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Tuberculosis infection and disease among asylum seekers in Norway

Screening and follow-up in public health care

Thesis for the degree of Philosophiae Doctor

Trondheim, January 2011

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Tuberkulose: infeksjon og sykdom hos asylsøkere i Norge. Screening og oppfølging i det offentlige helsevesen.¨

Årlig får åtte millioner mennesker i verden tuberkulose. En regner med at en tredjedel av verdens befolkning er smittet (latent tuberkulose), og av disse blir omtrent en av ti syke. I Norge får omkring 300 personer tuberkulose hvert år og over 80 % av pasientene er fra land hvor tuberkulose fortsatt er vanlig. I henhold til norske retningslinjer skal alle asylsøkere som kommer til landet undersøkes like etter ankomst med tuberkulintest og røntgen av lungene for å se om de er syke eller smittet av tuberkulose. Ved forhøyet tuberkulintest skal de vurderes i kommunehelsetjenesten eller henvises direkte til spesialist. Dersom røntgenbildene gir mistanke om tuberkulose, skal de undersøkes av spesialist før de sendes videre i mottakssystemet.

Målet med studien var å finne ut hvordan screeningen fungerer; blir alle undersøkt, blir alle med forandringer på lungerøntgen eller forhøyet tuberkulintest fulgt opp, og hva er resultatet av oppfølgingen? I tillegg ble det gjort en vurdering av om en spesiell blodanalyse kunne være av nytte i screeningen.

Data fra alle asylsøkere som kom til Norge i 2005-2006 ble gjennomgått. Alle som enten hadde forhøyet tuberkulintest eller forandringer på lungerøntgen ble fulgt opp ved å sende spørreskjema til helsevesenet. Senere ble data for alle disse krysset mot Tuberkuloseregisteret hvor alle som enten har fått påvist sykdommen tuberkulose eller fått behandling for latent tuberkulose er registrert.

Halvparten av asylsøkerne, 2237 personer, som kom i den aktuelle perioden hadde positive funn ved ankomstscreening og ble derfor inkludert i studien. Tuberkulintest var registrert hos 97,5% mens opplysninger om røntgenbilde var tatt, ikke var registrert i personenes medisinske journal. Blant asylsøkere med forandringer på lungerøntgen var 2/3 blitt fulgt opp av spesialist, mens 1/3 var blitt vurdert i primærhelsetjenesten.

Aktiv tuberkulose som et resultat av screeningen ble påvist hos 15 personer, og 28 fikk behandling for latent tuberkulose. Det var ingen sammenheng mellom alvorlighetsgrad av screeningfunn og om personen ble undersøkt i kommunehelsetjenesten. Kvinner fra Somalia hadde økt risiko for å få tuberkulose. Personer med sterkt positiv tuberkulintest hadde økt sjanse for å få behandling for latent tuberkulose.

En stor andel av asylsøkerne som hadde tuberkulose ved ankomst til landet ble diagnostisert raskt gjennom screeningprogrammet. Imidlertid var det mange med røntgenfunn som ikke fikk noen diagnose. I kommunehelsetjenesten var det svært variabel grad av oppfølging og dårlige rutiner for oppbevaring av helseinformasjon.

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Contents

Acknowledgements

The background for this PhD project was a study initiated by The Tuberculosis Committee of the Norwegian Association for Pulmonary Medicine in association with The Norwegian Health Association of the screening of asylum seekers and treatment of latent tuberculosis in Norway. First part of that project was to study the routines for arrival screening and information flow, while the second part a comparison of Qquantiferon TB Gold and Mantoux test results in asylum seekers at Tanum arrival center (the QFT study). Adviser at the National Institute of Public Health Brita A Winje, was principal investigator of the QFT study and has later given important input into and also shared data with this PhD study. We are grateful for that. Dr Einar Heldal made important contributions to the QFT study and contributed later as co-supervisor of the current PhD study.

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Trondheim, December 11th 2010

Ingunn Harstad

List of papers

Paper 1: Tuberculosis screening and follow-up of asylum seekers in Norway: a cohort study.
Ingunn Harstad, Einar Heldal, Sigurd L. Steinshamn, Helge Garåsen and Geir W. Jacobsen. BMC Public Health, 2009, 9:141

Paper 2: Screening and treatment of latent tuberculosis in a cohort of asylum seekers in Norway.
Ingunn Harstad, Einar Heldal, Sigurd L. Steinshamn, Helge Garåsen, Brita A. Winje and Geir W. Jacobsen. Scandinavian Journal of Public Health, 2010, 38: 275-282

Paper 3: The role of entry screening in case finding of tuberculosis among asylum seekers in Norway.
Ingunn Harstad, Geir W. Jacobsen, Einar Heldal, Brita A. Winje, Saeed Vahedi, Anne-Sofie Helvik, Sigurd L. Steinshamn and Helge Garåsen
Revision submitted to BMC Public Health

Paper 4: Predictive values of QuantiFERON®-TB Gold testing in screening for tuberculosis disease in asylum seeker
I. Harstad, B.A. Winje, E. Heldal, F. Oftung, G. W. Jacobsen
Inernational Journal of Tuberculosis and Lung Disease 14(9):1209-1211

I.

Abbreviations and specifications

TB: Tuberculosis
MDR-TB: Multi drug resistant TB
XDR-TB: Extensive drug resistant TB
PHC: Primary public health care
IGRA: Interferon-γ release assay
TST: Tuberculin skin test
PPD: Protein purified derivate
QFT: QuantiFERON TB GOLD
CI: Confidence interval
OR: Odds ratio
IR: Incidence rate
BCG: Bacille Calmette-Guérin
MDG: Millennium development goal
UN: United Nations

TBNET: A formal network of mostly European, research oriented clinicians, microbiologists, mycobacteriologists and epidemiologists interested in tuberculosis and mycobacterial disease. The goal is to promote clinically oriented research in tuberculosis.

DOTS: (directly observed treatment, short course) The WHO TB Control strategy

Smear: Microscopy of sputum smear stained after the Ziehl Neelsen method. The smear is recorded as positive when at least one acid fast rod is detected in 100 fields with an enlargement of 10x100.

Summary

Introduction

About 80% of new tuberculosis (TB) cases in Norway occur among immigrants from high incidence countries in Africa, Asia and Eastern Europe, and most of them are infected on arrival. Tuberculosis screening of immigrants from such countries is compulsory with a Mantoux test of everybody and a chest X-ray of all above 15 years of age. The aim of the screening is to identify cases of active tuberculosis in order to give treatment and stop transmission of the disease, and to offer treatment or follow-up for cases with latent tuberculosis.

Asylum seekers are screened at the National Reception Centre in Oslo before they are transferred to other asylum seekers centres or relocated to municipalities around the country. Internationally, there is an ongoing discussion about screening of immigrants, as well as the indications for treatment of latent tuberculosis.

Aim

The aim of the study was to assess the conduct of entry screening among asylum seekers, and the follow-up of results for active and latent tuberculosis. A secondary aim was to assess the predictive properties of QuantiFERON-TB Gold (QFT) as a potentially new screening tool for tuberculosis disease.

Methods

All asylum seekers above the age of 18 who arrived at the National Reception Centre from January 2005 to June 2006 were eligible for inclusion in the follow-up study. They were included if they had either a Mantoux test $\geq$ 6 mm, a positive chest X-ray, or a positive QFT test. The latter regarded the subset of asylum seekers who arrived between September 2005 and June 2006. Potential participants were excluded if they left the Reception Centre without a new address or left the country directly. Information about the study and a data collection form were sent to the health authorities in the municipalities where the asylum seekers moved to. In case anyone had moved on to another municipality in the meantime, the same information and study form were sent to the authorities in their new place of residence. If we received information that a study participant had been referred to specialist health care, a second form was sent to the health institution in question. All included study subjects were later matched with the National Tuberculosis Register which contains information about everybody diagnosed with active tuberculosis, or who have started treatment for latent tuberculosis.

An additional aim of the study of the above mentioned subsample, was to compare QFT and the Mantoux test. Everyone with a valid QFT test result where name and birth date were available were later matched with the National TB Register.

Results

Of 4643 available asylum seekers, 2237 were included in the follow-up study. We found a valid Mantoux test result in 97.5% of them. We were on the other hand unable to ascertain and document the exact number of X-rays that were taken at the Reception Centre. Fifteen cases of tuberculosis, mainly pulmonary TB, were identified through the screening programme within two months after arrival. Altogether 28 cases of active TB had been diagnosed by the end of May 2008. Female gender, Somalian origin and a positive X-ray on arrival were all associated with active tuberculosis.

Of 314 persons with a positive X-ray, 62% had been seen by an internist in order to get a conclusive diagnosis. Similarly, of 568 asylum seekers with a Mantoux ≥ 15mm, 16% had been examined by a specialist. Only one third of persons with an elevated Mantoux test had been assessed at the community level and there was no association between the characteristics of the screening result (positive X-ray, and size of Mantoux) and the probability of being assessed.

Altogether 30 cases of latent TB were started on treatment, which took place a median 17 months (range 3-36) after arrival. A Mantoux ≥ 15mm was the only characteristic that was associated with treatment induction.

The positive and negative predictive values (PPV and NPV, respectively) for Mantoux and QFT were the same. The negative predictive value for a Mantoux ≥ 6mm in combination with a negative QFT was as good as the NPV for Mantoux <15mm alone.

Conclusion

The conduct of the screening programme for asylum seekers was by no means in accordance with the official guidelines. Asylum seekers were screened with Mantoux on arrival, but we were unable to document the exact number who had been screened with chest X-ray. The main concern is the lack of a specialist examination of persons with a positive X-ray, but also of persons with a Mantoux ≥ 15mm. Compared to other studies, a reasonable number of cases were diagnosed with active TB within 2 months after the arrival screening. Two cases were diagnosed from 3-6 months after

arrival and were probably missed by screening, but an unknown number of cases may have been lost because of insufficient follow-up of X-ray results. Six of eight cases of extra-pulmonary TB were diagnosed more than four months after arrival and could well have been ill for months before diagnosis. At the primary health care (PHC) level there was an obvious lack of a common strategy for taking responsibility for the follow-up of TB screening results.

A secondary finding was that QFT was as precise as Mantoux in predicting TB, and the negative predictive values for a Mantoux ≥ 6mm with a negative QFT were equally as precise as for a negative Mantoux alone.

1: Introduction

1.1: Tuberculosis epidemiology

The global burden of tuberculosis

Since 1997 WHO has made a yearly assessment of the global TB epidemic and the effect of control measures. For the year 2007 the organisation estimated a total of 9.27 million new (incident) and 13.7 million existing (prevalent) cases of tuberculosis worldwide (1). More than half (55%) of the new cases occurred on the Asian continent and 31% in Africa. The fact that 13 of the 15 countries with the highest incidence rates were located in Africa (Figure 1) is probably due to the simultaneous high rate of TB and HIV infection on the continent. Among new TB cases in 2007, 4.1 million were estimated to be smear positive and 1.4 million to be HIV positive. Further, 500 000 individuals were estimated to have multi-drug resistant TB (MDR-TB), i.e. the bacteria were resistant to both isoniazid and rifampicin. WHO has also estimated that 1.3 million of HIV-negative and about 450 000 HIV-positive TB cases died of their disease in 2007 (1).

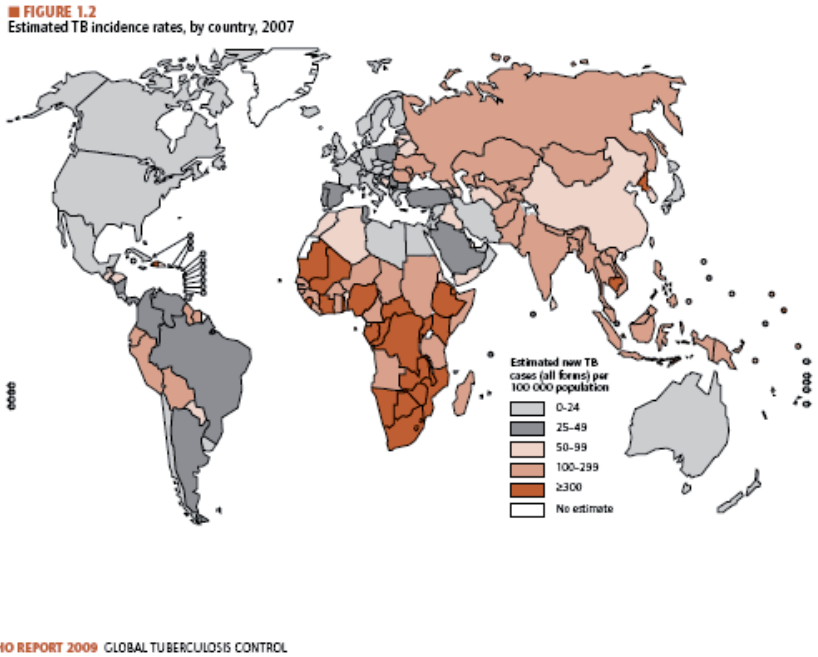

Figure 1. Estimated TB incidence rates by country, 2007.
Reprinted with permission from WHO report 2009: Global tuberculosis control (1).

Roughly estimated one third of the world's population has been infected with tuberculosis (2). However, there is a great diversity between countries, and in rural India 80% of the population had a positive interferon-γ release assay (IGRA) test (3). Around 1% had a positive TST in a study among Western teenagers born in Norway, and only 6% of these had a positive IGRA test (4).

The targets for the millenium development goals (MDG) for global TB control are: 1) to stop the overall increase and start reducing the incidence of TB by 2015, 2) to reduce the prevalence and death rates by 50% in 2015 compared to 1990, 3) to successfully treat at least 85% of patients with active tuberculosis, and 4) to detect and treat 70% of smear positive cases through directly observed treatment, short course (DOTS) programmes. The DOTS programme includes a) political commitments, b) case detection by bacteriological examination of symptomatic patients reporting to the primary health care, c) standardised treatment with supervision and patient support, d) an effective drug supply system, and e) a monitoring and evaluation system (1, 5).

The incidence rates, prevalence and mortality rates have fallen globally since 2004, but are still not expected to be halved in all regions by 2015 as is the MDG. In 2007 the global treatment success rate was 85%, and 63% of smear positive cases were detected and treated under DOTS programmes (1). In general, the African and European regions (including the former Soviet Union) had the lowest success rates.

Tuberculosis in Norway

Around the year 1900 about 6000 people died yearly of tuberculosis in Norway. In 1920 the incidence of pulmonary TB was 300/100 000 in the population(Figure 2), and a study in 1927-1928 by Heimbeck showed that 100% of working class people were infected before they reached the age of 30 (6). The number of new cases declined steadily from around 1920 until the late 1980s (Figure 2). For example in 1945 3814 new cases were registered which gave an incidence rate (IR) of 125/100 000 for that year for the population as a whole (7).

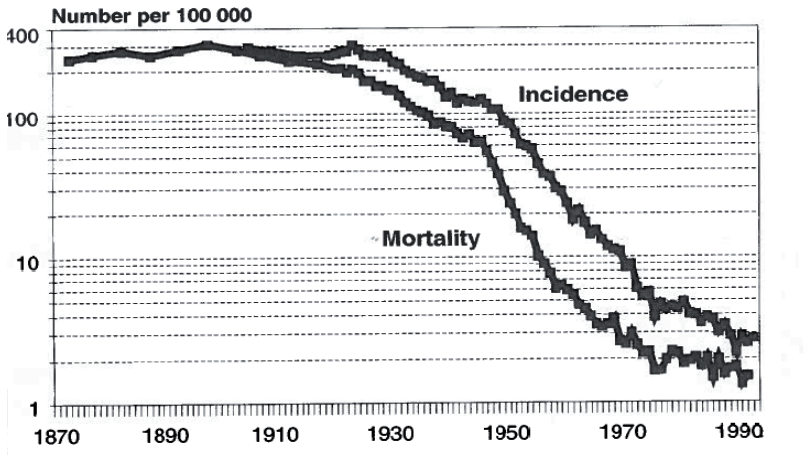

Figure 2. Mortality from TB and incidence from infectious pulmonary TB in Norway. Reprinted with permission from E. Heldal (8)

In the mid 1970s around four percent of new cases occurred among persons who were born outside Norway (9). That proportion increased from 66% in 1999 to 79% in 2007 (10) (Figure 3). Another typical trend is that the majority of the foreign born cases were young persons. For instance, in 2007 the median age of new cases was 29 years which was clearly different from the median age of 74 years for new cases diagnosed among the ethnic Norwegian population (10). In 2007 the overall IR in Norway was 6.5/100 000 inhabitants, yet it was 1.5/100 000 and 54.6/100 000 for Norwegian and foreign born individuals, respectively (10). Since the year 2000 three to four new cases of MDR-TB have been registered each year, mainly among people who come from Eastern Europe (11). Altogether three cases of extensive drug resistant TB (XDR-TB) where the bacteria are resistant to at least isoniazid, rifampicin, a fluoroquinolone, and either amikacin, kanamycin or capreomycin, have been registered in Norway (11). Molecular studies have suggested that most cases of TB were due to imported strains and that about 80% of the cases were reactivation of previously contracted TB infection (12).

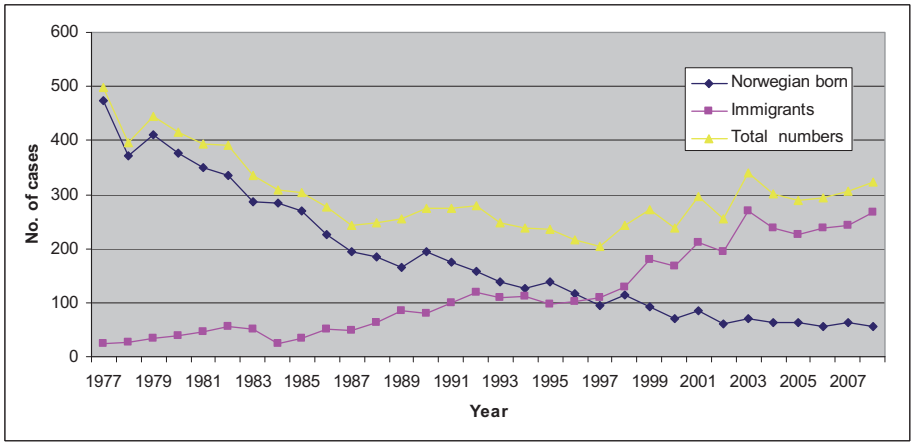

Figure 3. Incidence of TB in Norway by status of origin. 1977 – 2009

Information obtained from the National Tuberculosis Register

1.2: Migration, refugees and asylum seekers

People migrate between countries for many different reasons. According to the United Nations (UN), the total world population was 6.5 billion in 2005 of whom a total of 190 millions were international migrants. Roughly 64 million immigrants lived in Europe and 44 millions in North America (13).

Based on information from the High Commissioner for Refugees in the same year (2005), there were an estimated number of 13 millions refugees (13). Classification of different immigrant groups such as refugees, asylum seekers, immigrant workers and others may differ between countries and is in most cases a question about legal status. In Norway asylum seekers are defined as such if they have asked for protection and recognition as a refugee. Refugees on the other hand are those who already have been granted protection (14).

A European TB study has estimated that the proportion of undocumented migrants varies greatly (5-30%) between countries (15). The total number of such immigrants was 5-8 million and they represented 5-10% of all TB cases.

In 2005 the total Norwegian population was 4 606 363. Among them, 176 089 (3.8%) were immigrants from Asia, Africa, South- America, or Turkey (16). The immigrants

had come either as UN refugees, asylum seekers, for family reunion or they were labour immigrants or students. Altogether 54 256 immigrants came from Eastern Europe. Still, the most frequent countries of origin were Pakistan, Iraq and Somalia (16).

1.3: Tuberculosis control programmes

Tuberculosis control programmes in Norway

The occurrence of tuberculosis increased during the last part of the 19th century, and in 1900 the first enactment about tuberculosis was passed (17). It became mandatory to report all cases of tuberculosis to the community health board that could decide about isolation of cases, prohibit persons with tuberculosis to do certain kinds of work, and carry out contact tracing. In some cases the public authorities would pay for a patient's stay in a sanatorium. The general aim of the law was to protect the public from persons with infectious disease and to control transmission of infection. General cleanliness, nourishing food and fresh air were advised both to protect healthy people and to cure patients. Extensive health education campaigns were performed both by non governmental organisations (NGOs) and public health officials. One well known part of the campaign was posters with a message against spitting. The number of sanatoria gradually increased, and in the 1920s and -30s treatment of patients became gradually more important. In particular, surgical procedures that aimed to limit the disease of individual patients were increasingly performed (17).

