isoniazid prophylaxis is that it decreases the likelihood of infected tuberculosis persons from developing active disease. The efficacy of isoniazid prophylaxis in preventing tuberculosis reactivation has been shown to range from 60-80% (1). On the other hand IPT is not free of side effects. Chapter three presents results of the RNLAs experience with using isoniazid chemoprophylaxis between 1984 to 1995 among 739 persons. The study showed that isoniazid-associated adverse events were present in 10.6 percent of the study population. Of all adverse events associated with isoniazid, liver damage, which occassionally is severe and fulminant is the most dreaded complication. Among the 739 persons in this study, liver transaminase levels were

assessed during therapy. Elevated transaminase levels were observed in 5.4% of the study population with evidence of hepatic damage in 1.4 percent of these. The majority of transaminase level elevations were less than 2x upper limit of normal. The frequency of transaminase level elevation in this study was much lower than that reported by authors from elsewhere (2,3). For instance a United States Air Force study found a percentage of 22 percent among those on IPT (2). The difference between the Dutch Army series and the US Air Force Study is possibly related to the age of patients and the duration of IPT, six month versus one year. In this Dutch study over 96 percent of the study subjects had a mean of 22 years while the US Air Force study had subjects with a mean age of 30 years. Age is an important factor in the decision of initiating isoniazid prophylaxis. Usually in persons older than 35 years, isoniazid chemoprophylaxis is not recommended unless the patient is at a very high risk of developing active tuberculosis. This recommendation is based on the finding that isoniazid hepatotoxicity is three times greater among patients aged ≥35 years than those aged <35 years (4). This RNLA study did not register any form of fulminant hepatitis and no fatalities were seen. Perhaps this had to do with regular clinical and hepatic enzyme monitoring that these patients underwent. In this study discontinuation of therapy happened in 19 persons and this represented 24% of all those persons who developed adverse reactions attributed to isoniazid therapy. Eight of the persons in the group in which therapy was discontinued were among those with asymptomatic elevated transaminase levels. Side effects to isoniazid occurred throughout the study period with 77%of these events happening in the first three months. Although the frequency of isoniazid associated side effects in this study were much lower than in many other studies, guidelines should be devised to even minimise these further. This study recommends that regular clinical and hepatic enzyme monitoring should at least take place during the first three months of therapy.

Currently Mantoux skin testing with purified protein derivative is the only practical test in discriminating between those with *M. tuberculosis* from those without and hence determining who qualifies for enrolment into the IPT programme. However the interpretation of this test is not always a straight forward "positive" or "negative". The interpretation of the Mantoux test depends on a number of clinical circumstances of patients. For instance the Centres for Disease Control (CDC) in the United States recommends that a 5 mm cutoff point be considered for persons with HIV infection or those who have had close contact with someone with infectious tuberculosis and a 10 mm cutoff point for foreign-born persons (5). An induration of at least 15 mm in persons with no risk factors for tuberculosis is considered as positive. Another important aspect that must be taken into account while interpreting the Mantoux test results is the role of nontuberculous mycobacteria (NTM). The PPD used in the Mantoux skin test is a mixture of different mycobacterial antigens, which partially cross-react to species of nontuberculous mycobacteria. These mycobacteria are present in a wide range of

environmental sources making these organisms a common sensitiser of human populations. Therefore in populations with a low prevalence of tuberculosis infection and a high nontuberculous mycobacteria prevalence, the usefulness of the tuberculin test will be limited. The prevalence of nontuberculous mycobacteria among RNLA recruits was therefore studied in a period of three years, 1986-1988, among a total of 37,755 persons with the *M. scrofulaceum* sensitin. The use of this sensitin as a test antigen was because it cross-reacts more broadly with all other nontuberculous mycobacteria (6). The results of this investigation are presented in chapter four.

The prevalence of nontuberculous mycobacteria sensitivity among the entire recruit population observed in the three study years was 7.8 percent. A Dutch study conducted among school children in the Delft area of the Netherlands showed an even higher prevalence of about 13 percent (7). This Dutch Army study clearly demonstrates that there is a high prevalence of sensitivity to nontuberculous mycobacteria in recruit populations. The practical importance of this is that the delineation of reactions due to nontuberculous mycobacteria from those attributed to *M. tuberculosis* infection is necessary if isoniazid prophylaxis is to be given to those who are truly infected with tuberculosis and not to those who as a result of NTM infections react positively to a Mantoux skin test employing PPD Rt Tween 23.

Chapter five presents the results of a study whose objective was to improve upon the PPD skin testing procedure so as to provide a better distinction between reactions due to *M. tuberculosis* from those that result from NTM infections. During the first part of the study, from 1986-1988, army recruits were tested simultaneously with PPD RT 23 and *M. scrofulaceum* sensitin. During the second part of the study, from 1989 to 1993, recruits reacting to PPD RT 23, with an induration in the range of 10-15 mm, underwent a second skin test with *M. scrofulaceum* sensitin. The total study population consisted of 237,692 non-BCG-vaccinated recruits. The results showed that from 1986-1993 an average of 0.45% persons reacted with indurations ≥10 mm to PPD RT 23. An average of 7.7% army recruits reacted with indurations of ≥10 mm to *M. scrofulaceum* sensitin during the first part of the study. Using a modified ITSC (International Tuberculosis Surveillance Centre) model, 48% of the persons reacting to PPD RT 23 with indurations in the range 10 mm and 15 mm were classified as false positive. False-positive persons were then excluded from INH chemoprophylaxis. This study recommends that in areas with a high prevalence of nontuberculous mycobacteria infection the use of a double Mantoux skin testing might be useful in differentiating between indurations due to tubercle bacilli and those due to infection with nontuberculous mycobacteria. This will limit the prescription of isoniazid to persons who are truly infected with the tubercle bacilli and therefore will benefit from it. This study also proposes a standardization of

the double Mantoux test as a tool in avoiding the unnecessary use of INH chemoprophylaxis.