In 1927 the BCG vaccine was introduced in a study among voluntary nursing students in Oslo (6). The vaccine was compulsory for school children (12-14 years old) from 1947 until 1995. Since then it is being recommended (11). BCG vaccination of newborn children of parents from high incidence countries has been recommended for many years (11).

In 1947 a new enactment on tuberculosis became effective. This included mandatory BCG vaccination (see above), tuberculin testing of certain groups, and mass radiography screening of adults (18). However, the National Mass Radiography service had already started in 1943 and gradually covered the whole adult population

(19). The aim was to stop the transmission of TB through early case finding. From 1966 to 1974 the public health approach changed from a general to a risk based selection of people for X-ray screening (20). From the mid 1990s on, chest X-ray screening is only used for selected groups, i.e. for contact tracing and for other groups with an increased risk (21).

The number of new cases has decreased continuously since 1900. This occured during a time period when TB laws and corresponding preventive measures were introduced, the social conditions were improved, and immunisation of the population started. After the Second World War modern drug treatment was introduced and this further reduced the transmission of infection (18). In the 1950s and -60s the number of TB cases, both new and existing, declined dramatically. During that same period most of the specialized TB care became an integrated part of regular health care provision (18).

In 1956 screening for TB became compulsory for foreigners who applied for work in Norway, and in 1977 for all immigrants from high incidence countries.

Tuberculosis control programme during the study period

New governmental regulations about TB screening and treatment were issued in 2002 (22). They emphasised that screening of high risk groups was mandatory. The aim of these regulations was to prevent transmission of infection and development of disease in infected persons. In addition, teachers and health care personnel returning from long-term stays in high incidence countries must also be screened in order to avoid that they transmit a possible infection to vulnerable groups (22). The need for treatment for latent TB was underscored, yet the guidelines did not state what the definite treatment indications for latent TB are. For patients from high incidence countries treatment is recommended when the chest X-rays have fibrotic abnormalities, and treatment should be considered when the Mantoux test is elevated. Before treatment for latent infection is decided, a history of previous tuberculosis, the risk of recent infection, relevant clinical symptoms, the result of chest X-ray, the size of the Mantoux test, and other risk factors must be weighed against treatment contraindications and the patients age (23).

Local health authorities are responsible for TB screening of all refugees, persons who arrive for family reunion as well as other immigrants from high TB incidence countries when they arrive in their municipalities. The screening programme is organised differently for asylum seekers than for other groups of immigrants, but includes the same procedures. They are a Mantoux test for all regardless of age, and a chest X-ray for everybody above the age of 15. An interview about previous tuberculosis disease and relevant symptoms is compulsory, but the guidelines do not state where this interview should be performed. Nevertheless, a positive X-ray and/or a Mantoux test ≥ 15mm, previous TB, or any symptoms of the disease shall lead to a direct referral to specialist health care. A Mantoux test result between 6 and 14mm shall be assessed by a local public health physician. In the latter case and based on all available information, the patient shall be referred to specialist care whenever clinically indicated.

Patients are referred to the local hospital, most often to the department of pulmonary medicine, department of paediatrics (persons under 18 years), department of infectious diseases, or general internal medicine. The hospital specialist will also take a history, for which an interpreter is often required, and then conduct a clinical examination which usually includes a sputum test. A repeat chest X-ray is most often taken. The final decision will be a) to start treatment for active tuberculosis, b) start treatment for latent tuberculosis, c) that further observation is necessary, or d) that no treatment or follow-up is needed. If active tuberculosis is diagnosed or treatment for latent tuberculosis is started, a nominal notification is sent to the Norwegian National Tuberculosis Register.

Tuberculosis control programmes in other low incidence countries

There is no uniform policy for TB control programmes in low incidence countries, which is defined as countries with less than 10 new cases of tuberculosis per 100 000 population per year. In Western Europe most countries have given universal BCG vaccination, but as the TB epidemic declined in the general population, they have gradually stopped doing it or concentrated their efforts on high risk groups (11). A study that covered the European region of WHO, included the former Soviet Union, was performed in 2004. The response rate was quite low (26 of 51 countries responded). However, 50% of the countries who did respond, confirmed that they

carried out some kind of screening for new entrants, i.e. all of them screened refugees, but none carried out pre-entry screening (24). All of the reported programmes used chest X-ray as a screening tool, but none had the same clinical approach. Tuberculin testing (TST) was used in ten countries, whereas eight treated certain groups of cases with latent tuberculosis (24). Another study from 2006 evaluated several screening units in Norway, the UK, the Netherlands and Switzerland (25). This study showed considerable variations in screening services offered, i.e. between centres as well as countries. In general, few output data were routinely and systematically collected (25). Neither USA nor Canada have introduced BCG vaccination in their programmes, but have instead treated latent tuberculosis more extensively (26). Together with Australia, these two countries have implemented pre-entry screening for immigrants (26).

1.4: The National Tuberculosis Register

The National Institute of Public Health is responsible for surveillance of transmittable diseases in Norway and the National Tuberculosis Register is part of that surveillance. All cases of suspected or verified tuberculosis disease or TB cases that have started on treatment are nominally reported to the register. Both clinicians and medical laboratories that diagnose TB have an obligation to notify individual cases. Also patients who have started on treatment for latent TB must be registered. For quality assurance purposes this register is regularly matched with the register of TB drugs at the National Hospital Pharmacy where all prescriptions are handled.

1.5: Relocations of asylum seekers and screening for tuberculosis

Arrival screening

Almost every person who seeks political asylum in Norway is admitted via the National Reception Centre at Tanum outside Oslo. Any acute medical needs and legal issues are attended to. The compulsory tuberculosis screening with a Mantoux test and chest X-ray is also done here (Table 1 & Figure 4). Asylum seekers are only interviewed about health issues or given a clinical examination if they have acute or serious medical complaints. A test for HIV is not compulsory, but taken if clinically relevant. Asylum seekers spend on average between five days and two weeks at the Reception Centre. Normally they leave when the X-ray results have been cleared.

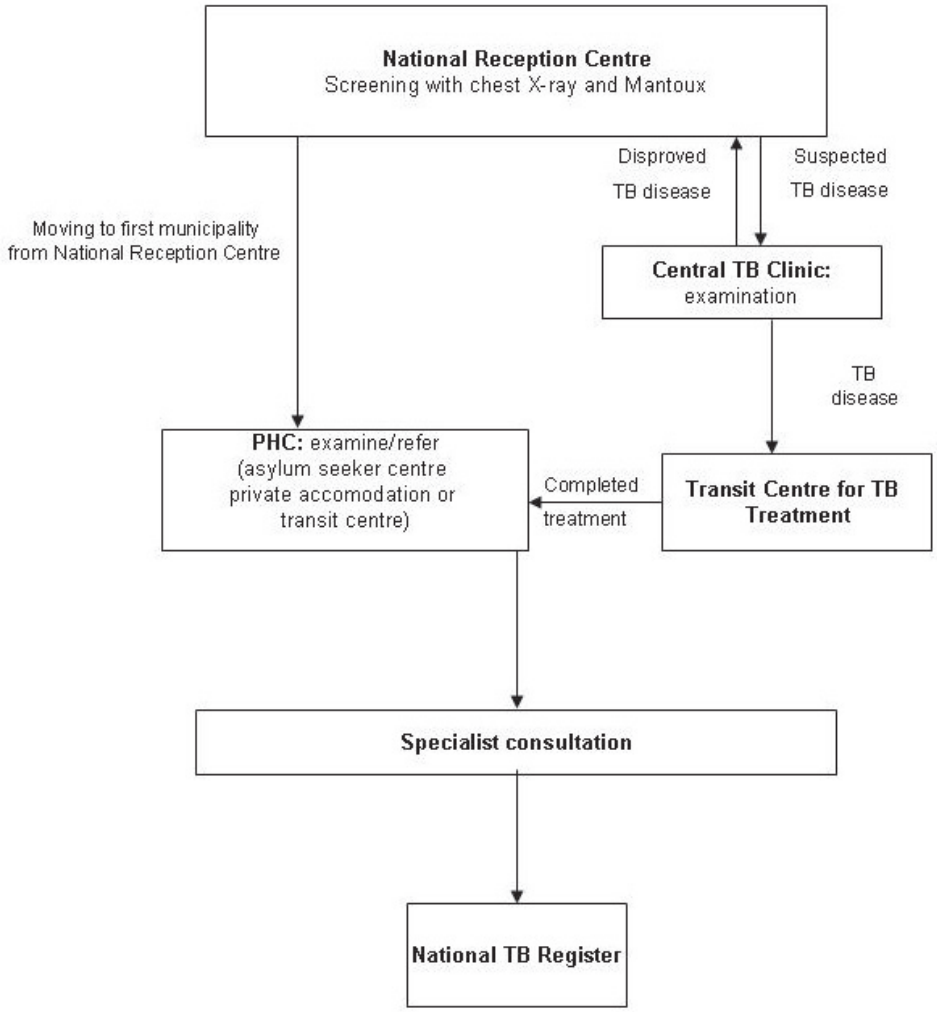

Figure 4. Description of relocations of asylum seekers, and referrals, and notification of confirmed or suspected cases of tuberculosis disease

In case of any clinical symptoms or X-ray findings that may be related to tuberculosis, the persons in question are referred to the Central TB Clinic at Ullevål University Hospital in Oslo. The main focus here is to rule out active TB, and the physicians decide from the X-rays which patients must be summoned for further diagnostic work-up. The result of each consultation is reported to the Reception Centre or to the

special Transit Centre for TB Treatment which is another central institution in the Oslo area. If tuberculosis is diagnosed, the asylum seeker is kept at the latter centre for the treatment period. Asylum seekers are also kept there while they still wait for their test results, or if a family member needs treatment. Patients, who need hospital treatment while staying at the Transit Centre, may be admitted to any hospital in the Oslo area.

Whenever an asylum seeker is relocated to a transit or asylum seekers centre, the health and other relevant information is normally sent to the public health nurse who is in charge of that centre. In case an asylum seeker leaves the National Reception Centre and moves directly to some private accommodation, the screening results are sent to the public health officer in that particular municipality.

Follow-up of screening results

According to the national guidelines, the local public health care (PHC) is responsible for assessing the TB screening results of all asylum seekers and to follow them up (23). As a result of the assessment, a decision is made if there is a need for further examinations or referral to specialist care, or that no more follow-up is needed. Suspected cases can thus be referred to specialist care directly from the National Reception centre or from PHC.

Asylum seekers may move from the National Reception Centre to a new location in several ways (Table 1 & Figure 4). As a first possibility, they may move to the Transit Centre for TB Treatment. Second, they may be directed to one of the four transit centres that are located around Oslo. This is an alternative for asylum seekers who have not yet been interviewed by the police, or have arrived through another Schengen country and await deportation, or some other decision. Third, as is most often the case, the asylum seekers move to asylum seekers centres that are located in different parts of the country (Figure 4). Finally, some few may move directly from the National Reception Centre to private accommodation.

After staying in a transit centre or asylum seeker centre for a shorter or longer period of time, many may move again, i.e. either to another asylum seeker centre or to private accommodation in a municipality. Some may leave the country.

Table 1. Type and characteristics of institutions for asylum seekers in Norway

Institutions (total numbers)	Functions	Health care level	Staff	Source of information for the study
National Reception Centre (1)	Short term. All asylum seekers (AS) who arrive to Norway. Screening with chest x-ray and Mantoux.	Primary health care (PHC) paid for by national government.	PHC officer or nurse	Information from the computer system of the National Reception Centre.
TB Treatment Transit Centre (1)	Short or long term. Treatment of patients with active TB, or potential patients waiting for consultation or examination results. Family members are included.	PHC paid for by national government	PHC officer or nurse	Filled in PHC registration forms
Central TB Clinic (1)	Out patient. AS referred directly from the National Reception Centre or from other health care levels. Focus is on active TB.	Hospital based specialist health care.	Specialists in pulmonary medicine	Returned specialist registration form
Transit centre (4)	Short term stay. AS who wait for an interview by police or for being deported.	PHC paid for by national government	PHC officer or nurse	Returned PHC registration forms
Asylum seeker centre (ca 100 when study started, Jan 2005)	Longer stay. AS stay till they get a permanent residency or are deported.	Municipal authorities directly responsible for health care.	PHC officer or nurse	Returned PHC registration forms
Specialist health care	Out patient. Examine and treat AS for TB after referral from primary health care	Hospital based specialist care.	Hospital specialists in pulmonary or internal medicine	Returned specialist registration form

Each time the asylum seeker moves, the public health officer is expected to forward the tuberculosis screening results to his or her colleague in the next municipality.

1.6: Screening tests

Chest X-ray

The most common screening procedure for detecting tuberculosis disease is a frontal chest X-ray that was developed in the late 1930s and early 1940s (19). Thus, mass examination in Norway was first introduced in 1940 (19). X-rays are normally used as a first screening procedure to select persons for further examinations. Positive X-ray findings can not be used as the only diagnostic criterion (27).

The value of an X-ray result depends not only on the quality of the film and the uptakes, but also on how the film is read. Screening programmes do not normally include lateral uptakes which implies that some pathology may be overlooked (28). In general, intrabronchial disease does not show well on an X-ray (29). Several studies have documented that there is a problem with within as well as between reader variability. Further, while under-reading has been a frequently noted problem, over-reading has been much less so (27, 30, 31). The quality and size of the films, the experience of the reader, and the complexity of the reading code may all affect these factors (27, 28, 30, 31).

Another problem with chest X-ray screening is related to the tuberculosis disease. Naturally, chest X-rays can only detect pulmonary pathology while the disease can affect all body organs. Thus, a patient can be seriously ill of tuberculosis, but have no signs of pulmonary pathology. Many different pulmonary diseases, previous and current, can give pathological changes on X-ray, and inversely, there is no X-ray findings that are exclusively found in tuberculosis (27). Finally, X-ray can not differentiate between active and inactive TB except through repeated examinations (31).

There is an ongoing concern if and to what extent patients with pulmonary TB can have a normal X-ray. Thus, X-rays of culture positive cases have been used in several studies to find the proportion of negative X-rays and factors that are associated with a

negative finding. The proportion of X-ray negative TB cases has varied between 0.5 and 9 % and with the highest proportions in studies with the highest number of HIV positive cases (29, 32, 33). In HIV positive tuberculosis patients, with decreasing CD4-cell counts an increasing number of atypical findings have been observed (34, 35).

In a review that evaluated the cost-effectiveness of TB screening, the sensitivity of a chest X-ray was found to lie between 59 and 82% and the specificity between 52 and 63% for pulmonary TB (36). However, different diagnostic criteria were used in these studies, and they were done in populations with a different prevalence of both tuberculosis and other lung diseases.

Tuberculin skin tests

A tuberculin skin tests (TST) has been used for almost a hundred years with different application forms like Mantoux, Heaf test and Pirquet. In Norway the Pirquet method with Old Tuberculin was used until 2004 when the tuberculosis control programme changed to the Mantoux test (11). The protein purified derivative (PPD) that is used, have several different standard concentrations and volumes. PPD consist of a mixture of antigens, with a culture filtrate of *M. tuberculosis*, which induces a delayed cell mediated immune reaction. In most use now is the Mantoux test, where PPD is injected intradermally and can be read as an induration of the skin after 48-72 hours (37). TST measures a mycobacteria specific T-cell response and can not distinguish between tuberculosis infection and disease.

The sensitivity, and even more the specificity of TST varies widely depending on the population the test is applied to (38). The BCG vaccine and most atypical mycobacteria give a cross reaction with TST (37). In two reviews where TST was compared to interferon-γ release assays (IGRAs), TST had a specificity of 56 and 57% in BCG vaccinated populations, 97 and 98% in unvaccinated populations and 66% in a mixed population (39, 40). The sensitivity was 71 and 77% in two published reviews.

In general the TST reaction is reduced in immune-compromised persons, and may increasingly wane with time after infection with TB (37, 41). Further, the TST does

not revert after treatment for active or latent TB. Repeated tests can boost the reaction, in particular if the person is BCG vaccinated or has previously been infected (37, 39).

TST results are measured on a continuous scale and different cut-off values are used for different risk groups (38). Accordingly, the predictive values will depend on both the risk of the group under study, and the cut-off values used (37, 38).

Interferon gamma release assays

Because of the limitations of the TST, a more specific test to diagnose latent TB and predict later development of active TB has been wanted. Two new blood tests are available commercially. They are different versions of QuantiFERON-TB Gold, and T-SPOT.TB which was formerly named ELISPOT. Both are based on the cellular immune response and measure blood T-cell interferon gamma (IFN-γ) response to antigen stimulation, QFT measures the IFN-γ by an ELISA technique (39). The two *M. tuberculosis* specific antigens ESAT-6 and CFP-10 have previously been used, but some current versions of the test have added another antigen, named TB7. IFN-γ is measured on a continuous scale, but a certain cut-off level between a positive or negative test is decided. When the IFN-γ production after unspecified antigen stimulation is reduced, the positive control fails and the test result is indeterminate (42). This could happen e.g. in HIV infected persons with low CD4 cell counts.

Neither TST nor IGRAs can differentiate between active and latent TB and there is no microbiological method to diagnose latent tuberculosis. Thus, in most studies a culture positive TB has been used as a reference for the sensitivity of various tests. At the same time, the specificity has been assessed in populations where the probability of tuberculosis disease is quite low. In two reviews, a pooled specificity of 97.5 and 98% was found, whereas the pooled sensitivity in both was 76% (39, 40). Concordance with IGRAs and TST at different cut-off levels have been used to evaluate the tests (39, 43). In contacts of cases of pulmonary TB, correlation between the degree of exposure and a positive test has been compared for TST and the IGRAs. However, for both these methods the results have been diverse (39, 44, 45). Fewer studies where IGRA tests have been compared to TST have been performed in high

incidence countries, where the TST seemed to perform better than IGRAs and better than in low incidence countries (46).

Only a few reports with a relatively short follow-up time have studied how IGRAs can positively or negatively predict later development of tuberculosis (44, 45, 47, 48). First, a German study with two years observation of contacts of active TB cases showed higher TB progression rates for a positive QFT than for a positive Mantoux (44). Further, two Japanese studies of contact tracing among students found no cases of active TB among QFT negative students after 3 to 3.5 years of observation (45, 47). And third, an Austrian study of HIV infected individuals, showed that only those with a positive QFT test developed active TB in the follow-up period (48). In contrast, a study from Gambia with ELISPOT showed that equal proportions of household contacts with positive ELISPOT and positive TST progressed to active TB in a two-year follow-up (49).

The predictive properties of the new tests are still uncertain and there are many other questions and concerns that must be resolved, e.g. the repeatability, stability, boosting, waning, and their use in immune compromised patients (39, 49-55). However, the main benefit of the IGRA tests compared to TST is that the former are not affected by BCG vaccination and only to a limited degree by atypical mycobacteria (56). Another advantage of the blood test is that the patient needs to see the health care provider just once.

1.7: Risk factors for tuberculosis

Risk factors for tuberculosis can be divided into two main groups: risk factors for being infected and risk factors for being ill. Some risk factors are related to both groups, and may be difficult to separate. The overall most important risk factor is poverty (57).

Risk for infection

Risk factors for infection have mainly been investigated through population based cross sectional studies, sometimes with a regular follow-up, or through contact tracing. Until recently only tuberculin tests were used to measure infection

prevalence, but now studies with interferon gamma release assays have been performed as well (43). It is necessary to inhale *M. tuberculosis* to become infected which in turn depends on circumstances that increase the risk of inhalation. Living close to a contagious patient in small rooms with no ventilation will increase the possibility of being infected. The same is the case for poor living conditions, crowded households, and poverty in general (57, 58).

Risk factors for disease

Risk factors for disease include both risks for primary and reactivated (post primary) TB. Such risk factors have mainly been investigated through prevalence studies, and case control or retrospective studies after the TB cases were diagnosed (59-61). In addition ecological studies (57) and use of population based registers have been used (58). Individual factors and diseases that affect immunity, like HIV infection (58), malnutrition, low body mass index (62) and immunosuppressive treatment are important for development of disease. Recent infection (60), former untreated active tuberculosis (59), age (63) and life style factors like alcohol and tobacco use are other known risk factors (64, 65). Several studies show an increased risk for males and some have shown an increased risk for unmarried people (61).

Before starting treatment for latent tuberculosis the individual risk for reactivation must always be assessed. The probability that a positive test for latent TB represent an infection with *M. tuberculosis* may vary between different risk groups (38). Further, different cut-off values for TST have been used in different studies (38, 39). In addition, in some populations a high degree of re-infection takes place (66). Altogether, these factors could probably explain why the assessed risk for reactivation of active TB varies greatly in different studies (67, 68).