The RNLA has not been oblivious of the public health problem of tuberculosis among her ranks and files. Through the years, the army has used all available tuberculosis control tools to provide better care for all servicemen. Although the prevalence of tuberculosis infection in the Army is extremely low it is unlikely that tuberculosis will become a historical curiosity within the Service. Many countries still have a very serious tuberculosis problem with disease prevalence rates above 200 cases per 100,000 persons. The consequences of this high prevalence rates from such regions ensure that the eradication of tuberculosis in the near future are unlikely. The army deployments around the globe, especially in peace-keeping missions, will certainly come into contact with tuberculosis in areas where it remains a major public health problem.

In chapter six, an account of exposure to tuberculosis during a military deployment abroad is provided. The incident underscores the value of a tuberculosis screening programme for personnel deployed to areas with a significant tuberculosis problem. In 1991, a tuberculin skin testing exercise was carried out in a Dutch Military Unit returning from a three months deployment in Turkey. It was found that ten of those tested had acquired tuberculosis infection during deployment. Further investigation found that all 10 were among a group of 69 who had stayed at the same hotel. One person developed multiple drug-resistant (MDR) tuberculosis five months later. It was likely that the other persons were infected with MDR-TB as well. This report underscores the fact that tuberculosis transmission can occur in the course of deployments. The chapter also highlights the fact that although it is possible to skin test individuals and provide isoniazid to those with tubercle infection, the emergence of MDR TB is a challenge that will not only limit itself to highly affected geographical areas.

The control of tuberculosis in the RNLA has always been adapted in such a way that it conformed to new developments and insights in the field of tuberculosis epidemiology within the Netherlands and from elsewhere. In spite of the fact that the Netherlands is considered as a low endemic country for tuberculosis, attention for the disease in the RNLA has not been slackened. On the contrary. More and more attention has been paid to the disease. The reason for this being that in recent years the Army has been involved in a number of overeseas operations with servicemen deployed to high tuberculosis endemic countries. Besides the shift from a conscription to a professional Army has resulted in a considerable change in the demographic and soical composition of the service. Consequences of this being that the tuberculin prevalence figures that were calculated based on young Netherlands-born males is no longer a reflection of the current tuberculosis prevalence status of the new professional Army. The possible

deletrious effects of MDR tuberculosis as discussed in chapter six have also sharpened the control efforts.

Mantoux skin testing is the pillar of the RNLA tuberculosis control programme and during group screening it continues to identify persons infected with tuberculosis. In addition the results of the Mantoux skin testing provides the necessary data required in estimating the now complex issue of the tuberculosis prevalence in the Netherlands. The double Mantoux skin testing outlined in this thesis offers a better discrimination between infections due to the tubercle bacilli and those due to NTMs and is now an integral part of the army tuberculosis control programme. This methodology has led to an almost 50% reduction in persons requiring isoniazid among those with indurations between 10-15 mm. This procedure has also been adapted by some civilian organisations to screen tuberculosis low risk persons. This can be viewed as a positive spin-off benefit to general public from the army tuberculosis programme.

Meanwhile the tuberculosis control policy within the RNLA has been aptly defined. In summary, the main areas of focus are as follows:

- a standard Mantoux skin testing is performed for all persons at induction into the Army, before and after overseas deployment and for all persons in high risk groups. The latter group undergoes an annual skin testing procedure. For all indurations between 10-15 mm among non-BCG-vaccinated persons, a double Mantoux skin test as described in the thesis is performed.
- the results of the tuberculin skin testing are processed and stored in a computerised data base. This provides information which serves as basis for evaluating the Army tuberculosis control efforts.

With these measures it is hoped that the current global TB epidemic will be kept at arms-length in the Royal Netherlands Army.

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Samenvatting

Tuberculose controle heeft in het Nederlandse leger sinds de Tweede Wereldoorlog altijd een belangrijke rol gespeeld in de militaire gezondheidszorg. De uitvoering van deze taak is na 1945 ondergebracht in een aparte, daartoe uitgeruste Dienst, welke later de naam Dienst Militaire Gezondheidszorg heeft gekregen. Het basis-principe van de tuberculose controle is door de jaren heen gericht geweest op het onderbreken van de transmissieketen in de veelal dicht opeen werkende militaire leefgemeenschap. Naast het in eerste instantie opsporen en behandelen van al dan niet sputum-positieve tuberculosegevallen, is in tweede instantie de identificatie en behandeling van geïnfecteerde personen met een niet actieve tuberculose een steeds belangrijker doelstelling geworden. Dit proefschrift beschrijft de methoden van tuberculose controle die in het Nederlandse leger zijn gebruikt en bespreekt belangrijke knelpunten die voortvloeiden uit de gebruikte verschillende controle-technieken. In het bijzonder wordt aandacht besteed aan het tuberculine-onderzoek en de tekortkomingen hiervan. Nieuwe methoden, die bedoeld zijn om de effectiviteit en de specificiteit van de gebruikte testmethoden te verhogen worden belicht.

Hoofdstuk 2 beschrijft het tuberculose controleprogamma van het Nederlandse leger vanaf de invoering ervan in 1936 en hoe dit na 1945 is veranderd. Hoewel de basis-principes van de tuberculose controle grotendeels onveranderd zijn gebleven sinds Robert Koch M. Tuberculosis als de veroorzaker van tuberculose beschreef, hebben opsporingsmethoden, diagnostiek en behandeling van tuberculose een indrukwekkende vooruitgang geboekt. In het begin berustte de opsporing van tuberculose uitsluitend op de bevindingen bij lichame-lijk onderzoek. Dit werd later aangevuld met een röntgen-diagnostiek, eerst d.m.v. rontgen-doorlichting en later de (indirecte)röntgenfotografie van de thorax. De (massa)-röntgen-doorlichting als middel van screening werd voor het eerst in 1933 geïntroduceerd in het Nederlandse leger. In de jaren 1936 tot 1939 ondergingen 90.000 recruten bij hun entree in het leger een röntgenborstonderzoek. Het leger had eindelijk een screenings-methode gevonden die veel voordelen opleverde zoals een vroegere diagnostiek van longaandoeningen, waardoor er een vroege behandeling van opgespoorde ziekten mogelijk werd, er daardoor een daling van het aantal ziektegevallen volgde en ziekteverzuim werd teruggedrongen. De verspreiding van tuberculose binnen het leger kon op deze wijze worden beperkt. Hierdoor kon veel menselijk lijden worden voorkomen of bekort. In 1945 werd de röntgenschermbeeld-fotografie geïntroduceerd. Met gebruik making van de transportabele "Watsons" werd deze techniek geoperationaliseerd en werd het voor het eerst mogelijk snel en efficiënt te screenen. De screening van nog grotere groepen militairen in een kortere tijd behoorde nu tot de mogelijkheden met de techniek van de Mass Miniature Radiography (MMR). Opmerkelijk was de bekorting van het screeningsinterval tussen de dag van opkomst onder de wapenen van de militair en de uitvoering van het röntgenborst-

onderzoek. Zo was deze periode in 1960 meer dan gehal-veerd tot drie dagen t.o.v. het gemiddelde interval van 6.8 dagen in 1951. Tenslotte werd het in 1967 door verbeterde technologie en operationele voorzieningen mogelijk om alle recruten op de eerste dag van hun binnenkomst in het leger te onderwerpen aan een röntgenborstonderzoek en zodoende te screenen op tuberculose.

Deze methode van röntgenborstonderzoek als middel van screening op tuberculose werd daarna regelmatig geëvalueerd en getoetst op zijn kosten-baten verhouding. Zo werd, mede door toedoen van een algehele daling van tuberculose in Nederland, tenslotte in 1989 geoordeeld dat het routinematige röntgenborstonderzoek bij recruten een zodanig geringe opbrengst aan tuberculosegevallen opleverde dat deze niet meer kosteneffectief was. Bovendien werd een onnodige blootstelling aan röntgenstraling meer en meer onaanvaardbaar geacht.

Voor het opsporen van een actieve, besmettelijke vorm van tuberculose, welke overigens na 1980 nog maar zelden bij recruten tijdens hun opkomst werd aangetroffen, was men dus in eerste instantie weer aangewezen op fysisch-diagnostisch onderzoek. Evenwel was voor het identificeren van niet infectieuze tuberculosegevallen en tuberculosebesmettingen binnen het leger inmiddels het tuberculine-onderzoek geïntroduceerd. Deze onderzoeksmethode bleek uitstekend geschikt en meer op zijn plaats om personen met tuberculose vroegtijdig op te sporen.

De tuberculineproef bij voorkeur werd de Mantoux-huidtest. Deze test werd in het leger in 1955 in gebruik genomen. Tussen 1955 en 1960 werd een studie uitgevoerd onder recruten om vast te stellen of er regionale verschillen in tuberculine-huidgevoeligheid bestonden. De studie toonde aan dat de tuberculine-huidgevoeligheid varieerde en toenam van 14% in de meer noordelijk gelegen provincies naar 30% in de meer zuidelijk en westelijk gelegen provincies. Deze waarneming werd verklaard doordat in het noorden en het noordoosten van het land de rundertuberculose voor het eerst werd bestreden. Door het verdwijnen van rundertuberculose en de natuurlijke daling van de besmettings-prevalentie werden tenslotte in 1975 de percentages in de noordelijke, zuidelijke en westelijke provincies min of meer gelijk. Naast het aantonen van deze belangrijke regionale verschillen en de veranderingen ervan in de tijd werd de systematische registratie van de tuberculineonderzoeksresultaten binnen het leger gebruikt voor het bepalen van de jaarlijkse prevalentie van de tuberculine-huidgevoeligheid onder de recrutenpopulatie bij binnenkomst in het leger. Deze registratie heeft door de jaren heen een unieke set aan gegevens opgeleverd welke inzicht verschafte in de jaarlijkse trend van tuberculose-besmettingen onder jonge Nederlandse mannen. Deze gegevens werden tevens gebruikt voor het berekenen van het jaarlijkse infectierisico in Nederland.