Recent infection, and the high probability that a positive test for latent TB represent an infection with *M. tuberculosis*, has been shown among contacts to cases of active tuberculosis. Infected contacts have a 2-5% risk of developing TB within the first two years (69). The life-time risk was 10-15%, i.e. if the contacts in question were infected at a relatively young age and included reactivation at old age (69). In immune compromised patients the risk for reactivation of TB infection was found to be up to 5-15% per year (69). Two Canadian studies of different risk groups showed

quite diverse results with high rates in household contacts increasing with TST size in one study, and a considerably lower risk in TST positive screened subjects without any known risk factors in the other (67, 68).

In a "State of the art" paper on treatment for latent TB all comparisons were made with an infected person with no known risk factors (70). For patients with AIDS, the risk for reactivation was increased up to 110-170 times. Correspondingly, the increase for patients with a recent TB infection was 15 times. The risk for reactivation was 1.5-5 times for persons treated with steroids, diabetes mellitus, underweight, who smoked, and were young when they were infected. Individuals with X-ray findings that suggested an inactive TB in combination with no report of any adequate treatment, also had an increased risk for reactivation compared to other similar groups (70).

Refugees as a particular risk group

Several studies suggest that refugees have a high risk for TB disease following immigration to Western countries, and that the increased risk lasts for years (71, 72). High incidence rates for TB in refugees from Somalia and ex-Yugoslavia were found in a Dutch study (71). An Australian cohort of mainly Southeast Asian refugees with negative X-rays and a positive TST that was followed for an average of ten years after arrival, showed that the incidence rates increased with increasing TST size and remained high for several years (72). One study from USA found that the risk for TB among refugees was twice as high as for other immigrants, while another US study showed that refugees from Bosnia Herzegovina had a three times higher TB rate than the registered rate in their home country (73, 74). Poor living conditions or nutrition before immigration, e.g. as a result of war or living conditions during or after immigration may explain some of the reasons for this increased risk in refugees (75, 76).

1.8: Latent tuberculosis

Definitions of latent tuberculosis

The TBNET (European network for clinically oriented TB research) consensus statement defined latency as a state of persistent mycobacteria-specific T-cell

responses, in the absence of clinical evidence of tuberculosis (69). However, a positive TST or a positive IGRA test in absence of active disease is commonly used as a working definition of latent tuberculosis (40).

Pathology

The traditional view has been that an infection with *M. tuberculosis* leads either to primary TB, life-long latent TB, or latent TB developing to reactivation (post primary) TB (77). Reinfection has also been documented to cause TB (78). The main discussions have been about latent TB, but also about reactivation and reinfection (69, 77).

The relationship between infection, latent TB and reactivation has been based on the observations that old people who had been infected in their youth and were without any possibility for a recent infection, nevertheless became ill. It has also been based on the positive association between a positive TST and later development of active TB (72, 79). Another fact that has supported this theory, is that treating persons with a positive TST reduces the risk for later development of active TB (80). Some new studies with genetic typing of bacteria have detected the same bacteria in TB among contacts of cases up to 33 years after the primary case was detected (81).

Does everybody who is infected have viable bacteria? Must the bacteria replicate in order to stimulate an ongoing immune response, or can they be dormant for a long period? How and where can the bacteria survive? Why is treatment effective when isoniazid is not effective against dormant bacteria but only against bacteria which are replicating? These are some of the questions about latency, and not all of them have as yet a satisfactory answer. Several old autopsy studies cultivated bacteria both from granuloma and from lung tissue elsewhere. Although these studies have been criticised for their methodology, their results still indicate that persons with latent tuberculosis often have viable bacteria (77, 82). Within a granuloma it seems that some bacteria of the same strain of *M. tuberculosis* replicate slowly while others do not replicate at all (69, 77, 82).

Young and colleagues suggested a new model to explain bacterial load and immune response (77). The response to a TB infection, thus, includes a spectrum of events;

i.e. from elimination of bacteria without priming an immune response to fully developed clinical disease (Figure 5).

In some cases of previously treated TB, molecular studies have shown that a new occurrence of TB was actually a reinfection with a new strain of a different genotype and not reactivation of the former *M.tuberculosis* strains (78, 83). TB disease in cases of reinfection may be explained as a strong reaction from a previously primed immune system (69, 77).

There are still many unresolved questions about latency and reactivation. However, it seems that *M. tuberculosis* can persist and lead to active tuberculosis after a shorter or longer period of time (69, 77, 78, 82).

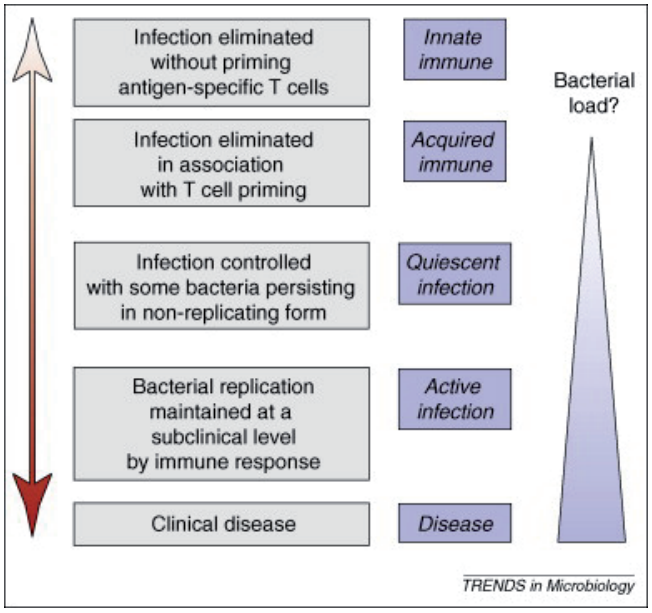

Figure 5. Theory on mechanisms of tuberculosis infection. Reprinted with permission from Young DB et al (77)

Treatment of latent tuberculosis

There are two different objectives for treating latent tuberculosis; the individual benefit of disease prevention and that of society and public health. European recommendations for tuberculosis control and elimination in low incidence countries was introduced by a working group in 2002 (84). According to this report, reducing the prevalence of tuberculosis infection is appropriate when low incidence countries approach the elimination phase (0.2-1 TB case/100 000 per year). Thus, the report advised more extensive use of preventive therapy for latent tuberculosis (84).

Before a decision is made about treatment for the individual patient, it is important to consider the probability of a true positive test, the risk for reactivation of disease, effect of treatment, risk for side-effects, and the likeliness that the treatment will be completed. The choice of treatment regimens is a balance between documented efficacy, probability of side effects from drugs, and the convenience of the patient. A large clinical trial with isoniazid detected a 93% reduction of TB cases in "completer-compliers" of 12 months treatment and 69% in 6 months treatment (80). However, in the longer treatment regimens default rates and side effects increased compared to shorter regimens (80). A Cochrane review on isoniazid intervention trials in HIV negative patients found a 60% reduced risk for TB in the treatment groups (85). Generally, in shorter regimens more patients complete a full course, and patients influence on choice of treatment also improves the adherence (86). Regimens that contain rifampicin are shorter and show better compliance, but are clinically not so well documented. However, in a meta-analysis a short-course therapy with rifampicin and isoniazid was compared with standard isoniazid therapy. The authors concluded that both alternatives had the same efficacy, proportions of side effects, and mortality (87).

Side effects, such as drug-induced hepatitis from isoniazid treatment, increase with age, and after 45 years the risk mostly outweighs the favourable effect in persons with long-standing infection, but not in persons with a recent one (69). Active TB is an absolute contraindication, and must be excluded before treatment of latent TB is started. For isoniazid treatment the relative contraindication is acute hepatitis, and for rifampicin simultaneous intake of protease inhibitors (69).

1.9: Previous studies of screening of asylum seekers in Norway

Several epidemiological studies have been performed on immigrants in Norway (9, 12, 43, 88). In addition, there have been two follow-up studies of the X-ray results after screening of asylum seekers (89, 90). Of the latter two, the first one was published in 1996 and showed that just 68% of asylum seekers with positive X-ray findings on arrival had been clinically examined when they were assessed three years later (89). In the other, 11 of the 76 TB cases that were diagnosed within one year after arrival, had a positive X-ray on arrival, but still had not been clinically examined (90).

An unpublished survey of information flow and follow-up of screening results of asylum seekers, conducted both in the primary and specialist health care, revealed several problems between the two levels of care. That effort nevertheless gave some important background information for the present doctoral dissertation research.

2: Aims and objectives

2.1: Overall aims

The overall aim of the research was to assess the effectiveness and efficacy of detection, treatment, and follow-up of active and latent tuberculosis among asylum seekers to Norway. The assessment included screening procedures at entry, the implementation of national guidelines at all levels of public health, and clinical follow-up of individual asylum seekers.

2.2: Specific aims for the individual papers

Paper 1: The aim was to assess to what extent the national regulations and guidelines for screening, treatment, and follow-up of tuberculosis disease and infection among asylum seekers had been implemented at the primary and specialist health care levels in Norway.

Paper 2: The aim was to assess the follow-up of the TB screening results of asylum seekers with emphasis on demographics, screening outcome, how follow-up was organised, and how this influenced treatment for latent tuberculosis. Another aim was to study reasons why asylum seekers were not examined and identify factors that influenced follow-up.

Paper 3: The aim of the paper was to assess the effectiveness of diagnosing active TB by the tuberculosis entry screening programme of a cohort of asylum seekers. We compared cases of active TB that were diagnosed by the screening programme with cases detected outside the programme. We further aimed to characterize all new cases with active tuberculosis.

Paper 4: The paper aimed to compare the predictive properties of QuantiFERON TB Gold (QFT) with the Mantoux test as an entry screening tool to identify individuals with concurrent or later tuberculosis disease.

3: Material and Methods

3.1: Study population

The study population is asylum seekers and almost every asylum seeker who arrives in Norway is sent to the National Reception Centre, Tanum, outside Oslo.

Inclusion into the follow-up study group

All asylum seekers above the age of 18 who arrived at the National Reception Centre from January 2005 till June 2006 were eligible for inclusion. They were included if they had one or more of the following characteristics: a Mantoux test of 6 mm or more, a chest X-ray with calcifications, pleural pathology or parenchymal pathology, or a positive immune globulin release assay test, QuantiFERON®TBGold. Asylum seekers who could not be followed up were excluded if information at the Reception Centre disclosed that they had left the centre without any kind of address, already had left the country or been deported, or had died. For these reasons 469 persons were excluded before and 56 after primary inclusion.

Inclusion into the QFT study

Asylum seekers above the age of 18 who arrived from September 2005 were further invited to participate in a separate substudy (QFT study) (43). The aim of that study was to enrol 1000 persons, a measure that was reached in June 2006. However, a conclusive QFT test result was available for only 912 participants. The reason for this was partly of a technical nature, that a number of participants later withdrew their consent, or that their TST result was missing (43). When the study identification number of these 912 individuals was matched with the list of names as well as with the cohort available for follow-up (see "total cohort", page 39), another 89 subjects were lost. Accordingly, 823 asylum seekers were matched with the National Tuberculosis Register and could be included in the analysis (Paper 4). All TB cases independent of time of diagnosis were analysed.

3.2: Test procedures on arrival to Norway

Chest X-ray

In general radiographers at the Reception Centre took the chest X-rays. In emergency cases or if necessary for other reasons, nurses who were available, did. During the

early phases of the study period the X-ray equipment used was Siemens Thoramat 100 mm film with manual development. This equipment was replaced by the digital system Axiom Aristos TX from August 2005. Until the middle of January 2006, the chest X-rays were read at the Reception Centre by two independent readers, one specialist in pulmonary medicine and one radiologist. In case of disagreement, the two discussed the X-ray together and the first reader made the decision. After that time the chest X-rays were sent digitally to Ullevål University Hospital where they were also read by two independent readers. Again they were a radiologist and a specialist in pulmonary medicine. Only X-ray findings that required a clinical follow-up at the Central TB Clinic at Ullevål University hospital were reported back to the Reception Centre.

One of the physicians who had read the X-rays at the Reception Centre, re-read the X-rays of the persons who were included in the QFT study. This was done in order to make the reports after mid-January 2006 comparable to the reports from before that time.

The written results of the X-ray examinations were recoded for the present study and separate codes were given for calcifications in lung, hilus or mediastinum, pleural pathology, and for parenchymal pathology. The latter included previous and current TB.

The Mantoux test

We employed the PPD; PPD: RT 23, 2TU (SSI, Copenhagen) for the present study. Four experienced nurses applied and read the test. A test was considered positive if the induration was ≥ 6mm after 72 hours. If the induration was very large, showed adverse reaction or was hard to read, two persons read the test and agreed about the result.

IFN-γ release assay

The blood samples were drawn at the National Reception Centre and analysed at the National Institute for Public Health. QuantiFERON®-TBGold in tube test (Cellestis Ltd, Carnegie, Victoria, Australia) was used and incubated, processed and stored according to the manufacturer's recommendation advice. A positive test was defined

as ≥ 0.35 IU IFN- γ/ml. Positive tests were confirmed by a reanalysis. The result was reported as non-conclusive when the confirmatory test was negative (43).

3.3: Data collection

The National Reception Centre

At the National Reception Centre information about demographics, screening results, referrals, and information about the relocation of asylum seekers were filed in a computerized system. In order to identify the study participants and study information, the operator for this computer system searched the files for certain words, groups of words, and dates (Appendix 1). If important study information was missing, e.g Mantoux results, the data files were searched manually in case the information could have been registered under a different heading.

Follow- up registration

To collect information from different parts of the health care system, study forms were sent to officials of primary (community) and specialist (hospital) health care, respectively. The forms collected information about demographics, registration and flow of information, previous medical history, TB risk factors, symptoms and results of clinical examinations, plans for follow-up or referrals, and relocation of study participants. Community health officials were asked if the asylum seeker had been examined or assessed, and we wanted to know the professional level of the examiner. Further, we asked if and why the asylum seeker had been referred to specialist health care. If no referral had taken place, we also asked for the reason why. In case an asylum seeker had been relocated to another municipality, a primary health care form was sent there (Figure 4 & Figure 6).

If a study participant had been referred to a specialist or hospital for further diagnostic work-up, a separate registration form was sent there. Personnel at the specialist health care level were asked more in detail about diagnosis, treatment indications, and treatment for latent tuberculosis for each asylum seeker who had been referred to them. Whenever information held at the National Reception Centre suggested that a patient had been referred directly to the Central TB Clinic at Ullevål University

Hospital, they received the same specialist form. A specialist form was also sent to that clinic for all cases who were registered with a positive chest X-ray finding on the initial screening.

In order to increase the response rate certain measures were taken. Thus, information about the study was given at meetings, and through the information channels of the National Health Institute and the Norwegian Chest Association. The PhD candidate personally visited all four transit centres and sent letters or made phone calls to remind health care personnel to return the study forms.

The data collection took place from February to December 2007. The time from the asylum seekers arrived in the country till data collection was completed ranged from 9 to 35 months and took a median of 18 months.

The Norwegian National Tuberculosis Register

The register contains information about all patients diagnosed with active tuberculosis. The registration includes date of diagnosis, results of bacteriological culture results, localization of disease, and treatment given. In addition, the register has information on everyone who has started treatment of latent tuberculosis. The register is regularly updated against the national register of drugs prescribed for tuberculosis.

Name and birth dates from all included study participants (n=2237) were matched with the Norwegian National Tuberculosis Register. The first match was done on December 31st, 2006 (Paper1), and the second one by the end of May 2008 (Papers 2-4). The matching was done by specially assigned personnel at the National TB Register. A separate match was done for the subgroup of participants who had a negative QFT result (Paper 4).

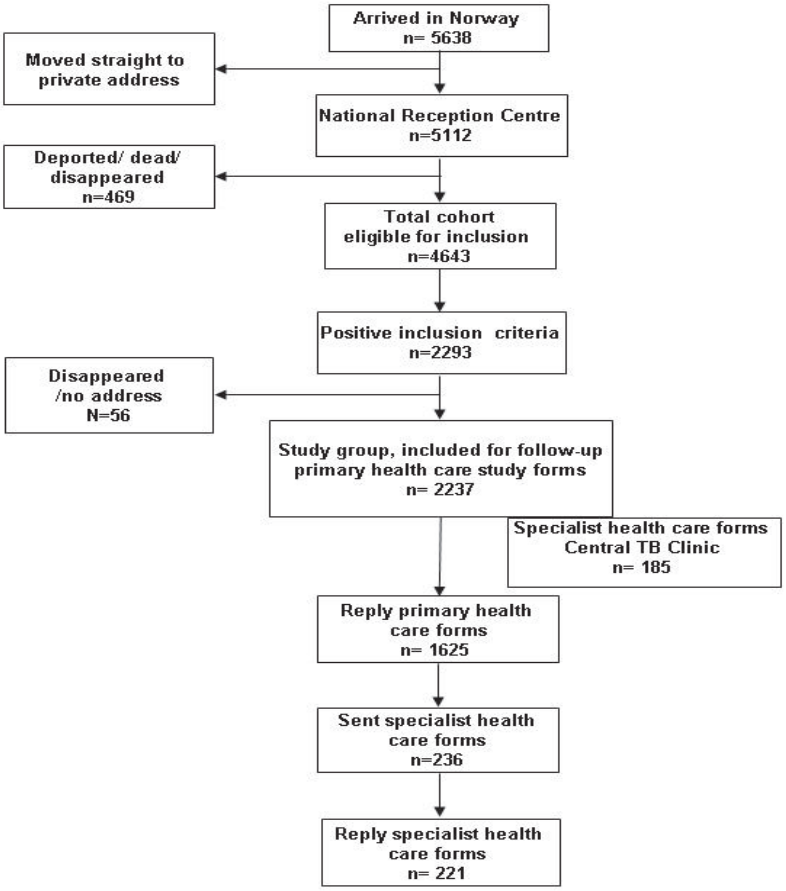

Figure 6. Flow of study forms

When an asylum seeker left the National Reception Centre, a primary care registration form was sent to the public health officials in the municipality where (s)he had moved. If we received information that the asylum seeker had been referred to specialist health care or we were informed that the asylum seeker had been examined at the Central TB Clinic, a specialist registration form was sent there.

3.4: Data registration and analysis

Scanning and quality check

Study registration forms were scanned and entered into SPSS for Windows, version 15 (Chicago, IL, USA) (Paper1 and 2) and version 16 (Paper 3 and 4). About 15-20% of the forms were controlled for errors in the scanning process. We found such errors on 0.5-1% of the forms. Comments and administrative information were coded manually and entered to the same data file.

Data analysis

In papers 1-3 frequencies were analyzed with proportions and 95% confidence intervals (CI). Groups with certain characteristics were compared and considered significantly different if the confidence intervals were not overlapping.
Logistic regression was employed in papers 2 and 3. Variables in the univariate analysis that changed the odds ratio (OR) of the other variables with 0.2 or more were entered into the multivariable analysis. Most variables were dichotomized whereas variables with more than two levels were categorised. All models were checked for correlations and interactions.

In paper 1 descriptive statistics was used as outlined above. Groups were compared on demographics, while positive X-rays were also compared using separate X-ray codes.

In paper 2 the asylum seekers at each follow-up level (Figure 7) were compared with descriptive statistics as described. The most critical stages for the referral process were analyzed with logistic regression. Those critical stages were: patients seen in community health care (yes/no), referred to specialist (yes/no), seen by specialists (yes/no), and started treatment for latent TB (yes/no). Variables with more than two levels were categorised with the youngest age group as reference for age and Europe as the reference for continent.

In paper 3 the study group and the TB cases were described by proportions and 95% CI. The primary outcome was diagnosed with active tuberculosis (yes/no) that was analysed with logistic regression. Again, age was categorised with the youngest age

group as reference, whereas Somalian origin (yes/no) was added as a separate predictor variable. The low number of cases limited the number of regressors that could be included in the multivariable analysis. The following were included; country of origin, gender, and either Mantoux ≥ 10mm or Mantoux ≥ 15mm, or a positive X-ray.

An important outcome was if the tuberculosis case had been detected by the screening programme or not. This outcome was studied by univariate logistic regression. Additional regressors were a pulmonary vs extra-pulmonary TB diagnosis and a positive vs negative bacteriological culture.

In paper 4 we compared the positive (PPV) and negative predictive properties (NPV) of the QFT and the Mantoux test used to identify current or later tuberculosis disease (91). We also estimated 95% CI for both PPV and NPV. Separate estimates for PPV were made with and without the exclusion of study participants who were treated for latent TB, as shown in paper 4.

3.5: Ethics

We did not ask for informed consent from the asylum seekers. The reason was that we estimated that about half of the study participants would have left the country before the study onset and that those still residing in Norway would be difficult to trace. Our arguments were accepted by the Regional Committee for Medical Research Ethics who gave their permission. The Norwegian Data Inspectorate, The Directorate for Health and Social Affairs, and The Ministry of Labour and Social Inclusion all gave their permission. The Research committee at Ullevål University Hospital gave their permission to collect information from the Central TB Clinic. The Directorate for Health later gave us a separate permission to match study participants who had a negative QFT test with the National Tuberculosis Register.