Gedurende de periode van 1956 tot 1969 daalde het percentage positieve mantoux-reacties onder de recruten van 19.2 % tot 4.4 %. Tot 1985 daalde de tuberculine-

huidgevoeligheid onder recruten voortdurend tot een prevalentie van om en nabij de 0.42 % werd bereikt. Hierna zette de daling zich niet verder voort.

Het verdient vermelding dat deze daling optrad in afwezigheid van een BCG-vaccinatiebeleid in het Nederlandse leger. Slechts 5% van de jonge recruten bleek in 1955 bij opkomst gevaccineerd te zijn met BCG. In Nederland is de BCG-vaccinatie onder de algemene bevolking nooit op grote schaal toegepast. Slechts "bedreigde" groepen zoals medisch personeel en langdurig in het buitenland verblijvende personen werden op aanraden van de Gezondheidsraad gevaccineerd. Ook binnen het leger volgde men deze aanbeveling en werden bijvoorbeeld rond 1966 de VN-eenheden, de Suriname Cie en het geneeskundig personeel met BCG gevaccineerd. Het grote nadeel van de BCG-vaccinatie was dat bij gevaccineerde personen de Mantoux-reactie niet meer bruikbaar was voor het opsporen van besmettingen met M.tuberculose. Mede hierdoor werd in die tijd de BCG-vaccinatie ook bij de zogenaamde bedreigde groepen steeds minder toegepast. In 1990 werd onder de merendeel autochtone recrutenpopulatie nog maar zelden een met BCG gevaccineerde persoon aangetroffen. Echter door een toenemende migratie van de wereldbevolking in de huidige tijd constateert men in het leger een toename van het aantal recruten dat afkomstig blijkt te zijn uit landen waar een BCG-vaccinatie bij de bevolking nog steeds op grote schaal wordt toegepast. In 1995 bleek dat van 306 recruten met een BCG-vaccinatie er 74 % van buitenlandse afkomst te zijn. Het tuberculineonderzoek bij deze personen heeft zoals eerder gezegd een zeer beperkte waarde in de opsporing van tuberculosebesmettingen. Een screening m.b.v. rontgenborstonderzoek werd dan ook standaard toegevoegd bij deze met BCG-gevaccineerde recruten. Naast het verzamelen van bruikbare informatie ten behoeve van de tuberculose-besmettingsprevalentie in het Nederlandse leger en de algemene Nederlandse bevolking, worden de resultaten van de Mantoux-huidtest gebruikt bij de selectie van kandidaten die in aanmerking komen voor preventieve therapie (INH).

INH als preventieve therapie werd in 1960 in het Nederlandse leger geïntroduceerd. Recruten die op de Mantoux-huidtest reageerden met een induratie van tenminste 10 mm kwamen in aanmerking voor INH. Echter, de beslissing om preventieve therapie te starten was gebaseerd op de afweging van de voor en nadelen van de INH-behandeling. Het belangrijkste voordeel dat voortvloeit uit het geven van de INH als preventieve therapie is het dalen van het risico dat zich later een actieve tuberculose ontwikkelt. De effectiviteit van INH-profylaxe in het voorkomen van een tuberculose (re)activatie wordt in de literatuur aangegeven in de orde van 60 - 80% (1). Echter de INH-therapie is niet geheel vrij van bijwerkingen.

In hoofdstuk 3 worden de resultaten besproken van de ervaringen met INH-profylaxe bij een groep van 739 recruten in de periode van 1984 tot 1995. De studie laat zien dat 10,6 % van deze studie-populatie bijwerkingen vertoont die aan de INH-profylaxe gerelateerd zijn. Van alle bekende bijwerkingen, die geassocieerd zijn met INH, is de chemisch geïnduceerde hepatitis de meest gevreesde complicatie. Deze kan ernstig zijn en fulmin-

ant verlopen. Bij alle 739 deelnemers aan deze studie zijn gedurende de therapie-periode de transaminasewaarden in het bloed gevolgd. Verhoogde transaminasewaarden werd bij 5.4 % van de studie-populatie geobserveerd waarbij in 1.4 % aanwijzingen bestonden op leverbeschadiging. De meerderheid van de verhoogde transaminase-waarden was minder dan twee keer de normaalwaarde. De frequentie van de verhoogde transaminasewaarden in deze studie was veel lager dan die welke gerapporteerd zijn door andere auteurs in de literatuur (2,3). Zo vond een studie van de US-Air Force bij 1000 personen een percentage van 22 % als complicatie bij hen met INH-profylaxe. Het verschil in resultaat tussen het Nederlandse onderzoek en dat van de Amerikaanse onderzoeksgroep is mogelijk te wijten aan de leeftijd van de onderzoeks-groep en de duur van de INH-behandeling, 6 maanden Nederland versus 12 maanden in de VS. In de Nederlandse studie had 96 % van de deelnemers een gemiddelde leeftijd van 22 jaar terwijl die bij de Amerikaanse studie 30 jaar bedroeg. Leeftijd is een belangrijke factor bij de afweging van het geven van INH-profylaxe. Bij oudere personen is men zeer terughoudend met het voorschrijven van INH-profylaxe. INH-profylaxe wordt dan ook niet aanbevolen voor personen ouder dan 35 jaar, tenzij de patiënt een hoog risico loopt t.a.v. het ontwikkelen van actieve tuberculose. Deze aanbeveling is gebaseerd op de bevindingen dat de hepato-toxiciteit t.g.v. INH drie maal groter blijkt te zijn bij personen ouder dan 35 jaar t.o.v. de jongere leeftijdsgroep (4). In het hier beschreven eigen onderzoek bij Nederlandse recruten werden geen gevallen van ernstig verlopende hepatitiden geregistreerd. Wellicht dat dit mede het gevolg is van een frequente monitoring t.a.v. het klinische beeld als wel de lever-enzymen bij hen die een INH-profylaxe volgden. In deze studie werd bij 19 personen de preventieve therapie onderbroken. Dit betekent een percentage van 24 van het totaal aan personen die bijwerkingen hebben ontwikkeld als gevolg van de INH-profylaxe. Bij 8 personen waren sterk verhoogde transaminasespiegels de reden dat de therapie vroegtijdig werd onderbroken. Bijwerkingen als gevolg van de INH-therapie kwamen in 77 % van de gevallen in de eerste drie maanden van de therapie-periode voor. Hoewel de frequentie van het voorkomen van bijwerkingen in deze studie veel lager was dan in vergelijking met veel analoge studies, is het toch aan te bevelen richtlijnen op te stellen om het optreden van deze bijwerkingen verder te voorkomen. Deze studie onderstreept nog eens de wenselijkheid om in de eerste 3 maanden van de therapie een geregeld klinisch onderzoek en bepaling van de leverenzymen te laten plaatsvinden.

Het Mantoux-onderzoek met PPD-Humanum is op dit moment de enige praktisch uitvoerbare test die een besmetting met M. Tuberculosis kan aantonen en bepaalt in belangrijke mate wie in aanmerking komt voor INH-profylaxe. De interpretatie van deze test is echter niet altijd eenduidig "positief" of "negatief". Deze interpretatie hangt namelijk af van een aantal klinische omstandigheden bij de onderzochte persoon. Zo kent bijvoorbeeld het Centres for Disease Control (CDC) in de Verenigde Staten de aanbeveling van een 5 mm "cut off-point" bij HIV-positieve personen en eveneens 5 mm bij hen die in nauw contact zijn geweest met een besmettelijke tuberculosepatiënt.

Voor uit het buitenland afkomstige personen (allochtonen) wordt door het CDC een 10 mm "cut off-point" aanbevolen (5). Tenslotte wordt door hen een induratie van tenminste 15 mm beschouwd als positief bij personen zonder vermeende risicofactoren. Een ander belangrijk aspect waarmee rekening gehouden moet worden bij de interpretatie van de Mantoux-test is de rol van de aspecifieke mycobacteriën (mycobacteriën anders dan de M.tub.hum.). De PPD gebruikt bij de Mantoux-test is een mengsel van verschillende mycobacteriële antigenen van PPD-humanum die gedeeltelijk kruis-reacties vertonen met de antigenen van diverse mycobacteriën anders dan M.tub.hum. Deze mycobacteriën komen wijd verspreid voor in de natuurlijke omgeving en zijn dien ten gevolge debet aan een uitgebreide sensibilisatie onder de algehele bevolking. Daarom geldt bij bevolkingsgroepen met een lage tuberculose-prevalentie en een relatief hoge prevalentie van aspecifieke mycobacteriële besmettingen, dat de bruikbaarheid van de huidige tuberculine-test zijn beperkingen kent. De prevalentie van aspecifieke mycobacteriële besmettingen onder Nederlandse recruten werd daarom bestudeerd over een periode van 3 jaar, 1986 - 1988, bij een totaal van 37.755 personen met behulp van het M. Scrofulaceum sensitine. Het gebruik van dit sensitine als test-antigeen is verkozen omdat het zich bevindt in het midden van het spectrum van de "aspecifieke" mycobacteriën en daarom kruisreacties vertoont met het merendeel van hen (6). De resultaten van dit onderzoek zijn beschreven in hoofdstuk 4.

De prevalentie van de aspecifieke mycobacteriële besmettingen onder de gehele populatie recruten over een periode van 3 achtereenvolgende jaren was 7,8 %. Een Nederlandse studie uitgevoerd bij schoolkinderen in Delft toonde zelfs een nog hogere prevalentie aan van ongeveer 13 % (7). Deze studie binnen het Nederlandse leger toont duidelijk aan dat er een hoge prevalentie bestaat van aspecifieke mycobacteriële besmettingen bij recrutenpopulaties. Het praktische belang van deze constatering is dat er onderscheid gemaakt moet worden tussen reacties die zijn veroorzaakt door aspecifieke mycobacteriën of door M. Tuberculosis. Om tot een juiste indicatiestelling voor INH-profylaxe te komen dient deze immers slechts te worden gegeven aan hen die zijn besmet met de "echte" tuberculosebacteriën en niet aan hen die door de kruisreacties van aspecifieke mycobacteriën toch positief reageren op de reguliere Mantoux-huidtest (PPD Rt Tween 23).