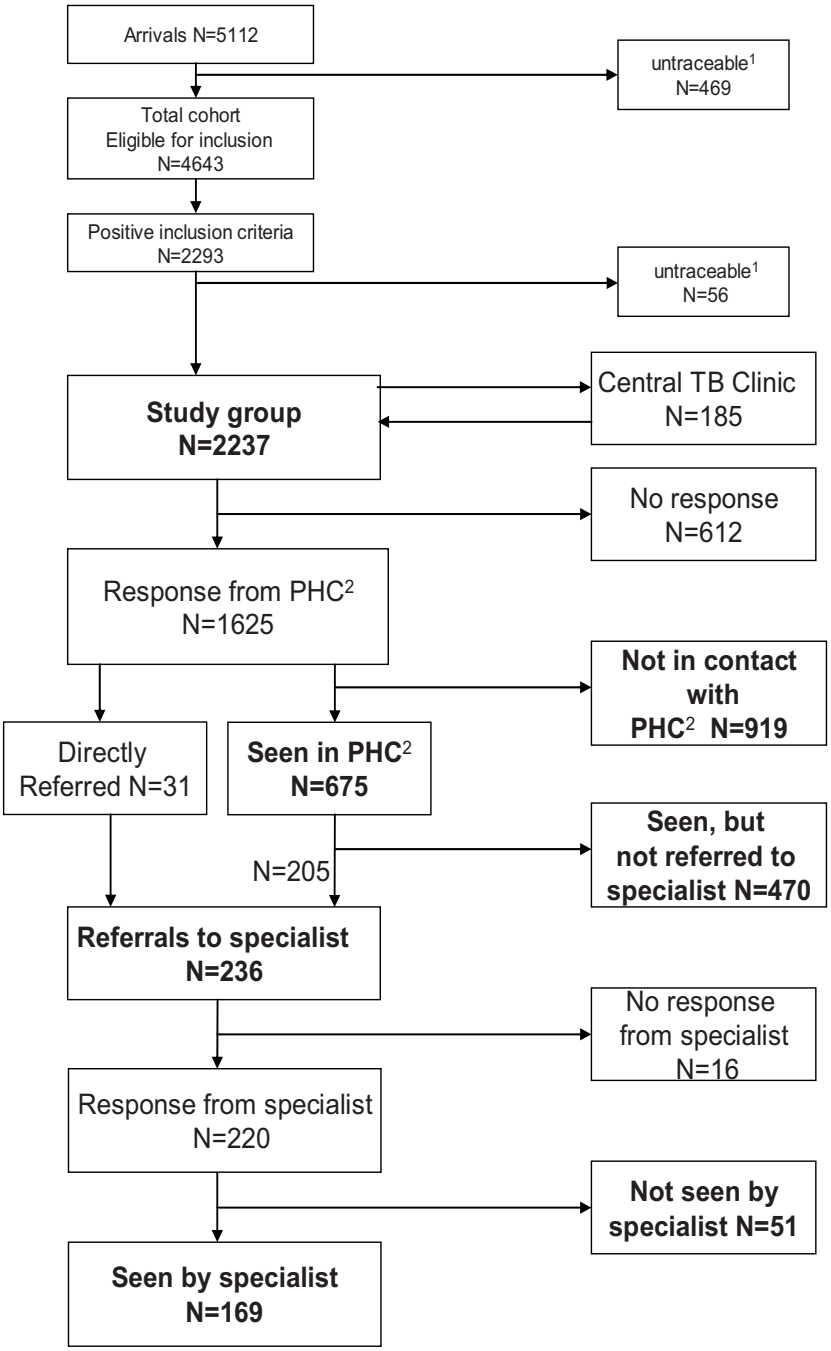

Figure 7. Study population and follow-up (from Paper 2)

[1] Asylum seekers were untraceable if they left the country without a forwarding address, were deported or died before leaving the National Reception Centre.

[2] Primary (community) health care. Bold letters indicate the critical stages of the referral process

4: Results

4.1: Description of the separate sub-cohorts

Total cohort characteristics

From January 2005 till June 2006, 5638 asylum seekers arrived in Norway, of whom 5112 arrived at the National Reception Centre. Because they were deported directly, disappeared, died or left behind no address when they left the Reception Centre, 469 of the latter group were excluded. Thus, 4643 were eligible for the follow-up study (Table 2 & Fig 7*)*. Among them, 3333 (73%) persons were 18-34 years old, 3222 (69%) were males, and 1883 (41%) were married. Nine hundred and sixteen (20%) persons came from Europe (exclusively from Eastern Europe), 1724 (37%) were Africans, while1819 (39%) came from Asia. The five most frequent countries of origin were Iraq (15%), Somalia (15%), Russia (8.2%), Afghanistan (7.2%), and Serbia and Montenegro (6.6%). Positive X-rays were found in 323 persons (including the ones that were re-read), and 2127 had a Mantoux test ≥ 6 mm.

Study cohort characteristics

Altogether 2293 persons had one or more of the inclusion criteria, but 56 of them were excluded because they left without an address or were deported. Thus, 2237 persons were included in the study cohort (Figure 7 & Table 2). Among those, 1447 (65%) were 18-34 years old, 1563 (70%) were males and 1034 (46%) were married. Altogether 390 (17%) came from Eastern Europe, 1007 (45%) were Africans, and 774 (35%) came from Asia. Again, the five most frequent countries of origin were Somalia (457; 20%), Iraq (224; 10%), Russia (182; 8.1%), Afghanistan (166; 7.4%). and Serbia and Montenegro (149; 6.7%).

Positive X-rays were found in 314 (14%) persons (including the X-rays that were re-read), 1440 had a Mantoux from 6 to 14 mm, 638 had a Mantoux ≥ 15 mm (Table 2).

Table 2. Total cohort and study cohort described by demographics and screening results with % and 95% CI

	Groups	Total cohort N=4643 (%) *(95% CI)*	Study cohort N=2237 (%) *(95% CI)*	Study cohort: Mantoux 6-14mm N=1440 (%) *(95% CI)*	Study cohort: Mantoux ≥ 15mm, N= 638 (%) *(95% CI)*
Age groups	**18-34 years**	3333 (72%) *(70-73%)*	1447 (65%) *(63-67%)*	984 (68%) *(66-71%)*	358 (56%) *(52-60)*
	35-49 years	1103 (24%) *(23-25%)*	656 (29%) *(27-31%)*	394 (27%) *(25-30%)*	224 (35%) *(31-39%)*
	>50 years	207 (4.5%) *(4-5%)*	134 (6%) *(5-7%)*	62 (4%) *(3-5%)*	56 (8.8%) *(7-11%)*
Gender	**Males**	3222 (69%) *(68-71%)*	1563 (70%) *(68-72%)*	1067 (74%) *(72-76%)*	375 (59%) *(55-63%)*
	Females	1421 (31%) *(29-32%)*	674 (30%) *(28-32%)*	373 (26%) *(24-28%)*	263 (41%) *(37-45%)*
Marital status	**Married**	1883 (41%) *(39-42%)*	1034 (46%) *(44-48%)*	656 (46%) *(43-48%)*	310 (49%) *(45-52%)*
	Not married	2769 (60%) *(58-61%)*	1203 (54%) *(52-56%)*	784 (54%) *(52-57%)*	328 (51%) *(48-55%)*
Continent of origin	**Europe**	916 (20%) *(19-21%)*	390 (17%) *(16-19%)*	244 (17%) *(15-19%)*	127 (20%) *(17-23%)*
	Africa	1724 (37%) *(36-39%)*	1007 (45%) *(43-47%)*	609 (42%) *(40-45%)*	347 (54%) *(51-58%)*
	Asia	1819 (39%) *(38-41%)*	774 (35%) *(33-37%)*	541 (38%) *(35-40%)*	154 (24%) *(21-27%)*
	South America	15 (0.3%) *(0-0%)*	2 (0.0%) *(0.0-0.0%)*	-	-
	Stateless	169 (3.6%) (3-4%)	64 (2.9%) *(2-4%)*	45 (3%) *(2-4%)*	10 (1.6%) *(1-3%)*
Mantoux test	**<6 mm**	2399 (52%) *(50-53%)*	146 (6.5%) *(6-8%)*	-	-
	6-9 mm	687 (15%) *(14-16%)*	680 (30%) *(28-32%)*	680 (47%) *(45-50%)*	-
	10-14 mm	777 (17%) *(16-18%)*	760 (34%) *(32-36%)*	760 (53%) *(50-55%)*	-
	≥ 15 mm	663 (14%) *(13-15%)*	637 (28%) *(27-30%)*	-	-
Positive x-ray code		323 (7%) *(6-8%)*	314 (14%) *(13-15%)*	77 (16%) *(13-20%)*	70 (11%) *(9-13%)*

The QFT study subgroup

Of the 823 persons who were included in the QFT substudy, 246 (30%) of the remainders had a positive QFT test and were included in the follow-up study (cf. page 31). They were compared with the 577 asylum seekers (70%) who had a negative QFT test (Paper 4).

Twenty-seven of the 246 participants with a positive QFT test (11%) had this as the only criterion for inclusion in the study cohort.

4.2: Results of the individual papers

Paper 1: Tuberculosis screening and follow-up of asylum seekers in Norway: a cohort study

Of the 4643 persons in the cohort, 97.5% had a valid Mantoux test. By end 2007 the primary public health services had assessed 758 (34%) of the included 2237 study participants. Among the 1326 persons with negative X-rays and a Mantoux test between 6 and 14, 372 (28%) had been seen in PHC. Overall, the assessment took place a median of 9 weeks after arrival in the country (range 0-124).

Altogether 328 persons were seen by a specialist. However, some 13 of them were seen both at the Central TB Clinic and by a different internist following a referral from PHC. Of the 314 persons who had a positive X-ray, 194 (64%) had seen an internist. Significantly more persons with parenchymal X-ray findings were seen compared to those with other X-ray pathology. Among 568 persons with a Mantoux ≥ 15 but negative X-rays, 86 (16%) were seen by an internist. The median time from arrival in the country till the patients were seen by an internist was 25 weeks (range 0-14).

In a match with the National TB Register on 31st December 2006, 23 cases of active TB and 11 cases who had started treatment for latent TB were identified. These figures have later been updated by May 2008.

Paper 2: Screening and treatment of latent tuberculosis in a cohort of asylum seekers in Norway

The study was based on the same 2237 asylum seekers who fulfilled the inclusion criteria (see "study cohort characteristics" above). There was no association between the screening results on arrival and whether they were assessed in PHC or not. However, the degree of follow-up at the community level was associated to female gender, being married, and an African background. There was also a positive association between referral to a specialist, and a positive X-ray and Mantoux ≥ 15mm.

By May 2008, 30 persons had started treatment for latent TB. The median time after arrival was 17 months (range 3-36). A Mantoux test ≥ 15mm on arrival was significantly associated to treatment.

Internist classified 41% of their patients who had a Mantoux ≥ 15mm and a normal X-ray as latent TB, and they concluded that there was an indication for treatment in 29% of them. Among those with both positive X-rays and Mantoux ≥ 6mm, 40% were classified by internists as latent TB, and they concluded that there was a treatment indication for 25% of them. Lack of a permanent visa among asylum seekers was a frequent reason for not starting treatment.

The organisation of medical information handling of individual patients was clearly insufficient, and the same was management of information of follow-up and referrals.

Paper 3: The role of entry screening in case finding of tuberculosis among asylum seekers in Norway

Among the 2237 persons in the study cohort of asylum seekers, 28 cases of tuberculosis were diagnosed 0-27 months after arrival in Norway. By the end of May 2008, the reported data from the follow-up study were matched with the National Tuberculosis Register. Fifteen cases were detected by the screening programme, which was defined as diagnosed within two months after their arrival. Two cases were diagnosed between three and six months after arrival and were probably missed by the screening. A positive X-ray on arrival was associated with detection. Female gender and Somalian origin increased the risk for active TB. Somalian background

was also positively associated to extra-pulmonary as compared to pulmonary TB. Seven of the cases that were diagnosed more than two months after arrival had not been subject to a proper evaluation and assessment of their screening results.

Paper 4: Predictive values of QuantiFERON-TB Gold testing in screening for tuberculosis disease in asylum seekers

Of 823 asylum seekers with a valid QFT result that was matched with the National TB Register, eight with a positive and one with a negative QFT were diagnosed with active TB. This occurred after a maximum of 32 months of observation. The positive predictive value (PPV) for QFT was 3.3%, and 2.3% for Mantoux ≥ 15mm, respectively. A Mantoux ≥ 6mm in combination with a positive QFT test gave a PPV of 3.3%. There were no significant differences in the predicting properties of QFT and the Mantoux test. The negative predictive value (NPV) for Mantoux ≥ 6mm in combination with a negative QFT was 99.5%. That combined test is thus equally as favourable as a Mantoux with cut-off of 15mm. IFN-γ levels where not different in tuberculosis patients with a positive QFT compared with those with a positive QFT but no disease.

5: General discussion

5.1: Study outcomes

Asylum seekers and their characteristics

The asylum seekers in our study came from countries where the TB incidences varied widely. The five countries with largest proportion of asylum seekers have reported incidence rates from 249/100 000 in Somalia to 56/100 000 in Iraq (92). The total cohort had more males than females and was dominated by young adults. The same have been found in similar studies (59, 72, 93, 94).

Gender affected follow-up in PHC, and married women were more likely to be assessed (Paper 2). May be they saw a health care provider more often in relation to pregnancy and problems with small children. Females, particularly of Somalian origin, had an increased risk of active TB (Paper 3). In studies from Western countries at the time when TB was more prevalent, females of fertile age had an increased TB risk compared to males of the same age (95). The low numbers in the present study or inequalities in health seeking behaviours in their home countries may explain why our results differ from other studies from developing countries where males have a higher risk (95-97). Several studies have shown that Somalian origin is strongly associated with TB (90, 98-100), as is the association with extra-pulmonary TB (98, 101). It is noteworthy that estimates made by WHO show that the incidence rates (IR) inside Somalia are lower than those shown in studies among Somalians who live outside their country (90, 92, 100). Still, there are some uncertainties related to these estimates. For instance, the number of cases inside Somalia could be underestimated. And it has been suggested that the IR among asylum seekers/refugees in general are higher than among other immigrants from the same countries (73). At the same time, other studies have suggested that asylum seekers /refugees have higher rates than the IR in their home countries (74). The latter is supported by the fact that before they reach their destination, asylum seekers and refugees often have been incarcerated. Thus, they have lived in camps, some have been in prison and in general, their living conditions before and after arrival often have been quite poor. As a consequence, a higher proportion may have acquired a recent infection, and experienced a general reduction in their immune defence.

Unfavourable living conditions during travel could also explain some of these findings (75).

Asylum seekers may be more difficult to trace than other immigrants because they move more frequently, sometimes without reporting their whereabouts to the authorities. Also, they may have been hesitant to reveal their identity for obvious reasons. Their names and/or birth dates may be changed, either because of misunderstandings or by intention. All of this will make them quite difficult to trace.

Finally, if their residence application has been refused, many asylum seekers are deported out of the country. Some of them may disappear from the official registers and either move abroad or choose to become illegal or undocumented immigrants. We do not know if or how many of them have tuberculosis and we do not know if any TB cases that occur among them are reported, either. Still, a study of tuberculosis among undocumented migrants showed that this is a problem that needs attention (15).

Organisational issues related to the location of asylum seekers and information flow

During this study we mapped the movements of asylum seekers and the flow of health information. We identified several pitfalls in how screening results were handled and often ended with lack of action. The central authorities cover the cost of health care at the National Reception Centres and the four transit centres. Further, the regional health authorities are responsible for all kinds of specialist health care, and the municipalities for primary health care. Without doubt, we concluded that the system for follow-up of asylum seekers is both complex and complicated. There are many steps, and there is a lack of coordination between the different levels of health care and between various authorities, e.g., the immigration and health authorities. Asylum seekers are forced to move several times before they may settle down or are deported permanently. Thus, the corresponding flow of health information was an overwhelming problem. Frequently, individual health data was not kept or handled according to the legislation and documentation requirements, and many municipalities rarely retained information on asylum seekers that had moved on.

For 38% of asylum seekers with a positive X-ray finding on arrival, we have no information if a clinical examination had taken place. And as shown in paper 3 we found three cases of active TB who were detected through screening and reported from hospitals in the Oslo area, but nevertheless went undetected by the follow-up study forms or files at the Reception Centre. Thus, probably more cases had been seen by a specialist than we were able to confirm. Still, many were not examined by a specialist in spite of a positive X-ray, which clearly is unacceptable. Pre-immigration screening with X-rays is performed in Canada. A follow-up study in immigrants with TB-related lung scarring, showed that less than half (45%) had been examined clinically after arrival (102). It turned out that 45 % had no valid address and never received a referral letter in the first place. This compares with the problems we had in tracing people and follow-up of X-ray results (102).

As we followed the asylum seekers through the health care system, we observed that only 43% of those we received information about had been examined in PHC. In addition, there was no association between screening results and the possibility of being examined (Paper 2). The reasons could be lack of information about each individual asylum seeker. Alternatively, it could also be due to lack of knowledge or interest, or to lack of priority of asylum seekers in the local communities. We were unable to observe any traces of a common strategy in the various municipalities in relation to how they took responsibility for follow-up of TB screening results.

The central health authorities have neither developed a documentation system for the outcome of the TB screening, i.e. in terms of a conclusive examination of individual asylum seekers, nor a quality assurance system. That is deemed necessary, and as a minimum for asylum seekers with a positive X-ray.

Screening tests

X-rays

Independent of the present research, the chest X-ray methods were changed during the study period. From January till August 2005 X-rays were taken on miniature film, after which a digital system was introduced. Further, a double reading of each X-ray was done at the Reception Centre. Later, the digital films were read at the Ullevål University Hospital. Thus, when the X-rays indicated that a follow-up was necessary,

the X-ray was classified as positive. This way of classification reduced the number of cases recorded with a positive X-ray. To get a more standardized classification for the entire QFT sub study, the X-rays of everyone who were included in that study after January 2006 were re-read by the physician who had read all the X-rays during 2005. This quality assurance procedure increased the number of positive X-rays from 288 to 314 cases. However, the extra positive X-rays from the re-reading were not reported to the health care authorities.

We classified parenchymal findings, pleural findings, or mediastinum, lung or hilus calcifications as a positive or abnormal X-ray. Thus, all the above 288 (Paper 2) cases should have been offered a diagnostic follow up by a specialist even if their individual risk for active TB varied. Yet, those who had parenchymal pathology were more often seen by a specialist than those with other pathological findings. We take that as a clear indication that some selection took place as regards the follow-up of asylum seekers with the highest risk.

The results of X-rays used in screening have varied widely depending on the population examined, the different methods used for taking and reading them, and the definitions of a positive result. Studies from The Netherlands, UK and Switzerland showed that 1.4-2.7% of immigrants had X-rays suggestive of TB (59, 94, 103). But when all abnormal X-rays were included in the Swiss study, the proportion increased to 8.4% (103). We found that 7% of our cohort had abnormal X-ray findings which are in accordance with the Swiss results.

Mantoux test results

According to our national recommendations and guidelines a Mantoux ≥ 15 mm should lead to a direct referral to specialist. This was not the case however, as only 16% with that test result had been seen by a specialist (Paper 1). Still, once persons were seen in PHC and had a Mantoux ≥ 15 mm, there was a strong probability that they were referred to specialist for follow-up (Paper 2). And once patients who were referred to a specialist, were actually seen and examined, there was also a positive association between a Mantoux ≥ 15 mm and treatment for latent TB (Paper 2). We found a similar association between Mantoux ≥ 15 mm and active TB in Paper 3.

The Mantoux test is one of the diagnostic tests for latent TB, but there is no conclusive agreement about how well it works. A false positive test can be the result of BCG immunisation, in particular if it is given after infancy or repeated. Another possibility is an infection with atypical mycobacteria (37). On the other hand, an impaired immune system may give a false negative test result. In our total cohort of 4643 asylum seekers 71% had a BCG scar as compared to 75% in the study cohort. Most of the asylum seekers came from countries where the BCG vaccine is given to young children which would not affect the TST result. However, in some Eastern European countries repeated vaccines are given which could influence the test results for these persons (104).

QFT

As a QFT test was not part of the screening programme when our study took place, we have not performed a detailed assessment of the use of it and the potential impact of a positive QFT on screening, follow-up and outcome.