Hoofdstuk 5 presenteert de resultaten van een onderzoek dat tot doel had het verbeteren van het huidige tuberculineonderzoek bij militairen door met meer nauwkeurigheid te kunnen onderscheiden tussen huidreacties veroorzaakt door M. Tuberculosis en die door besmetting met aspecifieke mycobacteriën. De theoretische achtergrond van dit vergelijkend tuberculine-onderzoek was gebaseerd op het feit dat de tuberculine-huidgevoeligheid bij een mycobacteriële infectie groter is bij de toediening van een homoloog antigeen dan bij een heteroloog antigeen.

Tijdens het eerste deel van de studie, van 1986 - 1988, werden recruten simultaan getest met PPD Rt 23 en PPD-Scrofulaceum. Gedurende het tweede deel van de studie, van

1989 - 1993, werden de recruten die positief reageerden op PPD Rt 23, met een induratie tussen de 10 en 15 mm, opnieuw getest met M. Scrofulaceum sensitine (PPD-Scrofulaceum). De totale studiepopulatie bestond uit 237.692 niet met BCG gevaccineerde recruten.

De resultaten laten zien dat in de periode 1986 - 1993 gemiddeld 0,5 % van de onderzochte personen positief reageerde op PPD Rt 23 (induratie > 10 mm.). Gedurende het eerste deel van de studie reageerde gemiddeld 7,7 % op M. Scrofulaceum met een induratie groter dan 10 mm. Gebruikmakend (om praktische redenen) van een gemodificeerd ITSC (International Tuberculosis Surveillance Centre) model, blijkt dat 48% van de personen die positief reageren op PPD Rt 23 met indurations tussen de 10 en 15 mm, kunnen worden geklassificeerd als fout-positieve reacties. Bij deze personen werd derhalve ook geen INH-profylaxe voorgeschreven. Deze studie toont aan dat in gebieden met een relatief hoge prevalentie van niet tuberculeuze mycobacteriële infecties, het gebruik van de dubbel-mantouxtest bruikbaar kan zijn in het maken van onderscheid tussen indurations veroorzaakt door de tubercelbacterie en die door infecties met atypische mycobacteriën. Het gevolg is dat INH meer gericht wordt voorgeschreven aan hen die daadwerkelijk met de tubercelbacterie zijn geïnfecteerd en dus profijt kunnen verwachten van de voorgeschreven preventieve medicatie. Deze studie beveelt dan ook aan tot de standaardisatie en de standaard uitvoering van de dubbel-mantouxtest bij bepaalde groepen recruten als middel om onnodig en ongewenst voorschrijven van INH te voorkomen.

Het leger heeft altijd veel aandacht besteed aan het tuberculoseprobleem binnen haar gelederen. Door de jaren heen werd gebruik gemaakt van alle beschikbare tuberculose-controlemiddelen met al.s doel een optimale zorg voor haar personeel in deze. De tuberculose-prevalentie binnen het leger is momenteel erg laag en een afspiegeling van die in de Nederlandse samenleving. Toch is het niet waarschijnlijk dat tuberculose in het leger een historische curiositeit wordt. Veel landen in de wereld hebben namelijk nog steeds te maken met een ernstig tuberculoseprobleem met soms een incidentie van meer dan 200 gevallen per 100.000 inwoners. Het gevolg van deze hoge incidentiecijfers in die landen is er de oorzaak van dat het uitbannen van tuberculose in de nabije toekomst ook in Nederland niet waarschijnlijk geacht mag worden.

Het uitzenden van legeronderdelen waar ook ter wereld, in het bijzonder tijdens "peace-keeping" opdrachten, garandeert onherroepelijk het in contact komen van militairen met tuberculose in gebieden waar de tuberculose-incidentie hoog is.

In hoofdstuk 6 wordt een voorbeeld gegeven van een dergelijke confrontatie van een uitgezonden legereenheid met het tuberculoseprobleem. Dit voorval onderstreept nog eens de waarde van het vigerende screeningsprogramma rondom uitzendingen.

In 1991 werd een tuberculine-onderzoek uitgevoerd bij een militaire eenheid die terugkeerde uit Turkije na een verblijf aldaar van 3 maanden. Het onderzoek leverde een

tiental personen op die recentelijk waren besmet met tuberculose. Bij nader onderzoek bleek dat alle besmette personen afkomstig waren uit een groep van 69 militairen die allen in hetzelfde hotel waren ondergebracht. Eén van hen ontwikkelde 5 maanden na terugkeer een Multi Drug Resistente (MDR)tuberculose. Aangenomen mag worden dat ook de andere 9 personen besmet geraakt zijn door dezelfde bron, een MDR-tuberculose. Bevestigd wordt nog eens dat tuberculosetransmissie tijdens de duur van een uitzending kan plaatsvinden. Bovendien blijkt uit dit relaas, dat ondanks een zorgvuldig uitgevoerd tuberculineonderzoek en de ingestelde preventieve therapie bij de positief (besmet) bevonden personen, de dreiging van MDR-tuberculose ook het leger aangaat en niet slechts een probleem is voor ingezetenen van landen met een relatief hoge prevalentie aan MDR-tuberculose.