QFT was nevertheless taken on a subgroup of our cohort, even if it was part of another study (43). The number of patients with active TB was low in this group, and we found no significant differences in the predictive properties between the QFT and the Mantoux test (Paper 4). The main objective of the IGRA tests is to diagnose latent TB, but we may still be interested in how well later development of active TB is predicted. Others have shown that persons with a negative QFT test do not develop active TB later on (45, 47, 48), and a contact tracing study found that PPV was higher for QFT than for Mantoux (44). In contrast, a Gambian contact study that compared Mantoux and ELISPOT found no difference between them in predictive properties (49). Studies that cover a longer follow-up time and various populations are needed to answer whether different IGRAs are as good as or better than Mantoux to predict active TB. Because of our low numbers, our analysis included patients with active TB when they were tested as well as those who became ill later. If we had restricted the analysis to patients who were diagnosed more than one month after arrival, no one with a negative QFT or a negative Mantoux would have been included. On the other hand, that would have improved the negative predictive values for both QFT and Mantoux.

Screening outcomes

A valid Mantoux test result was available for 97.5 % of the asylum seekers. On the other hand, we were unable to ascertain exactly how many study participants that had a chest X-ray taken and read. Thus, the implementation of the Mantoux test in the screening programme was quite good. We conclude that a new or improved recording system for how often an X-ray is taken and the result reported back to the National Reception Centre is necessary.

Within two months after arrival, 15 cases of active TB were detected which most likely was the result of the screening programme, and only two cases were detected between 3 and 6 months after arrival, probably missed by the screening (Paper 3). The majority of the TB cases had a positive X-ray on arrival and since the overall objectives of the screening programme were to diagnose pulmonary TB and minimize the risk of transmission, it seems that the intentions of the programme have been met. Because routines of a fast track examination of persons with a positive X-ray had already been established, this could have been expected. The yield of screening programmes, i.e. the number of cases identified with a correct diagnosis, varies and depends both of the characteristics of the screened population and the validity of the individual programme. Several studies of screening programmes reported TB prevalences that ranged from 0.1-0.5% (93, 94, 103, 105). However, a review of screening of immigrants in Europe found a median yield of 0.18% (*interquartile* range 0.10-0.35%) (106). The yield of 0.7% in our selected high risk group was higher than the median, but still it compares well with the above studies.

Thirty patients started treatment for latent TB, which took place 3-36 months after arrival (Paper 2). This was fewer than expected and was initiated after quite a longer time than expected. Even though other studies are not easily comparable with ours, they too, have shown that relatively few patients started treatment for latent TB as a result of screening (102, 107). We see our unexpectedly low number as a combination of first, unacceptably few assessments in PHC, second, still fewer referrals to specialist, and finally, reluctance among specialists to start treatment.

Health care personnel

We did not collect information among health care personnel about their knowledge and management of the screening programme. However, from written and spoken responses and comments we received it seemed that the recommended management of screening results to some extent were both unknown and misunderstood. In some cases lack of personnel or vacancies in PHC, or variation in the local practices were given as reasons for not completing and returning the forms, or for not handling the screening results according to guidelines.

The response rate from the specialist health care providers was 93%. We take that as an indication of professional interest in the issue. However, we received no reply to our questions whether latent TB had been diagnosed, and whether treatment was found to be indicated in 28% and 23% of cases respectively. Both community and specialist forms were filled in retrospectively using information the personnel had retrieved from their own health records. Thus, information that was necessary for answering our questions could have been unavailable or inaccurate.

None of the seven HIV positive patients that we detected, had received treatment for latent TB, and a positive X-ray was not associated with treatment. Thus, neither did the majority of specialists comply with the diagnostic criteria of latent TB nor did they follow the treatment indications in the guidelines. We have no possibility to conclude whether this was due to lack of interest, lack of knowledge, or for other reasons. We have identified a paper on knowledge, attitudes and clinical management of latent tuberculosis among physicians in California. Their replies to the various questions they were asked, were in 51-94% in accordance with a set of stated guidelines (108). Thus, they seemed to know their guidelines reasonably well, but the study said nothing about how they complied with them.

5.2: Study methods

Our knowledge of the study subject was quite limited when we started. Thus, a number of the challenges and limitations that we experienced, were unforeseen. At the same time, these limitations were also variables that explained some of the

difficulties in real life when we followed the asylum seekers through our health care system.

Systematic errors that are independent of study size include selection bias, information bias and confounding.

Selection bias

Selection bias occurs if the association between exposure and disease differs between individuals who participate in the study and those who do not. We studied a cohort of asylum seekers that was registered within a defined period of time (January 2005 to June 2006). We have no further information about the asylum seekers who left Tanum straight away and were not included in the study cohort, except that we know that many of them were deported or left the country. But we found that the characteristics of asylum seekers where we received a response from PHC were the same as for those where we did not (Paper 2). Therefore, we assume that the information we did receive from the municipalities was free of selection bias in the group.

We have not analyzed any differences between the municipalities who responded and those who did not. But in some cases an oral explanation was given. The lack of response was explained by lack of time or vacancies among health care personnel. In some cases the health personnel in question thought the study was at odds with the confidentiality of the clients. We may speculate whether the municipalities who did respond, were more interested in TB screening and control than the ones that did not. We found, however, that fewer persons in the latter municipalities had started treatment for latent TB which may be an indication in that direction. Still, we have no further information on this issue.

We have limited information about the group of asylum seekers who left the country voluntarily or were deported during the study period. They were characterized by the fact that they were not given a residence permit and hence, differed from those who were allowed to stay, e.g. in terms of nationality. As they left the country they would not have been reported to the Norwegian National TB Register if they came down with active TB later. Another group who probably also was different from the rest are

those who disappeared from the "official" world, went underground and took up a status as illegal or undocumented immigrants. As such and since they stayed on in Norway, they may quite well have become the source of later TB infection. It is unknown to us whether those potential cases would have been treated or notified to the register.

Information bias

Like selection bias, information bias is either differential or non differential. In the former case misclassification for an exposure is related to the disease or misclassification of a disease is related to the exposure (91). This may either result in an over- or underestimation of the measure of effect. On the other hand, since non differential misclassification is unrelated to exposure or disease, the estimated effect will be closer to the null or "diluted" (91).

The National TB Register was responsible for the information related to the diagnosis of active TB, and the initiation of treatment for latent TB. The TB Register receives information from several sources. There was uncertainty about the true identity of some of the participants. For instance, asylum seekers who arrived at the National Reception Centre, were not given a personal identification number and some of them obviously had changed their names or birth dates. Hence, it is quite likely that we retrieved underreported numbers from the TB Register. This would result in a non differential misclassification of information. The same reasons could have reduced the number of responses we received from both community and specialist health care.

We have not been able to clarify with the TB Register whether the cases were detected by screening or not, or the duration of the symptoms of individual patients before diagnosis. In paper 3 we chose to define a case as detected by screening when the diagnosis was made within two months after arrival. Under- as well as over - reporting of cases who were truly detected by screening could clearly be the result of our definition.

Misclassification may have occurred due to lack of study information. In some cases the information may have been misplaced, or lost, or was so insufficient that the data were of no value at all. Consequently, some municipalities may just have classified

them as missing. Several of the responses we did receive, had incomplete information, and dates were often missing. Since we thus did not know the time between arrival and examination, several subjects were excluded from the analysis. In some cases the dates were obviously wrong (e.g. arrival after departure), but most often the errors only regarded a few days. At any rate, we have no reason to believe that any misclassification was differential

Skin tests were read by experienced nurses and recorded on the basis of induration and size of the infiltrate. In case of uncertainty, the results were cross checked with another nurse and a consensus of results reported. Thus, misclassification of Mantoux tests as either positive or negative is quite unlikely. Even if the result of the skin test was not recorded, asylum seekers could be included in the follow-up study if the X-ray or QFT was positive. Since only 2.5% had no valid Mantoux test, a scenario like this would not make a substantial change of the results.

Twentyseven persons were included in the follow-up study based on a positive QFT even if they neither had a positive X-ray nor a positive Mantoux. However, the guidelines have no mention about the QFT. Accordingly, the precise number of asylum seekers that should have been followed up was 2210 instead of 2237. Our calculations were unaffected by their inclusion.

At the time of the study the QFT kit did not include a mitogen test (positive control). This might have led to some false negative results. Also, a negative QFT result *per se* could lead to under-diagnosis of active TB. This could have reduced the number of cases detected with active TB in this group (Paper 4), but only to a minimal and negligible degree.

X-rays of patients included in the QFT study that were taken in 2006 were re-read, cf general discussion, pp 46-47. As a result the number of X-rays classified as positive increased from the original 288 to 314. Since this was unknown at the time when the asylum seekers left the National Reception Centre and were relocated, some underreporting of positive X-rays may have occurred. In Paper 1 and 3 these 26 additional X-ray positive subjects were included in the analysis, but not in Paper 2 where the focus was the follow-up of screening results. It clearly would have been

inappropriate to expect that these 26 persons should have been followed up as long as their positive X-rays were unknown at that time. They should probably have been omitted from Paper 1 too, but including them in the analysis had a minimal effect on the outcome.

Confounding

A confounder is a factor that is associated both with the disease and the exposure, and in an imbalance between the different exposure groups (91). We restricted the number of explanatory variables, which on the other hand means that potential or unknown confounders could have been overlooked. For instance, when we analysed patients with active TB and those treated for latent TB (Paper 3) the number of cases was quite low and did not allow us to control for instance for age in any of the multivariable models.

Random errors

Random errors may still remain after the systematic errors have been eliminated. Also, they decrease as number of participants increase (91). The study cohort was selected from all asylum seekers who arrived during one and a half years. We regard well over 5000 eligible persons as a reasonably large study. However, because active tuberculosis is a rare disease, few cases were available for analysis. Also, fewer patients than expected were treated for latent tuberculosis. These low numbers naturally limited the number of variables that could be included in multivariable regression models. Due to this, random errors can not be entirely ruled out.

5.3: Implementation and organisational consequences

We have conducted a study of a cohort of asylum seekers in Norway. Since the numbers who arrive may vary from time to time, the follow-up rate may vary accordingly. There is also a variation of the composition of asylum seekers in terms of country of origin. This would in turn affect their characteristics and maybe also influence the follow-up and yield of the screening programme

Tuberculosis screening is mandatory in Norway for immigrants from high risk countries. But as we have shown in this study the follow-up of the screening results

in order to reach a conclusive diagnosis was fragmented and limited. When the mandatory part obviously is not managed more prudently, one may question how health problems among asylum seekers in general are taken care of.

Even if there are differences among countries regarding TB screening programmes, several Western countries have some kind of screening for immigrants from high incidence countries (24, 25, 109). Some of the factors identified in our study might be helpful in planning programmes in other countries as well as our own. For instance, it is well accepted that the predictive properties of QFT for tuberculosis depends on the population that is examined. Nevertheless, our study has given some increased knowledge about the test even though few cases were available for analysis.

A direct effect of this study could be a general increased awareness and knowledge among various categories of health personnel about tuberculosis disease. This could be due to the study itself, and via information and presentation of its results to professionals, health and other authorities, and the public. Health and immigrant authorities have already received some information about our results. Hopefully this will have an impact and enhance the cooperation between the involved authorities. The Norwegian Institute of Public Health is revising the recommendations for follow-up and treatment of tuberculosis in Norway, and this study may have influenced their contents.

All asylum seekers are screened at the National Reception Centre while the municipalities are responsible for the primary screening of refugees and other immigrants, and for the follow-up of all categories including the asylum seekers. The diagnostic and treatment responsibility for all with suspected, latent and overt tuberculosis disease on the other hand, lies with the regional health authorities. Even so, the overall responsibility for public and personal health care provision to all immigrants lies with the national health and immigration authorities. Since some of our findings most likely are as relevant for other immigrant groups in Norway as the one we have targeted, we find it reasonable to challenge the appropriate authorities to give more weight to that responsibility.

5.5: Future research directions

An assessment of the cost-effectiveness of the screening programme, and how it is possible to implement the guidelines in a real life situation could be most useful. Different models of follow-up could be tested in comparative studies.

Studies about treatment of latent TB where the attitudes and knowledge of specialists and patients are addressed are highly recommended, as are the study of factors that relate to – limit or enhance – treatment compliance for both active and latent TB.

Studies among high risk groups in Norway that assess their knowledge and attitudes related to active TB and treatment of latent TB would be particularly helpful. Also, it would be useful to unveil the barriers that negatively affect health seeking behaviour among the high risk groups. Finally, we would encourage studies of a programme for active case finding and for treatment of latent tuberculosis in the same groups.

Further knowledge about QFT or similar IGRAs, and their estimated predictive properties is needed. This would call for a large cohort study of individuals at high risk for active TB.

6: Conclusions

The objectives of screening of immigrants are to prevent transmission of infection and development of disease in infected persons. On arrival, most asylum seekers in Norway are screened with chest X-ray and a Mantoux test at one central unit. As a result of the present study we have documented that the Mantoux testing was satisfactory, but we were unable to ascertain the accurate number of asylum seekers that had an X-ray taken. The yield of screening was 0.7% and compares well with other studies. Only one out of three persons with an elevated Mantoux test were followed up adequately and assessed at the local public health care level. The clinical follow up by a specialist of persons with a positive X-ray or a Mantoux ≥ 15mm was also less than satisfactory. Specialists were reluctant to diagnose or treat cases of latent tuberculosis. The negative predictive values for a Mantoux ≥ 6mm with a negative QFT was equally as good as an Mantoux <15mm.

The current system for follow-up of screening results must either be reorganized, strengthened or abandoned. As a minimum, a quality assurance system must be established and better coordination between authorities and between levels of health care is clearly needed. Specialists in pulmonary medicine must be more involved in the revision and implementation of undisputable guidelines for treatment of latent tuberculosis. A special focus on groups with particular high risk should also be considered.

7: References

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8: Appendix

Appendix 8.1: Information retrieved from the computer system at the National Reception Centre

Second name
First name
DUF number
UDI number
Country of birth
Date of arrival at the reception centre
Date of departure from the reception centre
Date of tuberculin test reading
Result of tuberculin test
Complications of tuberculin test
BCG scar
Other tests (included QFT)
Screening results sent (date)
Asylum status (moved to new AS centre, left the country, sent out, died--)
Results of chest X-ray
Address when moving to private accommodation
Reserved time at the central TB clinic and report from the central TB clinic

General address list for asylum seeker centres, transit centres and municipalities in Norway.

Appendix 8.2: Information letter sent to primary health care about the study

Informasjonsbrev til kommunehelsetjenesten om studien

”Forebygging av tuberkulose blant innvandrere i Norge”

Høsten 2005 fikk to innvandrerungdommer på en videregående skole i Trondheim smitteførende tuberkulose. Dette ble slått opp i media og utløste usikkerhet og spekulasjoner fra bl.a foreldre, elever, skolen og i allmennheten. For helsevesenet førte det til en storstilt smitteoppsporing. En slik sak reiser spørsmålet om hvordan dette kan forhindres i Trondheim og landet ellers.

Bakgrunn:
Rundt 80% av pasientene med aktiv tuberkulose har innvandrerbakgrunn og de fleste er smittet før ankomst. Ved ankomst skal alle innvandrere over 15 år ta lungerøntgen og tuberkulintest. De som er smittet og ikke har fått behandling, skal etter planen følges opp de nærmeste tre år.
Forebyggende behandling antas å redusere sannsynligheten for sykdom med 60-90%. Veilederen ”Forebygging og kontroll av tuberkulose” (2003), anbefaler en mer aktiv holdning til behandling av latent tuberkulose enn tidligere. Foreløpig er det kun en liten andel av alle smittede som får behandling for latent tuberkulose.

Hvilke spørsmål ønsker denne studien å besvare?
Hvordan blir asylsøkere som kommer til landet fulgt opp i kommunehelsetjenesten, hvem prioriteres med tanke på vurdering, og hvem blir henvist videre i tiltaks- og behandlingskjeden?
Hvordan blir asylsøkerne vurdert i spesialisthelsetjenesten? Hvordan påvirkes vurderingene av den nye diagnostiske blodprøven QuantiferronTBGold?

Hvem og hva skal studien undersøke?
Studien gjelder asylsøkere som ankom Tanum asylmottak i 2005 og våren 2006 og er over 18 år. Dersom de har positiv røntgen thorax, Mantoux ≥6mm eller positive funn ved QuantiferronTBGold, blir de fulgt gjennom tiltakskjeden. Det sendes først et registreringsskjema (som er vedlagt) til mottakskommunen, dvs dere. Det inneholder spørsmål om hver enkelt asylsøker om hva som har skjedd med helseopplysningene fra Tanum, hvordan den enkelte ble vurdert og om han/hun ble henvist videre. Det er viktig med opplysninger om tidspunkt for vurdering. Opplyser dere at asylsøkeren er henvist til spesialisthelsetjenesten, vil det bli sendt et annet registreringsskjema dit.

Tilrådinger og tillatelser for studien:
Studien er vurdert og tilrådd av

- Regional komite for medisinsk forskning i Midt-Norge,
- Sosial-og helsedirektoratet (fritak fra taushetsplikt)
- Datatilsynet (konsesjon)
- Arbeids- og inkluderingsdepartementet: tillatelse til å spørre mottak hvor personene har flyttet

Partnere i prosjektet er:

- Nasjonalforeningen for Folkehelsen.
- NTNU, Institutt for samfunnsmedisin
- Nasjonalt folkehelseinstitutt.
- Prosjektansvarlig: Ingunn Harstad, PhD-stipendiat og lungelege

Kontakt og spørsmål: Ingunn Harstad, ingunn.harstad@ntnu.no, adresse: ISM, MTFS, 7489 Trondheim, tlf 99494996

Appendix 8.3: Information letter sent to specialist health care about the study

Informasjonsbrev til spesialisthelsetjenesten om studien

”Forebygging av tuberkulose blant innvandrere i Norge”

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Bakgrunn: Rundt 80% av pasientene med aktiv tuberkulose har innvandrerbakgrunn, og de fleste er smittet før ankomst. Ved ankomst skal alle innvandrere over 15 år ta lungerøntgen og tuberkulintest. De som er smittet og ikke har fått behandling, skal etter planen følges opp de nærmeste tre år.
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Hvilke spørsmål ønsker denne studien å besvare?
Hvordan blir asylsøkere som kommer til landet fulgt opp i kommunehelsetjenesten, hvem prioriteres med tanke på vurdering, og hvem blir henvist videre i tiltaks- og behandlingskjeden?
Hvordan blir asylsøkerne vurdert i spesialisthelsetjenesten mht forebyggende behandling? Hvilke behandlingsregimer brukes og hvor mange fullfører behandlingen? Hvordan påvirkes vurderingene av den nye diagnostiske blodprøven QuantiferronTBGold?

Hvem og hva skal studien undersøke? Studien gjelder asylsøkere som ankom Tanum asylmottak i 2005 og våren 2006 og er over 18 år. Dersom de har positiv røntgen thorax, Mantoux ≥6mm eller positive funn ved QuantiferonTBGold, blir de fulgt gjennom tiltakskjeden. Det sendes først et registreringsskjema til mottakskommunen med spørsmål om hver enkelt asylsøker, hvordan den enkelte ble vurdert og om han/hun ble henvist videre. Dersom det ble opplyst at asylsøkeren er henvist til spesialisthelsetjenesten, vil det bli sendt et annet registreringsskjema til dere. Det inneholder spørsmål om hvordan den enkelte er vurdert, undersøkt og om det er funnet indikasjon for forebyggende behandling.

Tilrådinger og tillatelser for studien: Studien er vurdert og tilrådd av:
- Regional komite for medisinsk forskning i Midt-Norge,
- Sosial-og helsedirektoratet (fritak fra taushetsplikt)
- Datatilsynet (konsesjon)
- Arbeids- og inkluderingsdepartementet: tillatelse til å spørre mottak hvor personene har flyttet

Partnere i prosjektet er:

- Nasjonalforeningen for Folkehelsen.
- NTNU, Institutt for samfunnsmedisin.
- Nasjonalt folkehelseinstitutt
- Prosjektansvarlig: Ingunn Harstad, PhD-stipendiat og lungelege

Kontakt og spørsmål: Ingunn Harstad, ingunn.harstad@ntnu.no, adresse: ISM, MTFS, 7489 Trondheim, tlf 99494996

Appendix 8.4: Primary health care study form

Registreringsskjema for kommune: skjema 2 **Studienummer:** ☐☐☐☐ ■

1: Fødselsdato: ☐☐.☐☐.☐☐☐☐

2: UDI-nummer: ☐☐☐☐☐☐☐☐☐☐☐

3: Fødeland: _____

4: Personen er registrert/kjent i kommunen ☐ ja ☐ nei ☐ ukjent

Hvis ja, dato: ☐☐.☐☐.☐☐☐☐

5: Mottatt helseopplysninger fra Tanum ☐ ja ☐ nei ☐ ukjent

Hvis ja, dato: ☐☐.☐☐.☐☐☐☐

Videre undersøkelse etter ankomst :

6. Klinisk undersøkelse ☐ ja ☐ nei Samtale ☐ ja ☐ nei

Hvis nei, videre til spørsmål 25, hvis ja, dato for undersøkelse: ☐☐.☐☐.☐☐☐☐

7: Gjennomført av hvem ☐ Lege ☐ Helsesøster ☐ Sykepleier ☐ Andre: _____

Dersom Mantoux er tatt i kommunen

8: Mantoux verdi ☐☐ mm ☐ vesikuløs ☐ lymfangitisk

9: Hvorfor ble ny Mantoux tatt?
- ☐ mangler tidligere verdi
- ☐ rutine på alle
- ☐ før BCG-vaksine
- ☐ har vært utsatt for smitte
- ☐ andre: _____

Anamnese:

10: Tidligere behandlet for TB ☐ fullstendig kur ☐ ufullstendig kur ☐ ukjent

Kroniske sykdommer:

11: Diabetes ☐ ja ☐ nei ☐ ukjent

12: HIV positiv ☐ ja ☐ nei ☐ ukjent

13: Røyker ☐ ja ☐ nei ☐ ukjent Hvis ja: ☐☐ antall sigaretter per dag

14: Risiko for smitte av TB de to siste år? ☐ ja ☐ nei ☐ ukjent

15: Opphold i fengsel de to siste år? ☐ ja ☐ nei ☐ ukjent

16: Opphold i flyktningeleir de to siste år? ☐ ja ☐ nei ☐ ukjent

50161

Studienummer: ☐☐☐☐

Symptomer:

17: Hoste ☐ja ☐nei ☐ukjent Hvis ja, hvor lenge? ☐☐☐ uker

18: Vekttap ☐ja ☐nei hvis ja, ☐☐ kg

19: Nattesvette ☐ja ☐nei ☐ukjent

20. Feber? ☐ja ☐nei ☐ukjent

21: Brystsmerter? ☐ja ☐nei ☐ukjent

Kliniske funn:

22: Objektive funn ☐ja ☐nei Hvis ja, spesifiser: _____

23: Nedsatt almenntilstand ☐ja ☐nei ☐usikker

24: Lungefunn ved klinisk undersøkelse ☐ja ☐nei

Hvis ja, spesifiser: _____

Fylles ut på alle:

25: Videre tiltak: ☐ja ☐nei Hvis nei, videre til pkt 30

26: Henvisningsgrunn: Mantoux-størrelse ☐☐ mm

Rtg-funn ☐ja ☐nei

Symptomer ☐ja ☐nei

Blodprøve-Quantiferron tatt ☐ja ☐nei Hvis ja ☐pos ☐neg

Mistanke om smitte de to siste år ☐ja ☐nei

Annen grunn til henvisning _____

27: Henvist Rtg thorax ☐ja ☐nei

Hvis ja, hvor _____ og dato ☐☐.☐☐.☐☐☐☐

28.Henvist spesialisthelsetjenesten ☐ja ☐nei

Hvis ja, hvor _____ og dato ☐☐.☐☐.☐☐☐☐

50161

Studienummer: ☐☐☐☐

29: Andre henvisninger ☐ ja ☐ nei

Hvis ja, hvor _____ og dato ☐☐.☐☐.☐☐☐☐

30: Grunnen til ikke henvist: Ingen indikasjon ☐ ja ☐ nei

Pasienten ønsker ikke henvisning ☐ ja ☐ nei

Annet: _____

Personen har reist:

31: Flyttet til annen kommune: ☐ ja ☐ nei

kommune: _____ dato ☐☐.☐☐.☐☐☐☐

32: Helseopplysninger sendt ☐ ja ☐ nei dato ☐☐.☐☐.☐☐☐☐

33: Sendt ut av landet ☐ ja ☐ nei dato ☐☐.☐☐.☐☐☐☐

34: Forsvunnet ☐ ja ☐ nei dato ☐☐.☐☐.☐☐☐☐

35: Død ☐ ja ☐ nei dato ☐☐.☐☐.☐☐☐☐

Kommentarer:

_____

_____

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Appendix 8.5: Specialist health care study form

Registreringsskjema for spesialisthelsetjenesten: skjema 3 **Studienummer:** ☐☐☐☐

1: Mottatt henvisning ☐ ja ☐ nei ☐ ukjent Hvis ja, dato ☐☐.☐☐.☐☐☐☐

Henvisning fra _____

2: Status: ☐ asylsøker ☐ flyktning ☐ midlertidig opphold ☐ ukjent

3: Tidligere unnlatt å møte til time ☐ ja ☐ nei ☐ ukjent

4: Konsultasjon dato ☐☐.☐☐.☐☐☐☐

Henvisningsgrunn:

5: Mantoux-utslag ☐☐ mm

6: Rtg-funn ☐ ja ☐ nei

7: Symptomer ☐ ja ☐ nei Hvis ja, spesifiser _____

8: Blodprøve-Quantiferron tatt ☐ ja ☐ nei Hvis ja ☐ pos ☐ neg

9: Mistanke om smitte de to siste år ☐ ja ☐ nei ☐ ukjent

10: Annen grunn til henvisning _____

Sosialt:

11: I jobb ☐ ja ☐ nei ☐ ukjent

12: Deltar på språkkurs ☐ ja ☐ nei ☐ ukjent

13. Kjent smitterisiko de to siste år ☐ ja ☐ nei ☐ ukjent

14: I fengsel før ankomst landet ☐ ja ☐ nei ☐ ukjent hvis ja, antall mnd ☐☐☐

15: Bodd i flyktningeleir ☐ ja ☐ nei ☐ ukjent hvis ja, antall mnd ☐☐☐

16: Tidligere fått påvist TB ☐ ja ☐ nei ☐ ukjent

17: Hvis ja: Fått behandling for TB ☐ ja ☐ nei ☐ ukjent

18: Hvis ja, antall mnd ☐☐

19: Antall medikamenter ☐☐ Hvilke _____

Andre kroniske sykdommer:

20: Diabetes Mellitus ☐ ja ☐ nei ☐ ukjent

21: HIVpositiv ☐ ja ☐ nei ☐ ukjent

22. Leversykdom ☐ ja ☐ nei ☐ ukjent

23: Røyker ☐ ja ☐ nei hvis ja, antall sigaretter per dag ☐☐

25595

Studienummer: ☐☐☐☐

Symptomer:

24: Hoste ☐ ja ☐ nei ☐ ukjent

Hvis ja, hvor lenge ☐☐ antall uker

25: Vekttap ☐ ja ☐ nei ☐ ukjent Hvis ja, antall kg ☐☐

26: Nattesvette ☐ ja ☐ nei ☐ ukjent

27. Feber ☐ ja ☐ nei ☐ ukjent

28. Brystsmerter ☐ ja ☐ nei ☐ ukjent

29. Andre symptomer: ☐ ja ☐ nei ☐ ukjent

Klinisk status:

30: Objektive funn ☐ ja ☐ nei Hvis ja, spesifiser

31: Nedsatt almenntilstand ☐ ja ☐ nei

32: Patologiske funn ved auskultasjon ☐ ja ☐ nei Hvis ja, spesifiser

33: Andre funn ☐ ja ☐ nei Hvis ja, beskriv

34: Videre tiltak: ☐ ja ☐ nei Hvi nei, gå videre til pkt 48

35: Videre utredning: ☐ ja ☐ nei

36: Hvis ja: ekspektorat ☐ ja ☐ nei

Indusert sputum ☐ ja ☐ nei

Bronchoscopi ☐ ja ☐ nei

CT-thorax ☐ ja ☐ nei

Blodprøver ☐ ja ☐ nei

Annet ☐ ja ☐ nei

Konklusjon:

37: Aktiv tuberkulose: ☐ ja ☐ nei

38: Latent tuberkulose: ☐ ja ☐ nei

25595

Studienummer: ☐☐☐☐ ■

Forebyggende behandling:

39: Er det indikasjon for forebyggende behandling ☐ ja ☐ nei

40: Er forebyggende behandling startet ☐ ja ☐ nei

41: Dersom nei, hvorfor ikke ☐ pasienten ønsker ikke forebyggende behandling
☐ legen tror ikke det lar seg gjennomføre
☐ andre grunner: beskriv _____

Dersom forebyggende behandling er startet:

42: MSIS-melding sendt dato ☐☐.☐☐.☐☐☐☐

43: Medikamentregime: ☐ 3mnd INH+rifampicin ☐ 6mnd isoniazid
☐ annet, beskriv: _____

44: Gitt som DOTS ☐ ja ☐ nei

Regelmessig dosett ☐ ja ☐ nei

Kun resept ☐ ja ☐ nei

Annen oppfølging ☐ ja ☐ nei beskriv: _____

45: Fullført forebyggende behandling ☐ ja ☐ nei

Hvis ja, avsluttet dato ☐☐.☐☐.☐☐☐☐ Hvis nei, gå til pkt 46

46: Hvis nei: hvorfor ikke ☐ forsvunnet ☐ sendt ut ☐ bivirkninger ☐ pasienten vil ikke
☐ andre grunner, beskriv: _____

47: Videre kontroller ☐ ja ☐ nei

Ved behov for videre kontroller, hvor lenge antall hele år ☐☐

48: Personene har reist: ☐ ja ☐ nei

Hvis ja: årsak

1: Flyttet til annet helseforetak dato ☐☐.☐☐.☐☐☐☐ Hvor _____

2: Helseopplysninger oversendt dato ☐☐.☐☐.☐☐☐☐

3: Sendt ut av landet dato ☐☐.☐☐.☐☐☐☐

4: Forsvunnet dato ☐☐.☐☐.☐☐☐☐

5: Død dato ☐☐.☐☐.☐☐☐☐

Kommentarer: _____

Paper I

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Research article

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Tuberculosis screening and follow-up of asylum seekers in Norway: a cohort study

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Abstract

Background: About 80% of new tuberculosis cases in Norway occur among immigrants from high incidence countries. On arrival to the country all asylum seekers are screened with Mantoux test and chest x-ray aimed to identify cases of active tuberculosis and, in the case of latent tuberculosis, to offer follow-up or prophylactic treatment.

We assessed a national programme for screening, treatment and follow-up of tuberculosis infection and disease in a cohort of asylum seekers.

Methods: Asylum seekers ≥ 18 years who arrived at the National Reception Centre from January 2005 to June 2006, were included as the total cohort. Those with a Mantoux test ≥ 6 mm or positive x-ray findings were included in a study group for follow-up.

Data were collected from public health authorities in the municipality to where the asylum seekers had moved, and from hospital based internists in case they had been referred to specialist care.

Individual subjects included in the study group were matched with the Norwegian National Tuberculosis Register which receive reports of everybody diagnosed with active tuberculosis, or who had started treatment for latent tuberculosis.

Results: The total cohort included 4643 adult asylum seekers and 97.5% had a valid Mantoux test. At least one inclusion criterion was fulfilled by 2237 persons. By end 2007 municipal public health authorities had assessed 758 (34%) of them. Altogether 328 persons had been seen by an internist. Of 314 individuals with positive x-rays, 194 (62%) had seen an internist, while 86 of 568 with Mantoux ≥ 15, but negative x-rays (16%) were also seen by an internist. By December 31st 2006, 23 patients were diagnosed with tuberculosis (prevalence 1028/100 000) and another 11 were treated for latent infection.

Conclusion: The coverage of screening was satisfactory, but fewer subjects than could have been expected from the national guidelines were followed up in the community and referred to an internist. To improve follow-up of screening results, a simplification of organisation and guidelines, introduction of quality assurance systems, and better coordination between authorities and between different levels of health care are all required.

Background

As tuberculosis (TB) in native populations in Western countries decreases, the relative importance of cases among immigrants increases. Latent tuberculosis is prevalent in immigrants, and may result in an increased incidence for many years after immigration [1,2].

Many Western countries carry out screening immediately after arrival, but programmes for immigrants from high incidence countries vary widely between them, and their documented impact is sparse. While some countries focus mainly on diagnosing active pulmonary tuberculosis, others follow up high risk individuals, or aim at preventing new cases through BCG immunisation or treatment of latent tuberculosis [3,4].

For public health it is most important to identify cases of pulmonary tuberculosis and the majority of them can be detected by chest x-ray [1,5]. Still many cases of extra-pulmonary tuberculosis and latent tuberculosis may thus be overlooked. A tuberculin skin test is often used in addition to x-ray, but has several limitations [6]. Recently, new interferon gamma release assays have been introduced, with promising results for diagnosing latent tuberculosis and may become a useful addition to the screening programme [7].

In Norway, the incidence of tuberculosis in the general population gradually decreased until the late 1980's. Thereafter the number of new cases has remained low and was 6.3/100 000 population in 2006 [8]. During the last 25 years the characteristics of incident cases have changed, and the active disease now stem from imported strains rather than person to person transmission within the country [9]. Somalia is the country of origin for most new cases.

Previously, the main focus of the Norwegian tuberculosis control programme was on early case detection of active disease and follow-up without treatment of the latent form. In 2002 the European working group on tuberculosis control and elimination in low incidence countries (WHO, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association) recommended a new strategy. It aimed to reduce the prevalence of tuberculosis infection and also included prophylactic therapy [10].

The same year new regulations for tuberculosis control were introduced in Norway. These emphasised a continued need to screen immigrants from high incidence countries after arrival, as well as others with high risk, and to follow up those with abnormal findings [11]. The corresponding national guidelines, that were issued by the national health authorities to all health personnel engaged in TB management and care, promoted more vigorous treatment of latent tuberculosis [12].

Public health care in Norway is organised in two levels where the municipal authorities are responsible for primary health care. This includes infectious disease control within the community. Patients in whom screening outcome implies a more detailed and targeted follow-up, are referred to specialist care in state-owned hospitals.

Recommended screening and management of tuberculosis

Asylum seekers and refugees (table 1) are subgroups of immigrants with particularly high risk for tuberculosis [13,14]. Hence, on arrival in Norway, all asylum seekers are referred to the National Reception Centre outside Oslo for registration, management of immediate medical needs, and compulsory tuberculosis screening (figure 1 and table 2). Screening includes a Mantoux test and chest x-ray for everyone over 15 years of age.

According to the guidelines, asylum seekers with a chest x-ray suggestive of tuberculosis disease, as well as everyone who reports symptoms of tuberculosis, should be referred directly to the Central TB Clinic at Ullevaal University Hospital, Oslo, for further examination. It is clearly stated that in addition to a positive x-ray, a Mantoux test ≥ 15 mm should lead to a direct referral to an internist [12]. When leaving the National Reception Centre, asylum seekers are directed to one of several local asylum seeker centres or transit centres in communities throughout the country. If an individual has to await the outcome of examination, or if treatment is started, the whole family will stay at one specially designated Transit Centre for TB Treatment until the treatment is completed (figure 1). Those who initially stay in a transit centre later move on to an asylum seeker centre. On the other hand, they may also leave the country on their own or be sent out at any time. Sometimes, asylum seekers find private accommodation on their own with help from family or others.

Screening results are mailed to the respective municipal health authorities, and everyone with a Mantoux test of 6–14 mm should be clinically examined in primary health care and interviewed about other TB risk factors [12]. An HIV test is not compulsory, but is taken if deemed clinically relevant. Whenever definite risk factors are identified, all patients should be referred to an internist who is responsible for ensuring timely clinical examination and a sputum test, and any other relevant diagnostic work-up. If tuberculosis disease is diagnosed or treatment for latent tuberculosis is started, a nominal notification is sent to the National Tuberculosis Register.

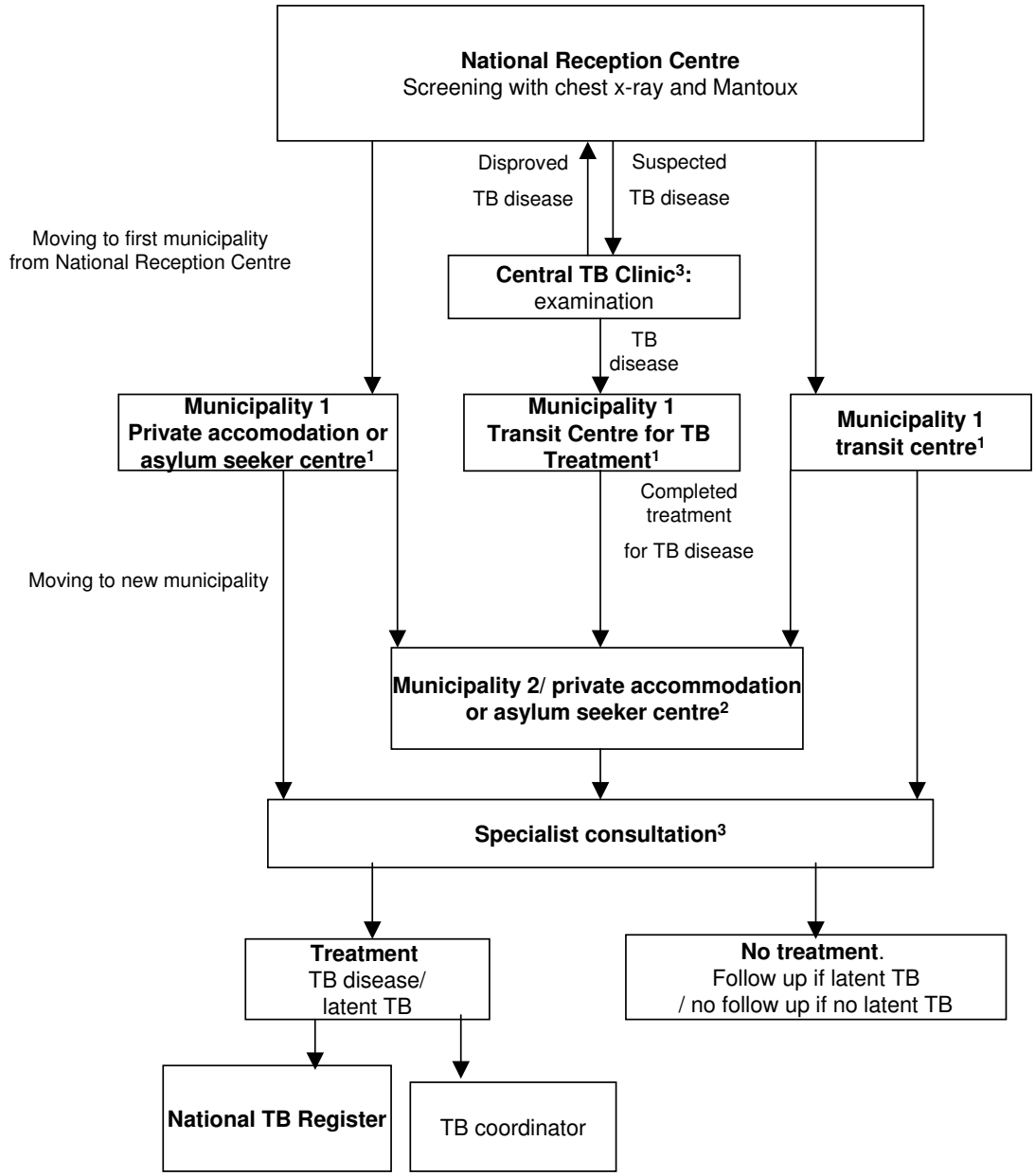

Figure 1
Flow of asylum seekers. Primary Health Care (PHC) form sent to first municipality (transit centres, asylum seeker centres, or private accommodation) 2: PHC form sent to second municipality (asylum seeker centres or private accommodation) 3: Specialist form sent to the Central TB Clinic and to other hospital based specialists (internists).

Table 1: Definitions of "asylum seeker" and "refugee"

Asylum seeker[1]	A person who on his or her own initiative, and without prior notification, asks the authorities in Norway for protection and recognition as a refugee. The person is called an asylum seeker until a decision has been made on the application.
Refugee	A person who either has been granted residence permit before arrival, through the UN system, or arrived as an asylum seeker and has been granted protection as refugee after application.

[1]http://www.udi.no/upload/English/FactSheet/FaktaarkAsylEngelsk.pdf

Information about asylum seekers is readily available since they are all received through a single National Reception Centre.

We aimed to assess to what extent the national recommendations for screening, treatment and follow-up of tuberculosis disease and infection among asylum seekers had been implemented at the primary and specialist health care levels in Norway [11,12].

Methods

Study population

All asylum seekers ≥ 18 years who arrived at the National Reception Centre from January 2005 to June 2006, were eligible for study inclusion except those that had left the centre without a forwarding address, had left the country, had been deported, or had died before leaving the centre.

Inclusion into the study group for follow-up was ascertained from information held in the data base at the National Reception Centre. The criteria for inclusion were either a positive Mantoux test or a positive chest x-ray. The former was defined as Mantoux ≥ 6 mm, (PPD: RT 23, 2 TU from SSI, Copenhagen, Denmark).