De tuberculose-opsporing en bestrijding in het Nederlandse leger heeft zich door de jaren heen steeds aangepast aan de nieuwste ontwikkelingen en inzichten van de tuberculosebestrijding in Nederland en daarbuiten. Ondanks het feit dat Nederland wordt beschouwd als een laag endemisch gebied voor tuberculose, is de aandacht voor tuberculose binnen het Nederlandse leger niet verslapt. In tegendeel, de aandacht wordt zelfs verscherpt. De reden hiervoor is dat het leger in toenemende mate wordt geconfronteerd met uitzendingen van personeel naar landen met een hoge tuberculose-prevalentie en -incidentie. Daarnaast heeft de verschuiving van een dienstplichtig leger naar een beroepsleger geresulteerd in een aanzienlijke verandering van de socio-demografische samenstelling van het militaire personeel. Het gevolg is dat de vroegere (jaarlijks) berekende tuberculine-indices (besmettingsprevalenties) en de trend hiervan, welke voorheen waren gebaseerd op de onderzoeken bij recruten - jonge Nederlandse mannen met een gemiddelde leeftijd van 20 jaar - , niet zonder meer maat zijn voor de tuberculosestatus van het huidige beroepsleger. Tenslotte heeft ook de confrontatie met MDR-tuberculose de aandacht voor tuberculosecontrole binnen het Nederlandse leger verscherpt.

De pijler van de tuberculosebestrijding binnen het leger is op dit moment het tuberculine-onderzoek met gebruik van de Mantoux-test. Tijdens individuele en groepsscreeningen worden nog geregeld met tuberculose besmette personen geïdentificeerd. Bovendien levert het tuberculineonderzoek nog steeds belangrijke informatie om het tuberculosebesmettingsrisico en de trend hiervan binnen het huidige Nederlandse leger te volgen. Het totaal aan onderzoeksgegevens zal naar verwachting zijn bijdrage blijven leveren aan de schatting van het tuberculose-infectierisico in Nederland.

Het dubbel-Mantouxonderzoek zoals beschreven in dit proefschrift is een verbeterde onderzoekstechniek om tuberculose op te sporen en onderscheidt tuberculosebesmettingen van besmettingen veroorzaakt door aspecifieke mycobacteriën. Inmiddels is deze onderzoeksmethode een integraal onderdeel geworden van de tuberculose-opsporing binnen het Nederlandse leger. Deze methode heeft geleid tot een bijna 50% reductie van het voorschrijven van INH-profylaxe bij hen die positief reageerden op tuberculine met

indurations tussen de 10 en 15 mm. Het merendeel van hen die positief reageren op de tuberculine-huidtest bevindt zich namelijk in het induratiegebied van de 10 tot 15 mm.

Inmiddels wordt deze methodiek ook bij sommige civiele organisaties (GGDen) gehanteerd, o.a. bij (low-risk)groepsonderzoek in het kader van contactonderzoek. Eén en ander kan worden gezien als een positieve spin-off van de resultaten bij het groepsonderzoek binnen het Nederlandse leger. Inmiddels wordt het tuberculosebeleid binnen het leger opnieuw gedefinieerd en valt dit samenvattend te beschrijven als :

- Een standaard Mantoux-test wordt uitgevoerd bij alle personen die nieuw het leger binnenkomen, voor en na uitzending naar hoog-prevalente tuberculosegebieden en bij alle personen die behoren tot een risicogroep. Deze laatste groep ondergaat jaarlijks een Mantoux-onderzoek. Bij alle gevonden indurations tussen de 10 en 15 mm bij nimmer met BCG gevaccineerde personen, wordt een dubbel-Mantoux-onderzoek uitgevoerd zoals beschreven in dit proefschrift.
- De resultaten van het tuberculineonderzoek worden opgeslagen in een data-base, van waaruit op reguliere basis evaluatie-onderzoek plaatsvindt om zonodig het vigerende beleid bij te stellen.

Met deze maatregelen hopen wij het Nederlandse leger te behoeden voor de dreigende gevaren van de wereldwijd heersende tuberculose-epidemie.

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het formuleren en uitschrijven van de vele concepten van het "tuberculose manuscript". En als de aandacht dreigde te verslappen door de drukte van mijn reguliere werkzaam-heden, was jij degene die mij s'avonds opbelde en mij aanspoorde met de worden "Hans, lets go and finish it".

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Bedanken wil ik ook hen die deel uit ma(a)k(t)en van de verschillende Mantoux-teams van de DMGZ en TNO. Zij zijn degenen die het tuberculineonderzoek zorg-vuldig uitvoerden en aldus bijgedragen hebben aan de betrouwbaarheid van de onderzoeksgegevens, die hebben geleid tot de onderzoeksresultaten welke worden uitgedragen in mijn proefschrift. De TNO-teams werden structureel ingezet naast die van de DMGZ en stonden onder de bezielende leiding van Osrenka Mislenovic, die een goede vriendin is geworden en gebleven. Osrenka jij bent samen Thijs en Robert een zeer belangrijke stimulans geweest om te blijven volharden in het uitschrijven van mijn proefschrift.

Ook de zorg en de hulp van de administratieve kern van de DMGZ heeft belangrijk bijgedragen aan de tot standkoming van mijn proefschrift. Lucia Birzwilks, bedankt voor de verzorging van de inwendige mens, die anders zwaar verwaarloosd was geworden tijdens mijn "tuberculose-sessies" op de Dienst en voor het verzekeren van altijd een parkeerplaats op de Knoopkazerne zodat ik niet steeds van ver weg, dragende al mijn tassen met tuberculosegegevens, behoefde aan te komen sjouwen. Jij besefte goed dat ik geen 30 jaar meer was!

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Tenslotte dank ik Rob Scheenstra, het huidige Hoofd DMGZ. Rob, tenslotte heb jij als baas van de Dienst oogluikend toegelaten dat vele medewerkers zich hebben ingezet voor de tot standkoming van mijn proefschrift.

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Ook wil ik de beide longartsen, Dr. Hidde Bok en Dr. Peter Sips bedanken. Met Hidde heb ik jarenlang de tienduizenden schermbeeldfoto's ("dubbel-reading") van de rekruten-lichtingen gelezen met als primaire doel de opsporing van tuberculose. Met

Peter heb ik veel gesproken over de indicaties en de samenstelling van de INH-profylaxe bij de "positief" reagerende rekruten. Beide collegae zijn altijd bereid geweest om gereed gekomen (deel)manuscripten door te lezen en te voorzien van hun commentaar.

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De DMGZ heeft altijd een goede relatie onderhouden met de KNCV. Hoewel natuurlijk het tuberculoseonderzoek bij de rekruten een belangrijk bindmiddel is geweest, hebben toch vooral de persoonlijke relaties gezorgd voor de bijna familiaire band die onderling is ontstaan. In de twaalf jaar die ik bij de "tuberculosedienst" (DMGZ) van het leger heb doorgebracht ben ik nauw verbonden geraakt met de KNCV en haar personeel. Deze KNCV wil ik bedanken voor zowel de administratieve ondersteuning (literatuuronder-zoek) als de materiële ondersteuning (onderzoekssubsidie). Bovendien dank ik Jaap Broekmans, Jaap Veen, Osrenka Mislenovic en nog anderen werkzaam binnen de KNCV voor hun enthousiasme en persoonlijke betrokkenheid t.a.v. mijn promotie-activiteiten.

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Met hem bedank ik ook de leden van de promotiecommissie voor hun welwillendheid zitting te willen nemen in de commissie en zich te verdiepen in de problematiek van de tuberculosebestrijding in het Nederlandse leger.

Niet omdat het nu eenmaal gebruikelijk is aan het einde van een dankwoord de gezins-belasting te memoreren maar omdat het van harte gemeend is, wil ik afsluiten met mijn vrouw Olivia en mijn kinderen Jan Willem, Janneke, Jenny en Tineke te bedanken. Zij hebben de laatste twee jaar veelal indirect en soms direct aan den lijve ondervonden dat haar echt-genoot respectievelijk hun vader niet altijd adequaat aanspreekbaar was en dat promoveren blijkbaar gepaard gaat met gelukkig meestal

beheersbare stressreacties bij de promovendus. Zij zijn het geweest die mij in deze veelal goed hebben opgevangen en ik dank het "thuisfront" dan ook voor hun liefde en geduld dat ze hebben opgebracht.

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 12 maart 1949 te 's-Gravenhage.

Na doorlopen van middelbare school ben ik in 1969 begonnen met de studie geneeskunde aan de Vrije Universiteit in Amsterdam. Toen in 1978 het artsexamen werd behaald heb ik aansluitend de huisartsenopleiding via het huisartsen instituut van de Vrije Universiteit gevolgd.

In 1979 werd ik geregistreerd als huisarts en in datzelfde jaar werd ik als dienstplichtige opgeroepen voor opkomst in werkelijke dienst bij de Koninklijke Landmacht.

Het "lot" bepaalde dat ik in 1981 koos voor een militaire artsen-loopbaan, welke startte als kapitein-arts bij het Opleidingscentrum Intendance op de Palmkazerne in Bussum.

In 1983 werd ik geplaatst bij de Dienst Militaire Gezondheidszorg op de (oude)Knoopkazerne te Utrecht in de functie van Hoofd afdeling Preventieve Gezondheidszorg.

Hier begon mijn affiniteit en enthousiasme te onstaan voor de tuberculosebestrijding in het Nederlands leger.

In 1991 werd ik Hoofd van de Dienst Militaire Gezondheidszorg in de rang van Luitenant-kolonel.

Tijdens mijn loopbaan binnen de Dienst Militaire Gezondheidszorg heb ik vele cursussen en opleidingen gevolgd waaronder de opleiding Algemene Gezondheidszorg. In die periode hebben de verschillende onderzoeken van mijn huidige proefschrift zich ontwikkeld.

In 1995 werd ik tenslotte geplaatst op mijn huidige functie als stafmedewerker Medisch Beleid bij de Gezondheidszorg Dienst Koninklijke Landmacht.