X-ray films were taken at the National Reception Centre and interpreted by two independent readers, a pulmonologist and a radiologist. The results were later recoded for this study. A positive x-ray included pleural pathology,

Table 2: Kind and characteristics of institutions attending asylum seekers

Institutions (total number)	Functions	Health care level	Staff	Source of information for the study
National Reception Centre (1)[1]	Short term. All asylum seekers (AS) on arrival to Norway. Screening by chest x-ray and Mantoux.	Primary health care (PHC) paid for by national government.	PHC officer or nurse	Information from the computer system of the National Reception Centre.
TB Treatment Transit Centre (1)[1]	Short or long term. Treatment of patients with active TB, or potential patients waiting for consultation or examination results. Family members are included.	PHC paid for by national government	PHC officer or nurse	Filled in PHC registration forms[2]
Central TB Clinic (1)[1]	Out patient. AS referred directly from the National Reception Centre or from other levels. Focus is active TB.	Hospital based specialist health care.	Specialists in pulmonary medicine	Filled in specialist registration form[3]
Transit centre (4)[1]	Short term stay. AS who wait for an interview by police or for being deported.	PHC paid for by national government	PHC officer or nurse	Filled in PHC registration forms[2]
Asylum seeker centre (ca 100, January 2005)	Longer stay. Staying there till they get a permanent residency or are deported.	Municipal authorities directly responsible for health care.	PHC officer or nurse	Filled in PHC registration forms[2] or [4]
Specialist health care	Out patient. Examine and treat AS after referral from primary health care	Hospital based specialist care.	Hospital specialists, pulmonary or internal medicine	Filled in specialist registration form[3]

[1]: Number of centres, [2]: PHC forms sent to the first municipality after the National Reception Centre, [3]: Specialist forms, [4]: PHC forms sent to the second municipality after the National Reception Centre

pulmonary, hilar or mediastinal calcifications, or parenchymal pathology.

An interferon gamma release assay test (QuantiFERON® TB Gold in-tube test, Cellestis Ltd, Carnegie, Victoria, Australia, QFT) had been performed in a previous study of a subset of 912 eligible persons [15].

Data collection

Information on demographics and initial screening results was collected from the data base at the National Reception Centre. Follow-up information was obtained by using two different study forms. First, a local primary health care (PHC) form was sent to the public health physician in the municipality where the asylum seekers had moved to. If the person in question had moved to a second municipality, the same form was sent there (figure 1).

Second, a specialist form was sent to the Central TB Clinic whenever findings at the National Reception Centre had indicated that a referral was indicated. It was sent to other hospital internists throughout the country when the PHC form positively confirmed that an individual had been referred to specialist care (figure 1).

Both forms collected information about demographics, registration and flow of information, previous history and other diseases, TB risk factors, symptoms, clinical examination and findings, plans for follow-up or referrals, and relocations of study participants. The municipalities were asked whether the asylum seeker had been examined or interviewed, and if so, by whom: physician, community health nurse, or regular nurse. Any referrals were recorded: x-rays, specialist health care, or others. In case of no referral, the reason why was recorded: not indicated, the patient did not want a referral, or other reasons. Relevant dates and numbers were also recorded.

Name and birth date on everyone included in the study group were checked against the National Tuberculosis Register. The latest update of the register took place on December 31st 2006.

Data handling and analysis

Study forms were scanned and entered into SPSS for Windows, version 14 (Chicago, IL, USA). Comments and administrative information were coded manually and entered to the same data file.

Frequencies were analyzed with proportions and 95% confidence intervals (CI). Groups were compared on demographics, and positive x-rays were also compared on x-ray codes. Prevalence < 0.05 were considered statistically significant.

Study ethics

The Regional Committee for Medical Research Ethics approved the study. The Norwegian Data Inspectorate, the Directorate for Health and Social Affairs, the Ministry of Labour and Social Inclusion, and the Research Committee at Ullevaal University Hospital all gave their permission.

Results

Among the 5112 asylum seekers ≥ 18 years who arrived at the National Reception Centre from January 2005 to June 2006, 4643 (91%) were eligible for study inclusion and are hereafter referred to as the total cohort. Among this cohort, there were 3222 (69%) males and 3333 (72%) were in the 18–34 year old age group. They came from 90 different countries, and Iraq, Somalia, Russia, Afghanistan, and Serbia and Montenegro contributed most, i.e. 2434 persons (52%). Coverage of a valid Mantoux test was 4526 (97.5%), the yield of a Mantoux ≥ 6 mm was 2127 (46%) and a positive chest x-ray 323 (7%) individuals, respectively. A positive QFT test was used as the only inclusion criterion for 28 participants.

The follow-up study group

Of the 2293 asylum seekers with at least one positive inclusion criterion, 2237 were included in the follow-up study because 56 individuals who were eligible for inclusion had left the National Reception Centre with no forwarding address, left the country, been deported, or died before leaving the centre.

The proportion of males was higher in the youngest age group. More participants came from Europe and Asia in the older age group while there were more Africans in the youngest one. The five most frequent countries of origin were the same as in the total cohort.

Registration forms to local municipalities were sent to 81 different asylum seekers centres. From January 2005 to January 2007 there was a reduction in the number of asylum centres from 100 to 65, i.e. many centres that were contacted initially, closed down during the study period.

We received information about 1625 (73%) of those asylum seekers who had moved out into the municipalities, and 220 (93%) of those who had been referred to specialists (figure 1).

Study end points

Among 1326 persons with negative x-rays and a Mantoux test result between 6 and 14 mm, 372 (28%) were seen in PHC, of whom 188 of 572 (33%) Africans were seen, compared to 45 of 221 (20%) Europeans and 129 of 494 (26%) Asians. Of the 568 persons with negative x-ray and Mantoux ≥ 15 mm, 86 (16%) were seen by an internist. Of all the observed proportions, the differences between Afri-

cans and Europeans seen in PHC with Mantoux 6–14 mm was the only one that was statistically significant ($p < 0.05$).

Further, of the 314 persons with abnormal x-ray findings, 194 ones (62%) were seen by an internist. While 165 of 235 (70%) with parenchymal findings were seen, 20 of 61 (33%) of those with other x-ray findings were seen and the differences were statistically significant ($p < 0.05$). Among subjects with positive x-rays, 76 of 115 (66%) Africans, 73 of 128 (57%) Asians and 38 of 55 (69%) Europeans were seen and the proportions were not significantly different.

Altogether 758 were assessed in one way or another in PHC (figure 2). Of these, 673/2237 (30%) persons had actually been seen by a physician (n = 380) or nurse (n = 293) at this care level. Another 85 persons were referred directly from PHC either for chest x-ray or to a specialist without being seen personally.

Personal encounters took place a median of 9 weeks after arrival (range 0–124). Thus, 302 of 439 (69%) persons with valid dates were seen within 13 weeks of arrival and 376/439 (86%) within 26 weeks.

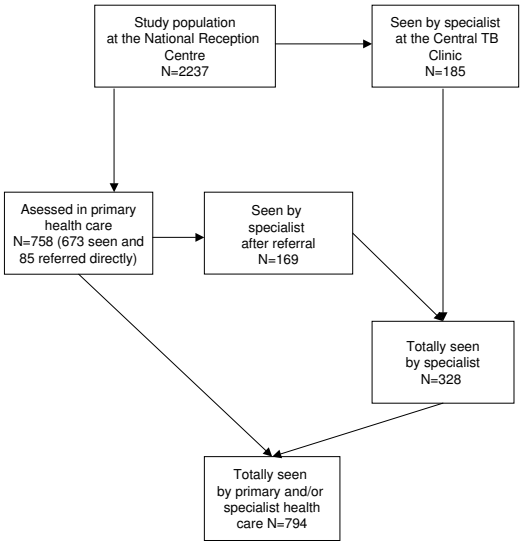

Figure 2
Total numbers of asylum seekers with an indication for follow-up of TB screening seen or assessed in Norwegian primary and/or specialist health care cf. text.

Three hundred and twenty-eight persons, i.e. 15% of the study group, were seen by an internist. They included 185 persons who were either examined at the Central TB Clinic and/or 169 who were examined by other hospital internists (figure 2). In all 236 persons were referred from PHC to an internist. Median time from arrival in the country to the internist visit was 25 weeks (range 0–114). The median time from the referral letter was received till the internist consultation took place was 10 weeks.

A total of 794 patients (35% of the study group) were seen either by primary and/or secondary health care providers.

When the cohort of 2237 asylum seekers were matched with the National Tuberculosis Register (31st December 2006), 23 (1028/100 000) cases of active tuberculosis were identified. Thirteen were diagnosed within 3 months of arrival, 14 within 6 months, and 19 within 12 months. Of those cases, 11 were from Somalia, three from Russia and two from Serbia and Montenegro. Four cases were reported among the 27% of asylum seekers with no reply from PHC, one was seen at the Central TB Clinic, while the other three were diagnosed five, 17 and 33 weeks after arrival. We further identified 11 cases who had started treatment for latent tuberculosis, all had a Mantoux test ≥ 10 mm, and seven came from Africa.

Discussion

Of 4643 asylum seekers, tuberculosis screening identified 2237 persons (48%) who should have been assessed and followed up by primary or specialist health care. Between 6–24 months after arrival, only one third of those at high risk had been assessed by community health care, while 15% had seen an internist. Twenty-three persons were diagnosed with tuberculosis disease and 11 had started treatment for latent tuberculosis.

Limitations of the study

The study design implied that information about assessment and referrals depended on an initial response from PHC. The lack of response clearly reduced the number brought to our attention about asylum seekers who were referred to and seen by a specialist. Information collected through the study forms was limited to what we could retrieve from patient records. Thus, if records were not found or were incomplete, the numbers assessed and/or referred could be too low.

We do not know if the 27% with no response from PHC were assessed and followed-up to the same degree as those with a response. One possibility is, on the whole, that municipalities that did not respond were less interested in TB than those that did.

We had no access to information about asylum seekers leaving the country, and if the interval before they did so made any difference to our results. This limits our potential to give exact rates for those that should have been seen in PHC or by a specialist. Because of insufficient registration, and since the systems for handling follow-up of screening results and referrals due to symptoms are mixed together, we cannot say exactly how many of the TB cases were found through the screening system or through referrals because of symptoms. We are also unable to assess the incidence of TB at certain times after arrival. If many had left at an early stage, the denominators would decrease, with a consequent increase in rates. Dates for assessment or referral were often left open on the forms or were obviously incorrect.

Because asylum seekers do not have a personal identifier, the cases found through the match with the TB Register could have been reduced, and this may also have reduced the numbers of study individuals recorded in the municipalities and hospitals to where the study forms were sent. Apparently, this would limit both their compliance to national guidelines and the numbers found through the TB Register.

Several local authorities could not provide health records for asylum seekers who had moved on, or where asylum seeker centres had been abandoned during the study period. This also limited the quality of our study.

Study endpoints

The entry screening was satisfactory and only 2.5% of asylum seekers had no registered Mantoux result. Voluntary screening at a similar centre in the UK reported that 94% were screened [16]. Most of the 469 asylum seekers who were not included in the total cohort left the country or were deported straight away and were of limited interest from a screening point of view. The number of the total cohort who actually got an x-ray taken, was impossible to retrieve from the data recording system at the National Reception Centre.

Everybody with a Mantoux 6–14 should have been seen in PHC, but only 28% of them were. Informal information given as reasons for this insufficient follow-up, were an absence of personal information (wrong address, name or date of birth), lack of resources, low priority, and insufficient knowledge of the guidelines or how they should be interpreted. Sometimes, patients were referred separately to x-ray, but not to a specialist. That procedure was appropriate given the previous guidelines, but not the current ones [11]. It took a median time of 9 weeks from arrival in Norway until assessment took place, but the range was 0–124 weeks. Thus, we speculate that several asylum seekers were not assessed unless they developed symptoms which brought them to the attention of the health authorities.

Follow-up of x-ray findings is the most important part of the screening, and we found that only 62% of those with initial positive findings were seen by an internist. This was most likely an organisational problem between the National Reception Centre and the Central TB Clinic. There was most probably some selection of follow up at the Central TB Clinic since relatively more cases with parenchymal findings were seen by an internist.

The guidelines recommend that all cases with Mantoux ≥ 15 mm should be referred directly to an internist, but they do not specify if the individual should be seen at the Central TB Clinic or at the nearest institution after they have moved to their new home municipality. Only 16% of those with Mantoux ≥ 15 mm were finally seen by an internist. Generally, they were not referred to the Central TB Clinic, and arguments such as an expected short stay at the National Reception Centre, the general high workload at the Central TB Clinic, and uncertainty about how long the asylum seekers would stay in the country were used to explain this. However, these subjects were not referred to a specialist after they had arrived in their new municipality, either.

The median time from the referral letter was received until the specialist consultation took place was 10 weeks. This seems appropriate if the question was an assessment for latent TB, but not if the question was to rule out active disease.

We matched study group individuals with the National Tuberculosis Register which allowed us to estimate point prevalence and an incidence rate. However, since many asylum seekers could have left the country without notification, this limited the exact population at risk. It also made it difficult for both health care levels to follow up the initial cohort. Conversely, these limitations realistically mimic the complexity of information flow and referral data for this group of individuals.

We identified 23 cases (1%) of the study group with tuberculosis disease between 6 to 24 months after arrival. Some incident cases that occurred after screening may have been mixed up with the prevalent ones, and we are unable to estimate how many cases of active TB we missed through lack of adherence to the guidelines. Studies from other countries have reported prevalences of between 0.1–1.2% [13,16-18], but valid comparisons between our and other studies require more information about the different study populations.

The number of asylum seekers who were treated for latent TB was lower than expected and potential reasons for this will be discussed in a forthcoming paper. National guidelines vary between countries, yet other studies show a lack of adherence to guidelines similar to ours [19,20]. Comparisons between studies are made even more difficult because treatment indications for latent TB vary considerably.

Information flow and data ascertainment

An overall problem was that the flow of health information between administrative levels did not keep up with the movements of individual asylum seekers. Similar difficulties have been reported by others and compare well with our results [19-21].

Lack of adequate information between asylum seeker centres and primary or specialist health care was another problem we identified.

Personal characteristics

Asylum seekers are registered with their name and date of birth on arrival, but do not get the personal identifier all Norwegian residents have until they have stayed in the country for several months. As a result of registration errors or because their name or date of birth are misstated, an asylum seeker may have several different identities and is not recognised in many public registers. Also, some may have entered Norway several times during the study period, resulting in a further negative influence on assessment or treatment. All these factors made follow-up quite difficult.

Asylum seekers move several times and frequently without reporting or informing authorities about their new address. They usually have little knowledge of the Norwegian language, their access to an interpreter is limited, and they may have a different conception of health issues. All are reasons why appointments were not kept.

Consequences for policy

Despite our current and detailed guidelines, we may speculate that the inadequate follow-up was due to a complex organisation, insufficient or inappropriate information handling procedures, insufficient awareness and adherence to the guidelines, and limited focus on the TB issue by the involved health care providers and society at large. Further data analyses may cast light on some of these assumptions.

We believe that both the organisation and the guidelines should be simplified. Furthermore, a quality assurance and a report system for information flow and personal follow-up are needed. Cooperation between immigration and health authorities should make sure that municipalities with asylum seekers centres have a more streamlined and efficient system for follow-up of tuberculosis screening with special staff dedicated to implementing it.

Conclusion

TB screening of asylum seekers identified a prevalence of 1% of active tuberculosis in the study group included for follow-up. In addition we found a considerable proportion of subjects at increased risk. We identified inadequate handling of screening results at all levels of care, with too few patients treated for latent tuberculosis.

To improve follow-up of screening results, a simplification of organisation and guidelines, introduction of quality assurance systems, and better coordination between authorities and between different levels of health care are all required.

Abbreviations

TB: Tuberculosis; QFT: QuantiFERON®TB Gold; PHC: Primary Health Care.

Competing interests

IH gave a lecture on challenges in mandatory screening of tuberculosis infection in the health care services paid by Astra Zeneca. The other authors declare that they have no competing interest.

Authors' contributions

This paper is part of a PhD-project named "How to prevent tuberculosis among immigrants in Norway". IH has done most of the work under supervision of the other authors. GWJ was the main supervisor through the planning and conduct of the project, and through the writing process. EH contributed with input about organisational issues during the planning, implementation and writing process. SLS contributed with clinical issues during the implementation and writing process. HG contributed with public health issues during the planning, implementation and writing process. All authors have read and approved the final manuscript.

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Paper II

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Paper III

The role of entry screening in case finding of tuberculosis among asylum seekers in Norway

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Abstract

Background

Most new cases of active tuberculosis in Norway are presently caused by imported strains and not transmission within the country. On arrival screening for tuberculosis with a Mantoux test of everybody and a chest X-ray of those above 15 years of age is compulsory for asylum seekers.

We aimed to assess the effectiveness of the tuberculosis entry screening of a cohort of asylum seekers. Cases detected by screening were compared with cases detected later. Further we have characterized cases with active tuberculosis.

Methods

All asylum seekers arriving at the National Reception Centre from January 2005 till June 2006 with an abnormal chest X-ray or a Mantoux test ≥ 6 mm were included in the study and followed through the health care system. Those included were matched with the National Tuberculosis Register by the end of May 2008.

Cases reported within two months after arrival were defined as being detected by screening.

Results

Of 4643 eligible asylum seekers, 2237 were included in the study. Altogether 2077 persons had a Mantoux ≥ 6 mm and 314 a positive X-ray. Among them, 28 cases of tuberculosis were detected, fifteen by screening, and thirteen 4-27 months after arrival. Positive X-rays on arrival were more prevalent among those detected by screening. Female gender and Somalian origin increased the risk for active TB.

Conclusion

In spite of an imperfect follow-up of screening results a reasonable number of TB cases were identified by the programme. Most of them having pulmonary TB.

Background

In recent years most new tuberculosis (TB) cases in Norway have occurred among immigrants from high incidence countries. Rarely, new cases are due to transmission within the country [1].

Low incidence countries have diverse policies on entry screening of immigrants from high incidence countries. They range from no screening at all, to pre-immigration screening or screening after arrival [2-4]. There is an ongoing discussion about the content and effect of screening programmes to control tuberculosis [5, 6]. Different studies of screening of tuberculosis among immigrants have given TB prevalences that vary from 0.1-1.2% [7-10]. Differences in the characteristics of the populations that were screened and the programmes themselves naturally will affect the yield.

Previous studies have shown differences between cases detected by or outside the screening programme. Cases found by screening have fewer symptoms and fewer positive cultures [11, 12]. Previous studies have shown that a quite high number of TB cases in immigrant populations were found several years after immigration [5, 6, 13].

Risk factors for tuberculosis can be divided into the risk for being infected and the risk for developing disease. Typical risk factors for being infected are for instance poverty and a history of being incarcerated. On the other hand, the risk for developing disease is related to recent infection, reduced immunity from other diseases like HIV or medical treatment, intake of alcohol, smoking, body weight loss and country of origin [14-19].

The tuberculosis screening programme in Norway

It is mandatory to screen all asylum seekers for tuberculosis when they arrive to Norway. The aim of the screening is to diagnose and treat active TB, and diagnose cases with latent TB either for treatment or a three year follow-up programme [20]. However, the programme does not clearly differentiate between screening for active and latent disease.

The National Reception Centre outside Oslo performs a Mantoux test of everybody and a chest X-ray of persons above the age of 15. Persons who report clinical symptoms of TB, or have a positive X-ray, has to be referred to the Central TB Clinic in Oslo for assessment of TB disease. Persons with a Mantoux test ≥ 15 mm shall be referred to the specialist health care, where a chest physician or an internist normally will see the patient for evaluation of TB disease or infection. Those with a Mantoux test 6-14 mm shall be followed up by primary health care (PHC). Whenever definite risk factors are found, the patient shall be referred to a specialist [21]. However, diagnosis of latent TB remains a challenge and recommendations for diagnosis and follow-up are ambiguous. TB disease is diagnosed on the basis of symptoms, clinical examinations, chest X-rays and the test of a bacteriological sample. In Norway, only specialists are allowed to start TB treatment. Whenever a TB diagnosis is confirmed and/or treatment for TB is started, a nominal notification is sent to the National Tuberculosis Register. When asylum seekers leave the Reception Centre they move to other asylum seekers centres throughout the country or to private accommodations.

Surveillance data for TB are available in Norway, but not for asylum seekers specifically. An earlier Norwegian study on chest X-ray results from entry screening of asylum seekers, concluded that an improved follow-up of persons with an abnormal X-ray was necessary [22]. Among cases not diagnosed by arrival screening

they found that 11(14%) had been inadequately followed up. A previously published paper of the present cohort showed that 194/314 (62%) with an abnormal X-ray had been seen by an internist, and altogether 758/2237 (34%) with a positive Mantoux test and/or an abnormal X-ray had been followed up at the primary health care level. Inadequate handling of screening results was found at all levels of care [23].

The aim of the present study is to assess the effectiveness of diagnosing active TB by the tuberculosis entry screening programme, in a cohort of asylum seekers. We are comparing patients who were diagnosed by the screening programme with those who were detected later. Further we aim to characterize all cases of active tuberculosis.

Materials and methods

Study population

All asylum seekers above the age of 18, that arrived at the National Reception Centre from January 2005 till June 2006 were screened with a chest X-ray and a Mantoux test. They were included in the study if they were available for follow-up and had an abnormal chest X-ray, a Mantoux test ≥ 6 mm and/or a positive QuantiFERON® TB Gold (QFT) test. During the study period 5112 asylum seekers were screened. Four hundred and sixty nine of them could not be followed up because they were either deported, dead or had no registered address. Of 4643 (called the total cohort) 2293 had positive study inclusion criteria. However, 56 were lost from the National Reception Centre and hence, 2237 study participants were included [23].

An abnormal chest X-ray was defined as parenchymal or pleural pathology, or calcifications. The X-rays were taken at the National Reception Centre, interpreted by two independent readers and later recoded for this study. A positive Mantoux test

was defined as ≥ 6 mm (PPD: RT 23, 2TU from SSI, Copenhagen, Denmark). An interferon-γ release assay test: (QuantiFERON® TB Gold in-tube test, Cellestis Ltd, Carnegie, Victoria, Australia, QFT) was done as a separate study on a subgroup of 912 participants [24].

Collection of study information

Information about demographics and screening results were collected from the data files at the National Reception Centre. Further information was collected by one registration form that was sent to the public health care official in the municipality to where the asylum seeker had moved, and if they reported that any person in question had moved on, the same form was sent to the appropriate municipality. If the PHC form indicated that a referral had taken place, a specialist form was sent to the appropriate internists. A specialist form was also sent to the Central TB Clinic when we received information from the National Reception Centre that an asylum seeker had either been referred there or had an abnormal X-ray. Both forms collected recorded information about assessment by health care personnel, plans for follow-up and why the patient had been referred. In addition we collected information about current addresses or relocations of study participants.

A match by name and date of birth between everyone who were included in the study group and the National Tuberculosis Register was done in May 2008. The register holds information about localisation of disease, culture results, the individual physician who had reported the case, and some background information about the specialist referral.

Cases reported to the National Tuberculosis Register within two months after arrival were categorized as detected by screening in contrast to those who were detected later.

Data registration and analyses

Study forms were scanned and entered into the SPSS program (SPSS for Windows, version 16, Chicago, Ill, USA). Comments and administrative information were coded manually and entered to the same data file.

The study group and the TB cases were described by proportions and 95% confidence intervals (CI). Time from arrival till notification to the Tuberculosis Register was approximated to closest number of total months.

The primary outcome diagnosed as active tuberculosis or not, were analysed with logistic regression. The assessed regressors were stratified age, gender, country of origin (Somalian or not), marital status (married or not), Mantoux (≥ 10 or not, and ≥ 15 or not) and X-ray (abnormal or not). Variables in the univariate analysis that changed the odds ratio (OR) of the other variables with 0.2 or more were entered into the multivariable analysis. The model was checked for correlations and interactions.

Due to low number of cases, the secondary outcome; i.e cases that were detected by screening or not, was studied only by univariate logistic regression. Additional regressors for the secondary outcome were a diagnosis of pulmonary TB (as opposed to extra-pulmonary TB) (yes/no) and a positive culture (yes/no).

Ethics

The Regional Committee for Medical Research Ethics approved the study. The Norwegian Data Inspectorate, Directorate for Health and Social Affairs, Ministry of

Labour and Social Inclusion, and the Research Committee at Ullevaal University Hospital all gave their permission.

Results

There were 3222 (69%) males and 3333 (72%) were between 18 to 34 years in the total cohort. Iraq, Somalia, Russia, Afghanistan and Serbia and Montenegro were the five countries of origin that contributed most of the asylum seekers, altogether 2434 (52%) [23].

Among the 2237 asylum seekers who fulfilled the inclusion criteria and were included in the study group, 1563 (70%) were males and 1447 (65%) were 18-34 years of age (Table 1). An abnormal X-ray was found in 314 persons, 2077 had a Mantoux ≥ 6 mm and 27 were included because of a positive QFT only. Compared to those not included, the study group had significant fewer persons in the lowest and more in the middle and oldest age group, more were married, more came from Somalia, and more had a BCG scar (data not shown).

Cases of tuberculosis

By end May 2008, 28 cases of tuberculosis were diagnosed and none of them got treatment for latent tuberculosis after arrival in Norway. The median time from arrival until notification was two months (range 0-27). Thus, 15 patients were diagnosed within two months of arrival, and 17 within six months. Eight patients were diagnosed later than one year after arrival (Table 2).

Twenty two cases had *M. tuberculosis* confirmed by culture, one case *M. Africanum*, while one was culture negative and four had unknown bacteriology. There were 18 patients with pulmonary and eight with extra-pulmonary TB, while the

localization was unknown for the remaining two. Somalian origin was associated with extra-pulmonary TB (data not shown). Twelve of the 15 women with tuberculosis came from Somalia. Their median age was 25 years (range 21-49). Mantoux ≥ 15 mm on arrival was found in 12 (43%) cases and Mantoux ≥ 10 mm in 20 (69%) cases (Table 2). Lack of a BCG vaccination scar was not associated with active TB (data not shown).

In a univariate analysis for all cases of active TB, a positive association was found with a positive chest X-ray, Mantoux ≥ 15 mm, Mantoux ≥ 10 mm, female gender, and Somalian origin (Table 3). In adjusted logistic regression models, gender and country of origin were entered into the model. A positive association with active TB was found for female gender and Somalian origin when either Mantoux ≥ 10 mm, or Mantoux ≥ 15mm, or a positive chest X-ray were included (Table 4).

The yield of screening

Fifteen cases were detected within two months after arrival. Twelve of the cases had positive X-ray findings when they arrived and 13 had symptoms of TB at the time of diagnosis. There were twelve cases of pulmonary and two with extra-pulmonary TB and one with unknown localization. Thirteen had a positive culture (Table 2 and 5).

All cases diagnosed by screening were reported from hospitals in the Oslo area. Of the 12 cases with an abnormal X-ray on arrival, six had visited the Central TB Clinic.

Two cases were diagnosed from three to six months after arrival, one with pulmonary and one with extra-pulmonary TB, and one of them was confirmed by culture. Eleven cases were diagnosed from eight to 27 months after arrival. Five had pulmonary, five extra-pulmonary TB and one unknown localisation. Nine patients

had the diagnosis confirmed by culture. Three patients had an abnormal X-ray on arrival screening and 12 patients had a Mantoux ≥ 10 mm (Table 2).

None of the two cases diagnosed four and five months after arrival had been examined at the Central TB Clinic. However, one reported having symptoms on arrival.

All three cases with an abnormal X-ray on arrival who were detected later than six months after arrival, had been examined at the Central TB Clinic just after arrival and were judged not to have TB disease at that time. They were advised to have further follow-up if there were a future doubt about the diagnosis. Thus, they probably have developed TB later. Ten of the late cases were diagnosed at different hospitals around the country. They had been referred from PHC due to clinical symptoms. One case diagnosed after ten months had been referred from PHC to specialist for assessment of screening results following a move to an asylum seekers centre in the community.

In univariate logistic regression of cases detected by screening or not, an abnormal X-ray showed an OR of 9.0 (1.6-50.7), while pulmonary TB vs. extra-pulmonary TB detected by screening gave an OR of 6.0 (0.9-39.2), however, the last OR is not significant (table 5). There were no other association between time of diagnosis and demographics or screening results.

Discussion

The total yield of the screening was 15 cases of TB. Two cases were diagnosed between three and six months after arrival and were probably missed by the screening. The other 11 cases were not diagnosed as a part of the screening programme. Cases

identified by screening more often had abnormal X-rays on arrival. Female gender and Somalian origin increased the risk for TB disease.

The TB prevalence in this high risk group was 15/2237 (0.7%) [25]. That prevalence was comparable to other studies of TB screening among immigrants where the prevalences ranged from 0.1.-1.2% [7-10].

A major objective of the screening programme is to diagnose pulmonary TB as early as possible to minimize risk of transmission within the country. This seemed to have been the case here as 12 of the 15 cases detected had pulmonary TB. Through the match with the Tuberculosis Register we detected several cases diagnosed at different hospitals in the Oslo area. However, we could not trace any information about referrals for these patients through the files at the National Reception Centre or the study forms. Previously we have reported that 62% of persons with an abnormal X-ray on screening and 70% of those with parenchymal findings had been seen by a specialist [23]. Thus, we have reasons to believe that more cases had been referred to specialist than we were able to detect in our study.

A pertinent question is whether cases that were detected later than two months after arrival could have been detected earlier or prevented. One patient who was diagnosed four months after arrival had been ill since arrival. And another who was diagnosed five months after arrival, and was found through contact tracing, had symptoms at the time of referral. However, we do not know the time from symptoms till diagnosis for any of the others. All the 11 patients who were detected later than six months after arrival had either abnormal X-rays or a positive Mantoux test at entry and should have been referred to a specialist or examined by PHC. Seven had not been referred to or seen by a specialist to reach a conclusion about entry findings. We believe that some cases could have been detected with active TB earlier or been given

treatment for latent tuberculosis if the guideline recommendations had been followed. However, the Norwegian guidelines do not give definite recommendations for treatment and a previously published study of the same cohort showed that only 30 persons were treated for latent tuberculosis [26].

Asylum seekers were not interviewed about symptoms on arrival, and registration of symptoms seems to be incidental. Possibly, a medical interview could have raised suspicion for some of the cases, particularly the ones with extra-pulmonary TB. On the other hand, screening for TB in a Brazilian prison showed that 1/3 of the TB cases denied any symptoms during an initial interview, and several patients with a cough of more than three weeks duration held that they had a "normal" cough [27].

As more cases found through screening in our study had abnormal X-rays and tended to have more pulmonary TB (Table 5), an abnormal X-ray was the main indication for an immediate follow-up. There were no differences in the proportion with positive cultures between the groups diagnosed inside or outside the screening programme. This could have been a spurious finding. Others have reported that cases detected outside the screening programme showed an increase in the number of positive cultures [11].

Other studies have also shown that regardless of any arrival screening there is an increased risk for active TB for several years after arrival. However, all these late cases have been interpreted as incident ones [5, 6, 28]. This is particularly the case for extra-pulmonary TB [6].

Origin from Somalia was associated with an increased risk for active TB. That compares well with several other studies [5, 22, 29, 30]. There was also an

association between Somalian origin and extra-pulmonary TB, which also has been shown in a previous Norwegian study [31].

In our study females had a significant increased risk for active TB. Further, 12 of the 15 females with tuberculosis were from Somalia. We have no information whether females from Somalia arriving in Norway have other risk factors. Low numbers in the present study or other health seeking behaviours in their home country may explain why our results differ from other studies from developing countries where males have higher risk [32]. However, studies from Western countries at the time when TB was prevalent, showed increased risk for females of fertile age [32].

We had data from the arrival screening for a complete cohort of asylum seekers where all subjects with positive findings on screening were matched with data from the National Tuberculosis Register. However, we did not match those without positive screening results as they are not supposed to be followed up, and we have no data on numbers of study subjects that left Norway during the study period. This may obviously have influenced the number of people who were available for analysis and made exact estimating of incidences impossible.

Asylum seekers frequently change name and/or date of birth which may have given an artificial reduction in the matching procedure with the National Tuberculosis Register. Also some underreporting of responses on study forms could have been caused by this change of names and birth dates.

Smear results were not available for analysis because very few were reported with this information to the National Tuberculosis Register.

Only persons with an abnormal X-ray or who had been traced at the National Reception Centre as referred to a specialist, were matched with the Central TB Clinic.

This procedure could have led to some underreporting of cases seen by specialist because a similar match was not done with other hospitals.

We defined patients who were diagnosed before two months of arrival as detected by the screening programme. Hence, misclassification of the cases may have led to over- as well as underestimation of the yield of the programme. In most cases, the files at the Tuberculosis Register gave no clear answer whether the clinical examination was the result of screening or not. Nor did they report the length of time between symptoms onset and the TB diagnosis. Some late cases may have been reinfected after arrival in Norway, but infection rate within the country is generally low [1].

More cases were found and more referrals done than we were able to detect from the follow-up study. Thus, in spite of an imperfect follow-up of screening results 15 of 17 TB cases were found through screening, most of which were pulmonary TB. As a consequence of this study, we will stress that an immediate follow-up of all with an abnormal X-ray should be verified by a quality assurance system. In cases of latent TB, treatment should always be considered. Special measures for all asylum seekers from Somalia should also be considered.

Further studies are needed to assess cost-effectiveness of the screening programme.

List of abbreviations used

TB: Tuberculosis
QFT: QuantiFERON® TB Gold
PHC: Primary Health Care
CI: Confidence Interval
OR: Odds Ratio

Competing interests

None of the contributing authors declared any conflict of interest.

Authors` contributions

This paper is part of a PhD project named "Tuberculosis infection and disease among asylum seekers in Norway". IH has done most of the work under supervision of GWJ, EH, and HG who all participated in the planning, implementation and writing process. SLS also supervised the implementation and writing process. BAW contributed with input in the implementation and writing process, information about the QFT study and matching with the National Tuberculosis Register. SV was responsible for the data collection at the Central Tuberculosis Clinic and contributed in the writing process. ASH supervised the data analysis and contributed in the writing process. All authors have read and approved the final manuscript.

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Table 1: Numbers, percents and CI by demographics and screening results for study group and TB cases

	Groups	Study group N=2237		TB cases N=28	
		Numbers (%)	95% CI	Numbers (%)	95% CI
Age groups	18-34 years	1447 (65)	63-67	22 (79)	63-94
	35-49 years	656 (29)	27-31	4 (14)	1-27
	>50 years	134 (6)	5-7	2 (7)	-2-17
Gender	Males	1563 (70)	68-72	13 (46)	28-65
	Females	674 (30)	28-32	15 (54)	35-72
Marital status	Married	1034 (46)	44-48	10 (36)	18-53
	Not married	1203 (54)	52-56	18 (64)	47-82
The five most frequent countries	Iraq	224 (10)	9-11	1(3.6)	-3-10
	Somalia	457 (20)	19-22	15 (54)	35-72
	Russia	182 (8)	7-9	4 (14)	1-27
	Afghanistan	166 (7.4)	6-9	1 (3.6)	-3-10
	Serbia and Montenegro	149 (6.7)	6-8	2 (7.1)	-2-17
Mantoux test	<6mm	146 (6.5)	6-8	1 (3.6)	-3-10
	6-9mm	680 (30)	28-32	2 (7.1)	-2-17
	10-14mm	760 (34)	32-36	8 (29)	12-45
	≥ 15mm	637 (28)	27-30	12 (43)	25-61
Abnormal X-ray		314 (14)	13-15	16 (57)	39-75

Table 2: TB cases diagnosed by screening or not by demographics, screening results and TB Register report

Case number	Diagnosed by screening	Arrival to diagn. (months)	Age on arrival (years)	Gender	Married	Country of origin	Mantoux result on arrival (mm)	X-ray findings on arrival	Culture results on diagnosis	Localisation of disease
1	Yes	0	25	F	Yes	Somalia	9	Parenchymal	Positive	Pulmonary
2	Yes	0	28	F	Yes	Somalia	No	Parenchymal	Positive	Pulmonary
3	Yes	0	24	M	No	Afghanistan	12	Parenchymal	Positive	Pulmonary
4[a]	Yes	0	24	F	No	Somalia	2	Normal	No	Pulmonary
5	Yes	0	43	M	Yes	Russia	18	Parenchymal	positive	Pulmonary
6	Yes	0	30	F	No	Somalia	16	Parenchymal	Positive	Lymphatic
7	Yes	0	25	M	No	Somalia	No	Parenchymal	Positive	Pulmonary
8	Yes	0	31	M	No	Serbia/Montenegro	No	Parenchymal	Positive	Pulmonary
9	Yes	1	49	F	No	Somalia	17	Parenchymal	Positive	Pulmonary
10	Yes	1	23	M	No	China	15	Parenchymal	Positive	Pulmonary
11	Yes	1	22	M	No	Serbia/Montenegro	No	Pleura	Positive	Pulmonary
12	Yes	1	24	F	No	Somalia	10	Normal	Positive	Unknown
13	Yes	2	50	M	Yes	Iraq	No	Parenchymal	Negative	Pulmonary
14	Yes	2	33	M	No	Algeria	10	Parenchymal	Positive	Pulmonary
15	Yes	2	29	F	Yes	Congo rep	20	Normal	Positive	GI/periton.
16	No	4	19	M	No	Somalia	15	Normal	Positive	Lymphatic
17	No	5	51	F	No	Yemen	15	Pleural	No	Pulmonary
18	No	8	26	M	No	Russia	8	Parenchymal	Positive	Pulmonary
19	No	10	37	M	Yes	Russia	20	Normal	No	Pulmonary
20	No	11	21	F	Yes	Somalia	11	Normal	Positive	Lymphatic
21	No	15	26	F	No	Syria	19	Normal	Positive	Pulmonary
22	No	15	26	F	No	Somalia	13	Normal	Positive	CNS
23	No	15	23	F	Yes	Somalia	13	Normal	Positive	Pulmonary
24	No	16	45	F	No	Somalia	17	Normal	No	Unknown
25	No	17	25	F	No	Somalia	20	Parenchymal	Positive	Lymphatic
26	No	20	31	M	Yes	Russia	14	Normal	Positive	Pulmonary
27	No	20	25	M	Yes	Somalia	15	Parenchymal	Positive	GI/periton.
28	No	27	24	F	No	Somalia	14	Normal	Positive	Lymphatic

[a]This case was included because of a positive QFT test

Table 3: Tuberculosis cases, univariate analysis

			Univariate analysis	
	Case N=28	Control group N=2209	OR	95%CI
Age 18-34	22	1425	1(ref)	
Age 35-49	4	652	0.42	0.14-1.2
Age ≥ 50	2	132	1.6	0.5-5.3
Male	13	1550	1(ref)	
Female	15	659	2.7	1.3-5.7
Unmarried	18	1016	1(ref)	
Married	10	1193	0.64	0.30-1.4
Not from Somalia	13	1767	1(ref)	
Somalia	15	442	4.6	2.2-9.8
Mantoux ≥ 10mm	20	1377	4.0	1.2-13.4
Mantoux ≥ 15mm	12	625	2.8	1.2-6.3
Abnormal X-ray	16	298	8,6	4.0-18.3

Table 4: Tuberculosis cases, multivariable analysis

	Mantoux ≥ 10mm		Mantoux ≥ 15mm		Abnormal X-rays	
Variables	OR	95% CI	OR	95% CI	OR	95% CI
Male	1(ref)		1(ref)		1(ref)	
Female	2.9	1.2-6.8	2.8	1.2-6.6	2.6	1.2-5.7
Not from Somalia	1(ref)		1(ref)		1(ref)	
Somalia	4.0	1.7-9.4	4.2	1.8-9.8	4.7	2.2-10.1
Mantoux ≥ 10mm	2.9	0.8-9.9	-----	-----	-----	-----
Mantoux ≥ 15mm	-----	-----	1.9	0.8-4.4	-----	-----
Abnormal X-ray	-----	-----	-----	-----	9.7	4.5-21.2

Three multivariable models where included variables are Somalia, gender, and either Mantoux ≥ 10mm, Mantoux ≥ 15mm or an abnormal X-ray

Table 5. Univariate analysis: cases detected by screening or not, by demographics, screening results, and characteristics

	Detected by screening n=15	Missing values	Not detected by screening n=13	Missing values	OR	95% CI
18-34 years	12		10		1.2	0.20-7.3
≥ 35 years	3		3			
Females	7		8		0.55	0.12-2.5
Somalia	7		8		0.55	0.12-2.5
Mantoux >10	8 (2)	5	12 (1)	0	0.33	0.03-4.3
Mantoux >15	5 (5)	5	7 (6)	0	0.86	0.16-4.5
Abnormal X-rays	12	3	4	9	9.0	1.6-50.7
TB pulm	12 (2)	1	6 (6)	1	6.0	0.92-39.2
Culture positive	13 (1)	2	10 (0)	3	0.001	

Brackets indicates negative numbers when there are some missing values

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66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS

136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.

165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART

196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT

221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)

250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION

279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY

305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS
324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97

334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT
350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.

362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES
379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES

393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY
410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?

422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES
436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY
437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97
438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS

449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS
452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS
453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE
461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY
462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE