Master's thesis

NTNU
Norwegian University of Science and Technology
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Department of Public Health and Nursing

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Does tuberculosis contact tracing work as intended in Norway? A retrospective register-based cohort study of tuberculosis patients and contact tracing data from 2016 to 2021.

Master's thesis in Global Health
Supervisor: Inngunn Harstad
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Abstract

Background: Tuberculosis (TB) is a persistent global health challenge that demands robust strategies for control and prevention. To reduce the global TB burden, sustainable, adaptable contact tracing routines are vital as countries approach pre-elimination. In line with Sustainable Development Goal 3.3 and WHO's End TB Strategy: to end the TB epidemic by 2030, nations in pre-elimination stages must assess and confirm the efficacy of current screening and tracing systems to identify limitations in achieving the goal of TB elimination.

Method: The retrospective register-based cohort study included a total of 1,233 TB patients diagnosed with active TB disease between 2016 and 2021 in MSIS, along with data on their 7,132 close contacts. After filtering out some patients, 775 individuals with TB and 698 with contact tracing data remained for further analysis. There is done descriptive analysis of the TB patients and their close contact information together with uni- and multivariable analysis of the characteristics of the TB patients association to six different outcomes of the contact tracing process.

Results: Contact tracing was done around 90% of the TB, where the proportion with contact tracing was higher among infectious pulmonary TB patient > 15 years (91.6 %) than among patients <16 years (66.2%). 54.6 % of contacts received preventive treatment and 7.2 % of the close contacts received a TB diagnosis of the contacts with a positive IGRA test. When looking at the vulnerable and particularly exposed contacts, the same number was 102.5 % and 16.7 % respectively. Being particularly exposed but not vulnerable had the same proportion receiving treatment as the total (55 %). A TB patients characteristic such as age, gender, geography, foreign background, period lived in Norway, and infectiousness had impact on the contact tracing results.

Conclusion: We found that guidelines and regulations seem to be followed, but that there are some aspects of the contact tracing that is missing regarding the follow-up of children with active disease and treatment outcomes of close contacts. Accurate data recording and reporting are crucial to address challenges and ensure reliable information and that research should target specific aspects, such as paediatric TB challenges, regional disparities, and the reasons behind age and gender difference. Overall, these findings shed light on crucial aspects of TB contact tracing and the factors influencing its success.

Keywords: tuberculosis; contact tracing; national guidelines; low incidence; close contacts; transmission; age groups; MSIS.

Sammendrag

Bakgrunn: Tuberkulose (TB) er en vedvarende global helseutfordring som krever robuste strategier for kontroll og forebygging. For å redusere den globale TB-byrden er bærekraftig og tilpasningsdyktig smittesporing avgjørende når land nærmer seg pre-eliminasjon. I tråd med bærekraftsmål 3.3 og WHOs Slutt på TB-strategi er målet å avslutte TB-epidemien innen 2030, må nasjoner i pre-eliminasjonsstadier vurdere og bekrefte effektiviteten av nåværende screening- og smitteoppsporingssystemer for å nå målet om TB eliminering.

Metode: Dette er en retrospektiv kohortstudie av 1 233 TB-pasienter diagnostisert med aktiv TB-sykdom mellom 2016 og 2023 i MSIS registeret ble inkludert i studien, sammen med data om deres 7 132 nære kontakter. Etter eksklusjons og inklusjonskriterier var det 775 TB pasienter som hadde kriteriene for å bli smitteoppsporet, av disse hadde 698 pasienter smittesporingsdata. Det er gjort deskriptive analyser av TB pasientene og smitteoppsporings resultatene, samt univariabel- og multivariabelanalyse for seks ulike utfall: om pasientene er smitteoppsporet, antallet kontakter funnet, om pasientene hadde kontakter som hadde blitt IGRA testet, fått IGRA positivt resultat, blitt henvist til spesialist helsetjenesten og om de har mottatt forebyggende behandling eller diagnostisert med TB.

Resultater: Smittesporing ble gjennomført for 90.1 % av TB pasientene. Andelen med smittesporing var høyere blant pasienter med smittsom lunge-TB over16 år (91,6 %) enn blant pasienter under 16 år (66,2 %). 54.6 % av nærkontakter mottok forebyggende behandling og 7.2 % av nærkontaktene mottok en TB-diagnose av andelen IGRA positive nærkontakter. Den samme andelen var henholdsvis 102.6 % og 16.7 % for særlig sårbare og spesielt smitteeksponerte nærkontakter. Spesielt sårbare kontakter hadde større andel som mottar behandling enn de ikke sårbare. Spesielt smitteeksponerte som ikke var sårbare hadde samme andelen med forebyggende behandling som alle kontaktene samlet (55 %). Karakteristikker hos TB-pasienter, som alder, kjønn, geografi, utenlandsk bakgrunn, periode bodd i Norge og smittsomhet, påvirket resultatene av smittesporingen.

Konklusjon: Resultatene viser at retningslinjer og reguleringer om smitteoppsporing blir fulgt, samtidig som det er deler av oppfølgingen som burde sees nærmere på. Oppfølging av barn med aktiv sykdom og behandlingsresultater for nærkontakter, dataregistrering og rapportering er noen av aspektene som burde sees nærmere på. Videre forskning bør rette seg mot TB-utfordringer hos barn, regionale forskjeller og årsakene bak alders- og kjønnsforskjeller. Samlet sett setter resultatene lys over viktige aspekter ved TB-smittesporing og faktorene som påvirker dens suksess.

Nøkkelord: tuberkulose; smitteoppsporing; nasjonale retningslinjer; lav insidens; nærkontakter; aldersgrupper; MSIS.

Acknowledgments

I would like to express my sincerest gratitude to my main supervisor, DR. PhD. Ingunn Harstad, for her support, encouragement, guidance, and patience throughout this process. I would also like to thank Dr. Trude Margrethe Arnesen, and the tuberculosis working group at the Norwegian Institute of Public Health for teaching me about tuberculosis disease, the National tuberculosis control programme and letting this thesis be part of the project trying to identify limitations in the current contact tracing routine trough looking at registration of close contacts to patients with pulmonary TB in Norway. For guidance in choosing the study design and methodological approach, I would like to give a special thanks to Hinta Meijerink PhD., and Melanie Stecher PhD.

Additionally, I want to thank all the professionals that is part of the National tuberculosis control program in Norway and all working in the Norwegian Surveillance System for Communicable Diseases. The results of this study reflect the already hard work that they have put into to control and monitoring of TB transmission in Norway. And I hope the results can help in the further process of TB control.

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List of Abbreviations

CI	Confidence intervals
COVID-19	Coronavirus disease 2019
HIV	Human immunodeficiency virus
LTBI	Latent tuberculosis infection
MDR_TB	Multi-drug resistant tuberculosis
MSIS	Norwegian Surveillance System for Communicable Diseases
NIPH	Norwegian Institute of Public health
NTNU	The Norwegian University of Science and Technology
RR	Relative risk
RRR	Relative risk ratio
RR-TB	rifampicin-resistant tuberculosis
SDG	Sustainable Development Goal
TB	Tuberculosis
UN	United Nations
WGS	whole genome sequencing
WHO	World Health Organization

1 Introduction

The aim of this section is to give an overview of the global burden of TB, underscoring its impact on public health, the TB transmission dynamics, the role of contact tracing, and the Norwegian context. Thereafter, we will introduce the aim and objectives of the.

1.1 Background

1.1.1 Tuberculosis history and epidemiology

Tuberculosis (TB) is a persistent global health challenge that demands robust strategies for control and prevention. TB was the first infectious disease to be declared a global emergency by the World Health Organization (WHO) in 1993 (1). Annually, over 10 million cases are reported, even though TB is known to be severely underreported and this is estimated to be only two thirds of all cases (2). In addition, the global burden of TB disease is high; TB is ranked as the 13th leading cause of death worldwide. Prior to the introduction of COVID-19, TB was the deadliest infectious disease (3).

One of the targets of the Sustainable Development Goals (SDGs) is to “end the epidemic of tuberculosis” in all countries by 2030 (SDG indicator 3.3.2) (4). The WHO also has the ´End TB Strategy` which calls for a 90 % reduction in TB deaths and a 80 % decrease in TB incidence rates by 2030 (5). Despite the efforts, TB still causes significant illness and death worldwide (6). The number of TB deaths declined by approximately 45 % between the year 2000 and 2019, still a total of 1,6 million people died from TB in 2021 (3, 7).

The COVID-19 pandemic has had a negative impact on the process to reduce the TB disease burden and providing essential TB services resulting in an increased incidence of Tb burden globally (2, 8). There was a particular big decline in newly diagnosed and reported TB cases from 2019 to 2020 (2): Only 5,8 million cases were reported of the approximately 10 million people that developed TB in 2020. Further, the number of TB patients receiving preventive treatment have decreased by 21 % in 2020 compared to 2019. From 2020 to 2021, the TB incidence rate has increased by 3.6 % (9).

Approximately 86-90% of the global TB incidence in 2021 is estimated to occur in the countries listed in WHO's high-burden countries (HBC) lists for TB, MDR/RR-TB, and HIV-

associated TB (10). The lists for the period 2021-2025 have the same definition and have a total of 45 countries between them, with 30 countries in each list. The purpose of these lists is to provide focus for global action in the countries where progress is most needed and to encourage national and international political commitment and funding (11). The HBC lists definition is previously described in detail (5, 11, 12).

TB is predominant in low- and middle-income countries, but it is also present in high-income countries. In most high-income countries surveillance data show relatively stable declines in TB rate over the past decades (13, 14). Still, it does not seem like TB is disappearing any time soon (14, 15). A low-burden country is typically defined as having a TB notification rate of less than 10 per 100,000 population (16).

The TB incidence in Europe and Norway has been declining and is among the lowest in the world (17). This was not always the case, in the early 1900s approximately one-fifth of all deaths in Norway were caused by TB, and around 60 percent of those who died were below 30 years old (18). Since TB was such a significant health problem, substantial resources were put into its eradication. Large-scale development of sanatoriums, measures to detect the disease early, trace sources of infection, and reducing transmission was the main measures. Mortality rates decreased during the 1900s, and TB had been significantly reduced. After World war II, large and systematic detection campaigns combined with vaccination and antibiotic treatment and better standard of living contributed to decline in TB prevalence, making TB a minor health issue in Norway in the second half of the 20th century (19, 20). Since 2016, less than 300 cases have been registered annually, and for the last four years (2019-2022), less than four cases per 100,000 inhabitants were registered. Now TB is predominantly found in foreign-born individuals. The proportion of foreign-born individuals have ranged between 82 % to 89 % of the total annual TB cases from 2017 to 2021 (21). As in the global setting the proportion of men with TB has been higher than for females in Norway until 2020. In the years 2020 to 2020 the proportion of female TB patients have been highest (20).

1.1.2 Tuberculosis disease and prevention

The TB infection is caused by the bacteria *mycobacterium tuberculosis* (M. tb), which is capable of persisting in its hosts tissues for decades without causing disease, so called latent tuberculosis infection (LTBI) (22). Of the around 25 % of the world's population infected

with TB, and approximately 5-10 % of them will develop TB disease during their lifetime (3). Risk of developing disease is highest within the first two years after infection (23).

TB can affect everyone, but some groups have a higher probability of developing TB disease, such as people living with human immunodeficiency virus (HIV), individuals with risk factors such as being immunosuppressed or having diabetes, and infants (24). People that have untreated HIV infection with LTBI have a considerable higher risk of developing TB disease (25). Because of their underdeveloped immune system, up to 40 % of infants can develop TB disease when infected and untreated (26).

Transmission of TB mainly occurs through individuals with untreated pulmonary TB disease. However, the disease can also infect all other organs (extrapulmonary TB) (17). M. tb is transmitted through respiratory droplets (aerosols) when a person with pulmonary TB speaks, laughs, sings, coughs, or sneezes. Then tiny infectious aerosols are released into the air and can infect others (27). The strain of M.tb can play a role in disease transmissibility and progression, since some M.tb strains are more virulent than others (28).

TB is both curable and preventable. Per date there is only one preventive and licensed vaccine for TB; the Bacille Calmette-Guérin (BCG) (29). The vaccine caused a particular big reduction in infant mortality, since it has found to protect against multiple infectious diseases, not only TB infection (30). The vaccine is mainly used to prevent severe disease in children, since its effect on preventing pulmonary TB in children and adults remain uncertain (31, 32). In addition, preventive treatment is available to prevent infection among individuals likely exposed to TB. This preventive treatment plan against TB infection has a duration of one to six months with one or two different first-line drugs (33). The (curative) treatment regime for TB disease is a 6 month regimen with four different first-line drugs (34). About 85 % of those who develop TB disease are successfully treated (35). Uninterrupted adherence to the antituberculosis treatment is crucial both for treatment success as well as to avert to development of drug resistance.

The M.tb bacteria can develop resistance to antimicrobial drugs (36), which usually develops after inappropriate use of the antimicrobial TB drugs (37). When patients are infected with a multidrug-resistant TB (MDR-TB) or rifampicin-resistant (RR-TB) TB bacteria, the treatment plan requires drugs that must be taken over a longer period (38). An alternative treatment plan requires drugs that often are both more expensive and have more side-effects (36). For TB patients diagnosed with MDR-TB and RR-TB around 50-75 % are successfully treated (39).

The cost of TB treatment can be steep for patients, especially for patients with low income and multidrug-resistant TB (40). The number of people acquiring infection, developing disease and the number of deaths caused by TB can be reduced by actions addressing TB determinants such as poverty, HIV infection, smoking, undernutrition, and diabetes (41). Furthermore, early diagnosis of TB through systematic screening of high-risk groups and close contacts, universal drug-susceptibility testing, preventive treatment for people at high risk and vaccination against TB are some of the main points to pillar 1 in the "End TB Strategy" (7). After United Nations (UN) held its first- ever high-level meeting on TB in 2018, all UN Member States agreed on a political declaration (42). At the meeting all existing commitments to the SDGs and WHO's End TB Strategy were reaffirmed, and new ones added (3, 10). Interrupting the transmission cycle of M.tb is crucial to achieving these global targets (43).

Routine screening and contact tracing do not have same effect in preventing transmission in high-burden countries, where the risk of transmission through dispersed and social mixing is high (44, 45). However in countries with lower TB incidence, the disease disproportionately affects groups in the society (46). TB disease usually gets more concentrated amongst vulnerable individuals, which challenges the opportunities for achieving elimination and improving interventions (47). Interventions that may not work when applied to the general population, can be cost-effective and efficient when applied to targeted high-risk groups (15, 48). Therefore, contact tracing around individuals diagnosed with pulmonary TB is essential to find others people who might have been exposed, or are already ill or infected, and provide them with testing, treatment, and as such reduce transmission, disease burden and mortality (49-51).

Sustainable and adaptable contact tracing routines are needed when countries reach pre-elimination stage. Countries that are already in a pre-elimination stage and have been using systematic screening and contact tracing over time, should evaluate and verify that these routines and systems work as intended (50). Improving the focus of contact investigations should be a public health priority, given deficiencies in contact tracing and the reality of limited public health resources (52).

1.1.3 Studies on TB prevention and control

Some studies in low-burden countries have looked at the efficiency and the effect of the TB control and prioritization (53-72). A study from Spain found that the risk of developing TB

disease was 1 % against 11.1 % after 5 years when comparing LTBI patients with and without preventive treatment (53). A study from Switzerland found that prevalence of LTBI in contacts was significantly related to exposure to the index case and to the contagiousness of the index case (54). An Italian study found that the TB contact investigation program in Piedmont should be extended to contacts of culture-positive TB cases, since they found higher rates of TB infection in contacts who was exposed to index patients living in the same household and had sputum-smear-positive or culture-positive tests (60). A study from USA compared the likelihood of TB infection and disease according to the characteristics of the index patient. They found that close contacts exposed to patients with smear-positive, cavitary disease diagnosed by chest radiograph were more likely to have TB infection or disease than those exposed to patients with only 1 or neither characteristic (61). These results indicate the importance of identifying TB patients who are most infectious as well as following up on the contacts that are closest.

In the Netherlands they found that 25 % of immigrant patients were not traced due to their contact tracing prioritization, which could have resulted in a significant number of infected contacts inland (57). Mulder et al. found that the effectiveness of TB contact tracing among migrants and the foreign-born population, they found that close contacts of foreign-born index cases had a slightly higher LTBI yield among contacts of compared with contacts of index cases from the general population (39.1 % compared to 33.7 %). But there was no difference when looking at TB yield (58). In comparison to the Netherlands, a Norwegian study from Dahle et al. found that outbreaks mainly were caused by strains of M.tb that had been circuiting in Norway for many years (68). When looking at the largest cluster of TB cases in Norway between the years 1997-2011, the researchers found that most cases in the first cluster was already infected upon arrival, and there was made changes to the screening regulations when entering Norway (70). At the same time a study from Farah et al. found that some immigrant groups were not infected before 7-years after immigration (73).

Other studies have found it usually is the closest contacts of a TB patients who get infected, and screening large number of contacts tend to not result in any further contact yield (23, 55). Further, studies have found that TB transmission is higher in urban settings (56, 69, 74). Where Zhou et al. found that living in urban settings had a higher risks of generating contact cases (56). Duarte *et al*. found that contact tracing procedures that included workplace and home was more effective for finding at-risk contacts then only finding contacts through interviewing (62). Two studies on school outbreaks in Norway found that there was no

obvious relation between the infectiousness of the index patient and the number of close contacts investigated (71). These findings indicate the importance to look at the TB patients' surroundings when contact tracing.

A study from Canada reported that over 70 % of childhood cases had close contact with someone with LTBI or TB disease, often someone within the family or living arrangements (63). A study from Finland, studying contact investigation among paediatric contacts, found that well-organised contact tracing can result in early diagnosis. In addition, they reported that the risk for TB infection or disease was higher among those who were born in a TB endemic country, had household exposure, or had contact with an index case who was sputum smear positive (66). A Norwegian study found that when exposed to a highly infectious individual for under 18 hours, was not associated with a higher risk for LTBI in healthy children (72).

May studies from both high- and low incidence countries have found that there was a need for strengthening the efforts to provide appropriate treatment to all contacts of TB patients, after looking at the current control programmes in their countries (46, 59, 75-78). These studies results show the importance to quality assess the TB control programs in countries to fin possible limitations and places of improvement in preventing TB transmission.

1.1.4 Routine screening and contact tracing in Norway

In Norway, TB screening is done among individuals who are at an increased risk of TB infection. The responsibility of these screenings lies with the municipalities of where the individuals residing in, while the healthcare regions are responsible to have enough resources for the screening process (79) This TB examination is mandatory for refugees and asylum seekers, and for those returning to Norway after they have been in a high TB incidence country for at least three months (including migrant workers, students, and family reunions) (80). Contact tracing is mandatory around each case with pulmonary TB (79). Additionally, a reduced contact tracing and testing of contacts should be done around children (≤15 years) with active TB disease, to find the source of infection (81). The main purpose of contact tracing in Norway is to; (1) identify individuals in the community that have TB disease, give them treatment, and stop the spread of infection, and (2) identify those with LTBI, and give them preventive treatment (82).

The routines and recommendations for contact tracing in Norway are based on the European recommendations for contact tracing in countries with low to moderate TB incidence (83), and have been developed by the Norwegian Institute of Public Health (NIPH) in collaboration

with the Norwegian clinical community, and some members of the European tuberculosis network who authored the new European guidelines (84).

Within Norway, there are special routines for notifying and following up TB patients. The Municipal Health Officer have the main responsibility for contact tracing and determines when it is appropriate to do contact tracing around TB patient (17, 85). For privacy reasons, the contacts identified and referred for an examination will not be information about the identity of the index patient. TB is a mandatory notifiable disease and thus all TB cases must be reported to the Norwegian Institute of Public Health (NIPH), by regulation from the Ministry of Health and Care Services (85). Municipal Health Officers are responsible for filling out the standardised validated contact tracing form, which needs to be submitted to NIPH after finalising the contact tracing. The contact tracing is considered finished when all the contacts have been examined, gotten their test results, and when those who need to be referred to a specialist in pulmonary medicine or childhood disease have been examined and those who get diagnosed with LTBI or TB disease, have started appropriate treatment (86, 87).

The contact tracing form from the municipalities are submitted to the Norwegian Surveillance System for Communicable Diseases (MSIS) (88). MSIS is a mandatory health registry under the Personal Health Data Registries Act § 11 and is regulated through (1) the Infectious Disease Control Act (Smittevernloven) and (2) Regulations concerning the collection and processing of health data in the Norwegian System for Communicable Diseases and for notification of infectious diseases (MSIS-forskriften) (86, 89-91). MSIS contains patient information from 71 different notifiable diseases reported by medical microbiological laboratories and clinicians (92).

In addition to the routine contact tracing in the municipalities, DNA studies (whole genome sequencing, WGS) is done on all M.tb samples. The reference laboratory continuously performs molecular epidemiological investigations of received MTBC isolates. At NIPH the DNA results are compared with MSIS data from contact tracing and clinicians, to assess possible domestic transmission (21). These results can be used when trying to trace a transmission route, by showing which lineage the bacteria come from, as well as to detect MDR-TB (17, 93).

1.2 Rationale

Sustainable and adaptable contact tracing routines are needed on a global level if we want to reach the SDG 3.3: ending the TB epidemic. Countries that are already in a pre-elimination stage and have been using systematic screening and contact tracing over time, should analyse and verify that the routines and systems in place work as intended. Finding contacts at an early stage can stop the infection before evolving into TB disease, where quality of life will be lower, and the treatment plan is longer (94). Ensuring that contact tracing efforts focus on those expected to have the highest risk is crucial and therefore evaluating the routines important. Concurrently, it is essential to conduct a quality assessment of the gathered data to ensure its relevance and significance. Data that lacks informative value consumes needless resources, time, and takes a toll on the individuals engaged.

1.2.1 The aim and objectives of this study

The aim of this study is to investigate whether contact tracing around TB cases in Norway can be improved with regards to finding individuals that are exposed, infected or ill with TB and provide the appropriate investigations and treatment. The specific objectives were as follows:

1. To investigate if contact tracing is performed around all TB patients recommended, namely infectious pulmonary TB patient over 15 years and all active tuberculosis patients below 15 years, in Norway during the period between 2016-2021.
2. To determine if the close contacts that are identified during contact tracing receive appropriate follow-up and treatment.
3. To identify demographic and medical characteristics of the index TB patients that are associated with performing contact tracing (yes/no) or the follow-up and treatment of identified close contacts.

1.2.2 Research questions

To address the aim and objectives of this study, we analysed the data to answer three research questions, where one is divided into five sub-questions. The following research questions were used:

1. For what proportion of infectious pulmonary tuberculosis patients over 15 years of age, and all active tuberculosis patients under 15 years of age, was contact tracing done in Norway during the period between 2016 and 2021?

2. Can the available close contact data provide information about whether the right people get followed-up and treated, and provide any idea of current limitations to the contact tracing routine?
3. Are the characteristics of the TB patient associated with various outcomes of contact tracing, including:
    a. likelihood of being registered with contact tracing?
    b. the number of close contacts identified during contact tracing?
    c. whether the TB patient has close contacts tested with IGRA?
    d. whether the TB patient has close contacts with positive IGRA test results?
    e. whether the TB patients has close contacts who have been referred to specialized healthcare services?
    f. the likelihood of close contacts either being diagnosed with TB or receiving preventive treatment?

2 Materials and Methods

2.1 Study population and study period

This thesis reports on a retrospective register-based cohort study using data on all patients with TB disease in Norway registered in the Norwegian Surveillance System for Communicable Diseases (MSIS) between January 1st of January 2016 and 31 of December 2021. This study period was chosen as contact tracing forms were updated in 2015.

Additionally, contact tracing forms must be sent to the NIPH within 1 year. To ensure both comparability and completeness of the data our study period was from 1st of January 2016 to 31st of December 2021 (87). The updated close contact form included different categories for close contacts. Previously close contacts were divided into several categories based on their relation with the TB patient, but after the update close contacts are categorized based on grade of exposure and how vulnerable the close contacts are (more details on the categorization of variables are given in (Appendix 1) (95). We focused the analyses on those where a contact tracing should be initiated, namely all infectious TB patients over 15 years, and all active TB patients aged 15 years and under, which will be referred to as "TB patients" from now onwards.

2.2 Data sources

The information in MSIS includes data collected from three sources: a) Medical reports and treatment reports that is supplied by clinicians at the hospitals, b) laboratorial information, such as WGS, is submitted from all microbiological laboratories, and c) information on close contacts is available sent in from the municipalities after they finalise the contact tracing form (96). To provide more detailed information, all forms are attached as Appendix 1.

The MSIS database provided three different datasets (I-III) (highlighted in light green and yellow in Figure 1) on 26th of May 2023, for this study. Dataset I included information on all TB patient registered with "active disease" in the register (n=1 243 patients). Dataset II included information on contact tracing for TB patients that was registered with "active disease" (738 patients). Dataset III includes aggregated data on people that are registered with preventive treatment (3 457 people).

For this study, we used dataset I and II, which included demographic information (e.g. sex, age, place of birth) and medical information (e.g. time of treatment start and end, direct microscopy, affected organs, indication for testing,) from patients with TB disease, together with contact tracing data (e.g., number of close contacts, number of close contacts who received preventive treatment) and WGS data (E.g., WGS number, VNTR number, cultivation result, bacterial resistance). The variable dictionary in Appendix 2. provides details on all the variables included in this study. Dataset III was not utilized in this thesis due to inherent challenges in its incorporation. The decision stemmed from the difficulty in effectively comparing the aggregated close contact data in Dataset II with the aggregated data from individuals receiving preventive treatment in dataset III. Two primary reasons underlie this decision. Firstly, the absence of individual-specific information hindered the ability to make meaningful comparisons between reporting and the actual individuals receiving treatment. Secondly, the lack of information regarding the timing of treatment administration in the close contact data prevented any meaningful comparisons. It was already known prior to obtaining the dataset that these limitations would exist. Nevertheless, an attempt was made to explore the potential for comparison by requesting information about the individuals receiving preventive treatment, which was unfortunately unsuccessful.

A total of 105 variables were initially considered, but only 100 variables were available for analysis. Certain variables in the MSIS dataset contained free-text values, such as patients' diagnosis, type of immunosuppressive state, and comments on contact tracing, and were therefor not used in the analyses. See section 2.6 for regards to data protection.

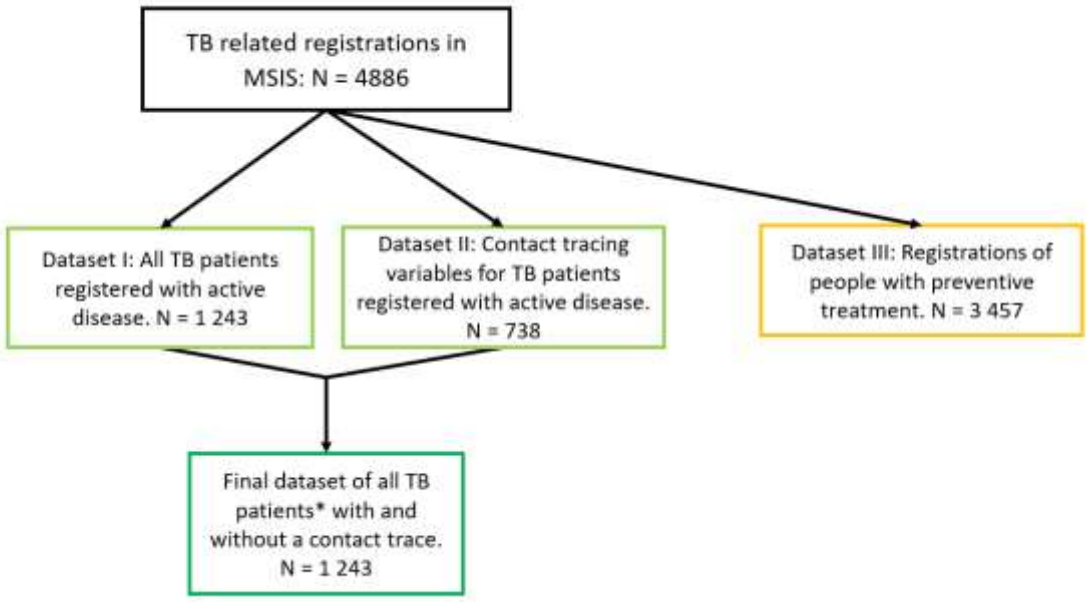

Figure 1. Flow diagram of datasets used in this study, which were provided by MSIS, and contain all patients of TB from 2016-2021. The study includes dataset I & II (light green boxes), which is made into one dataset for analysis (dark green box).

2.3 Data cleaning and preparation

The data was imported as an Excel file into a secure project area on the TSD platform (Services for sensitive data) (97) through an import link provided by MSIS. To begin the data cleaning and analysis process, STATA standard edition (SE) 17 was utilized (98). As shown in Figure 1 the two datasets were merged into one prior to analysis.

Variables were formatted as categorical or variables. Numeric variables were group to form categorical variable, such as age and number of contacts. In addition, some categorical variables were merged or values in these variables were combined. When multiple variables indicated the same characteristic, we wither combined them in a new variable containing the information from these multiple variables, or we chose one of the variables for analysis. The municipalities where the TB patients lived at the time of registration was used to make a variable indication the population size of the municipality, based on 2020 population data from Statistics Norway (SSB) (99). The county where the TB patient lived when registered was used to make a variable showing which of the four different regional health authorities the TB case belonged to (100). For more information about the coding of all variables included in this study see the data dictionary in appendix 2.

In the cleaning process, we did not substitute missing values for most of the independent variables. However, when a variable had more that 20% missing values or was considered

important to assess the association with one of the dependent variables, the variable got a new value indication “unknown”. This was done to ensure the population size for the different analysis would not be too small. An example of a variable with a high percentage of missing values is that indicating if a TB patient have been to a high incidence country for more than three months. Even though the contact form allows answering both yes and no, the variable only had values for 96 out of the 775 observations (12.4 %).

To answer **study question 2,** we needed to do a quality assessment of the close contacts data. The MSIS dataset contains six categories of contacts, where all the categories have six different types of outcomes, resulting in a total of 36 different close contact variables. The variable containing the total number of close contacts per TB patient registration may not always align with the sum of the other variables. To address this, new variables were created to calculate the total sum for each observation based on the respective variables. The outcome variable "total close contacts" is derived from the sum of the following variables:

1. total of especially vulnerable and especially close contacts,
2. total of especially vulnerable and other close contacts,
3. total of especially vulnerable and random close contacts,
4. total of not vulnerable and especially close contacts,
5. total of not vulnerable and other contacts, and
6. total of not vulnerable and random close contacts.

Further, to answer **study question 3** we needed to make new variables representing the close contacts that were not included in the different stages, since the data on the close contacts population is aggregated as total number per category and stage of the contact tracing. The “not IGRA tested close contacts” was calculated from “the total close contacts” minus the “IGRA tested close contacts” per observation. The “did not test positive close contacts” was calculated by using the number “IGRA tested close contacts” minus the “total close contacts with positive IGRA” per TB patient. This was also done to calculate the “close contacts not referred to SHS”, and for the “close contacts that had not received preventive treatment or been diagnosed with TB”.

2.3.1 Variable selection

This study focused on identifying variables that had potential effect on the outcome variables based on previous literature and the data provided. See section 2.4 for more information on the criteria set for variable selection in the statistical analysis.

To investigate if contact tracing is consistently conducted around those recommended (all infectious TB patients over 15 years and all active TB patients 15 years and under), the main outcome of interest is a categorical variable identifying if contact tracing was done for the TB patient ("Yes" or "No").

To investigate the impact of TB patients' characteristics and medical condition on the outcomes of contact tracing, six outcome variables were identified. One outcome variable is used for each of the sub-questions under **study question 3**. The following outcome variables were used:

a. Contact traced: "Yes" "No"
b. Number of close contacts: "0-2", "3 to 7", "8 to 20" and ">20". Categories were based on median and interquartile range.
c. IGRA tested close contacts: "Yes "No". The TB patients with no IGRA tested close contacts are defined as having zero IGRA tested close contacts and being registered with contact tracing.
d. IGRA positive close contacts: "Yes "No". The TB patients with no IGRA positive tested close contacts are defined as having zero positive IGRA-tested close contacts and being registered with contact tracing.
e. close contacts referred to SHS: "Yes "No". The TB patients with no close contacts referred to SHS are defined as having zero close contacts referred to SHS and being registered with contact tracing.
f. close contacts receiving treatment: "Yes" "No". The TB patients with "yes" are defined as having close contacts that are either receiving preventive treatment or close contacts diagnosed with TB and being registered with contact tracing. The TB patients with "no" is defined as having zero close contacts that were diagnosed with TB nor receiving preventive treatment and being registered with contact tracing.

2.4 Statistical analysis

2.4.1 Descriptive analysis

To answer **study question 1,** we excluded all individuals who did not meet the criteria for contact tracing, as they were over the age of 15 and did not have pulmonary TB. In addition, we excluded any second registration of the same individual. Further, we calculated the

proportion for categorical variables, stratified for TB patients with and without contact tracing to provide an overview of the demographics and medical characteristics of the TB patients from 2016 to 2021.

To answer **study question 2**, we provided an overview of the close contact data, where there is made a table of the total number of close contacts in the different stages of a contact tracing procedure, stratified by the categories of exposure and vulnerability. We calculated the proportion IGRA tested, and the close contacts referred to SHS based on the of the total close contacts. The calculations of the proportion of IGRA positive close contacts were based on the IGRA tested close contacts. The proportion of close contacts receiving preventive treatment or TB diagnosis was based on the close contacts with a positive IGRA test.

2.4.2 Univariable and multivariable analysis

In this study univariable and multivariable analyses were used to answer **study question 3**. For the univariable analysis, we used log-binomial regression to estimate the risk ratio (RR) and 95 % confidence intervals (95% CI) using the `binreg, rr´ command in STATA. Log-binominal was applied as it is considered more appropriate when the outcome is common, as it provides more accurate estimates compared to logistic regression, which is better suited for rare outcomes (101-103). For the univariable analysis with dichotomous outcome multinominal logistic regression was conducted using the `mlogit, rrr´ command in STATA, to compute relative risk ratio (RRR) and 95% CI were calculated to assess the precision of the estimated associations. In addition, we identified significant associations based on the 95%CI and associated p-values.

For all the multivariable analysis, relative risk ratio (RRR) and 95%CI were computed using multivariable logistic regression (104). The multivariable analysis allowed us to control for potential confounding factors and assess the independent effects of the variables in each model (105). Model selection included variables that showed an associated on the outcome of interest in the univariable analysis, as well as potential confounders on these outcomes identified by previous studies, such as being born in a TB endemic country, sputum smear positivity, contagiousness of the index patient, urban residence, immigration status, and culture-positive TB (56, 57, 60, 61, 66). The model was further refined based on the principles of model fit and parsimony (106). We used the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to compare and select the most appropriate models (107, 108). Pseudo R-Squared was also used when trying to improve model fit (109). To

address potential high correlations among predictor variables, the Variance Inflation Factor (VIF) was calculated to assess if further investigation or removal of variables from the model was necessary (110). A threshold of five was used to identify potential multicollinearity (111).

To determine any associations between characteristics and outcomes of the contract tracing, we used the methods described above. The listing is referring to respective sub-question of **study question 3**, also presented in section 2.3.1. To determine the characteristics associated with contact tracing, we included all TB patients (n=775). We did uni- and multivariable analysis as described above.

a. Accessing the characteristics associated with number of close contacts, we included only TB patient with contact tracing (n=698). Both univariable and multivariable analysis were conducted based on the methods described above.
b. For determining the characteristics associated with if a TB case had IGRA tested close contacts (n=698). We did multivariable analysis that included the variables that showed an association in the univariable analysis for study question 2a and 2b. We included "number of close contacts" as independent variable in the model, controlling for the associations with the original dependent variable.
c. For determining the characteristics associated with if a TB case had IGRA positive close contacts (n=698). Here we did the same procedure as for study question 3d.
d. For determining the characteristics associated with if a TB case had close contacts referred to SHS (n=698). We did uni- and multivariable analysis as described above.
e. For determining the characteristics associated with if a TB case had close contacts receiving treatment (n=698). We did uni- and multivariable analysis as described above.

2.5 Ethics approval

This study is part of a bigger quality assessment project, and for these type of quality assessment projects approval from the Regional Committee for Medical Research Ethics (REK) is usually not required (112). However, a request for approval was sent to REK (application number 536821) and the committee confirmed that the study could be carried out as planned and falls outside the Health Research Act, cf. §§ 2 and 4 letter a (Appendix 3).

Personally identifiable information from health registries and health surveys are confidential and subject to confidentiality (89). To access this information, an exemption to this confidentiality must be requested (113). We applied for an exemption from the duty of confidentiality from the Helsedataservice at the same time as we applied for the data for the study (Case number H-191). Since 15th of March 2023, the Helsedataservice has the authority to process applications for exemptions from the duty of confidentiality and applications for health data for eleven different health registers, including MSIS (114). Helsedataservice granted the application for exemption from confidentiality under the Health Registry Act § 19 e for information from MSIS on DATE (Appendix 4).

2.6 Data protection

None of the variables used in this study is directly identify to any specific TB patients. But the information can still be used to indirectly identify the study population, such as municipality, age, date for hospitalization and so on. Therefore, we did a Data Protection Impact Assessment (DPIA), which is always required before processing personal data (42, 43). The DPIA is made and stored through eprotokoll.no with the reference number 3890-3890.

Additionally, all TB patients was assigned a unique serial number prior to data extraction from MSIS to ensure anonymity. To protect patient privacy, sensitive data, i.e., about individuals with HIV and other rare or sensible registered comorbidities, the amount of medical information accessible, had to be limited. Therefore, the study focused on assessing the patients' risk of severe disease and its potential impact on their contagiousness, rather than specific immunodeficiencies. As a result, three variables were combined into a categorical variable to serve the purpose of the study prior to receiving the data. A value of 1 was assigned to this variable if a patient meets any of the following criteria: positive HIV status, immunosuppressive condition, immunodeficiency as an event type, or any information provided in the free-text variable "type of immunosuppressive state". Further, the municipalities the TB patients lived in was recode into a categorical variable indicating population size, and the TB patients registered county was used for the variable indicating what health region they belonged to.

2.7 Collaboration between NTNU and NIPH

NIPH is the owner of the project and the results in this thesis. NIPH was also responsible for the handling, storage of the dataset, as well as deletion of the datasets after the project end (31st of December 2024). NTNU is part of this project as data processor and owns the rights to the results of the thesis, including the attachments to it, and can use it for educational and research purposes. There is written two collaboration agreements as well as a data processor's management of personal data agreement between the two institutions.

3 Results

In this section the result of the statistical analysis is presented. First, we focus on the descriptive analysis of the study population and the close contact data to answer study questions 1 and 2. After, the results from the univariable and multivariable analysis to answer study question 3 are presented.

3.1 Descriptive analysis

3.1.1 TB patient population

Of the total 1243 registered TB cases between 2026 and 2021, we excluded 458 individuals who did not meet the contact tracing criteria and ten with a second registration in the database (Figure 2).

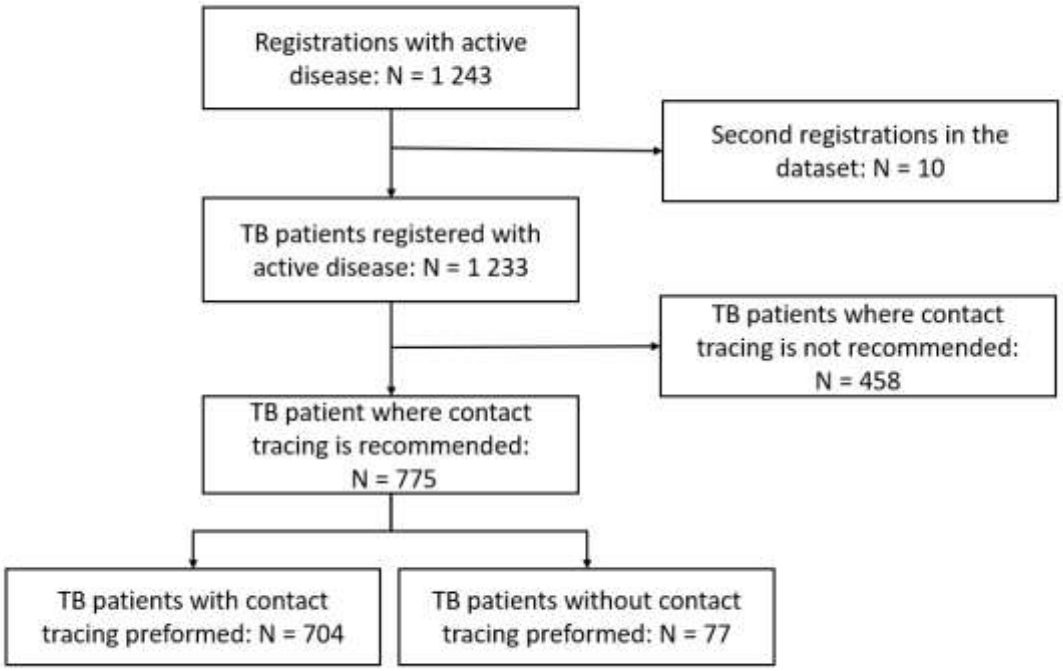

Figure 2. TB population included in this study with inclusion and exclusion criteria for further analysis, from TB patients registered in MSIS between 2016-2021.

Of the 775 TB patients included, 71 (9%) were children (≤15 years) with active TB and 704 (91%) were TB patient with pulmonary TB older than 15 years. Overall, contact tracing was reported for 90.1% (698 TB patients) of these TB patients. Contact tracing was done less often in children (≤15 years) that in the pulmonary TB patient (>15 years), namely 74.6% (n=53) compared to 91.6 % (n=645) (Table 1). Contact tracing was done in 91.7% of the female TB patients, while 88.8% of the male TB patients had contact tracing information.

There is a total of 704 are pulmonary TB patients over the age of 15, and 71 are TB patients under the age of 16 (47 with pulmonary TB). Meaning that 91,6 % of TB patients with pulmonary TB over the age of 15 has contact tracing information. Whereas the proportion of TB patients with active disease under the age of 16 years contact tracing is done for 66.2 %. All demographic and medical characteristics of the TB patients is presented in Table 1.

Table 1. Demographic and medical characteristics of TB patients, stratified by if the TB patient had contact tracing or not, between 2016-2021. MSIS

	TB-patients with contact tracing, N (%)	TB-patients without contact tracing, N (%)
Total	698 (90.1)	77 (9.9)
Age groups[!] (775)		
0-15 years	53 (74.6)	18 (25.4)
16-30	271 (92.2)	23 (7.8)
31-60	267 (92.4)	22 (7.6)
61+	107 (88.4)	14 (11.6)
Sex (775)		
Male	398 (88.8)	50 (11.2)
Female	300 (91.7)	27 (8.3)
At-risk Workplace[!]		
Unknown/not at-risk	380 (89.6)	44 (10.4)
Other at-risk professions	179 (91.3)	17 (8.7)
Education	105 (86.8)	16 (13.2)
Healthcare	34 (100)	0 (0)
Municipality size[!] (770)		
< 20 000	207 (81.5)	47 (18.5)
20 000 – 100 000	217 (93.1)	16 (6.9)
> 100 000	273 (96.5)	10 (3.5)
Hospital region[!] (628)		
South-eastern	424 (91.6)	39 (8.4)
Central Norway	77 (83.7)	15 (16.3)
Northern	62 (84.9)	11 (15.1)
Western	135 (91.8)	12 (8.2)
Deceased		
No	6 (66.7)	3 (33.3)
Yes	692 (90.3)	74 (9.7)
TB status (409)		
First time	598 (91.3)	57 (8.7)
Previous TB	54 (83.1)	11 (16.9)
Unsure category	46 (83.6)	9 (16.4)
Foreign born (775)		
No	116 (89.9)	13 (10.1)
Yes	582 (90.1)	64 (9.9)
Period in Norway[!] (775)		
Norwegian	115 (88.2)	20 (11.7)
Under 1 year	213 (89.9)	24 (10.1)
1-4 years	123 (87.9)	17 (12.1)
5-9 years	95 (94.1)	6 (5.9)
10 + years	117 (92.2)	10 (7.8)
Parents foreign born[!] (448)		
One or Both	335 (89.3)	40 (10.7)
No	66 (90.4)	7 (9.6)
From a high incidence country[!] (775)		
No	67 (91.8)	6 (8.2)
Yes	29 (96.7)	2 (3.3)
Unknown	602 (89.7)	69 (10.3)
Immigration status[!] (768)		
Norwegian	115 (89.8)	13 (10.2)
Other	197 (89.1)	24 (10.9)
Work immigrant	136 (97.1)	4 (2.9)
Immigrant/asylum seeker	245 (87.8)	34 (12.2)
Indication for examination[!] (771)		
Symptoms and signs	419 (91.5)	39 (8.5)
Other	34 (89.5)	4 (10.5)
Immunodeficiency	29 (90.6)	3 (9.4)
Contact tracing	44 (80)	11 (20)

Routine investigation of immigrant	170 (90.4)	18 (9.6)
Known exposure (666)		
Not examined	115 (88.5)	15 (11.5)
Yes	206 (88.4)	27 (11.6)
No	280 (92.4)	23 (7.6)
Immunosuppressive (775)		
No	598 (89.8)	68 (10.2)
Yes	100 (91.7)	9 (8.3)
Clinical symptoms (748)		
No	188 (90.4)	20 (9.6)
Yes	490 (90.7)	50 (9.3)
Treatment result (769)		
Not finished	56 (88.9)	7 (11.1)
Finished	615 (90.4)	65 (9.6)
Deceased	22 (84.6)	4 (15.4)
CT scan[!] (775)		
No	438 (89.8)	50 (11.3)
Yes	260 (90.6)	27 (9.4)
IGRA (712)		
Positive	488 (90)	54 (10)
Not done	40 (93)	3 (7)
Inconclusive	119 (93.7)	8 (6.3)
Culture result from respiratory[!] (699)		
No	568 (91.3)	54 (8.7)
Yes	67 (87)	10 (13)
Positive test from respiratory[!] (699)		
No	75 (87.2)	11 (12.8)
Yes	560 (91.4)	53 (8.6)
MDR-TB[!]		
No	671 (89.9)	75 (10.1)
Yes	27 (93.1)	2 (6.9)
Organ! (775)		
Other	12 (50)	12 (50)
Lunge	509 (90.7)	52 (9.3)
Lunge and other	177 (93.2)	13 (6.8)
Type of TB bacteria (698)		
Other	38 (90.5)	4 (9.5)
Tuberculosis, M.	596 (91.1)	58 (8.9)
Outbreak number[!] (775)		
No	482 (89.9)	54 (10.1)
Yes	216 (90.4)	23 (9.6)
Vaccinated (775)		
No	518 (89)	64 (11)
Yes	180 (93.3)	13 (6.7)

! The MSIS variables are changed or made into new variables for the purpose of this study. See variable dictionary in appendix 2 for details.

3.2 Contact tracing

To answer study question 2, we analysed the contact tracing data, results which are shown in Table 2. During contact tracing, identified close contacts are divided into "especially vulnerable" and "other" as well as based on the amount of exposure. Table 2 shows the number of close contacts identified per category for the 698 TB patients who were contact traced. Of the 7 486 identified contacts, 87.3 % had an IGRA test result, 15.5 % tested positive of the IGRA tested close contacts, 16.8 % were referred to SHS of total close contacts, and over half of the IGRA-positive started either preventive treatment (45.7 %) or were diagnosed with TB (7.2 %).

The proportion of close contacts referred to SHS, received preventive treatment and diagnosed with TB, is much higher for the close contacts in the vulnerable and particularly exposed to infection compared to the other groups and the population combined (Table 2). The number of close contacts receiving preventive treatment is higher than the number IGRA positive close contacts in the vulnerable and particularly exposed to infection group (123 vs 120). Vulnerable contacts had a much higher proportion of close contacts receiving preventive treatment and diagnosed with TB compared to the close contacts not categorized as vulnerable (Table 2).

When looking at particularly exposed contacts (i.e., household contacts or the equivalent) who are not categorized as vulnerable, the proportion who receive preventive treatment is the same as the whole close contacts population combined (55 %). The proportion receiving TB diagnosis is a bit higher when compared to the whole close contacts population (11.2 % vs 7.2 %).

Table 2. Close contacts in the different stages of contact tracing reporting, stratified by grad of exposure and vulnerability, from TB patients registered between 2016-2021 in MSIS.

Grad of exposure	Total CC	IGRA test response (%)[!]	IGRA positive (%)[?]	Referred to SHS (%)[!]	Received preventive treat. (%)[¤]	Diagnosed with TB (%)[¤]
Especially vulnerable contacts						
Particularly exposed contacts	570	487 (85.4)	120 (24.6)	243 (42.6)	123 (102.5)	20 (16.7)
Other close contacts	572	524 (91.6)	35 (6.7)	104 (18.2)	24 (68.6)	2 (5.7)
Random contacts	17	16 (94.1)	0 (0)	1 (5.9)	0 (-)	1 (-)
Other contacts						
Particularly exposed contacts	1 234	1087 (88.1)	313 (28.8)	368 (29.8)	172 (55)	35 (11.2)
Other close contacts	4 695	4254 (90.6)	520 (12.2)	514 (10.9)	139 (26.7)	12 (2.3)
Random contacts	398	167 (42)	28 (16.8)	24 (6)	6 (21.4)	3 (10.7)
Total	7 486	6535 (87.3)	1016 (15.5)	1254 (16.8)	464 (45.7)	73 (7.2)

! Proportion of total close contacts
? Proportion of IGRA tested close contacts.
¤ Proportion of close contacts with positive IGRA test.

When doing an analysis to see if there were any discrepancies in the number of close contacts registered in the different stages of contact tracing, we found that 157 TB patients had zero registrations of IGRA tested close contacts, 11 of those had 21 IGRA positive close contacts between them (Figure 3). Further, 18 of the TB patients without IGRA tested close contacts, had a total of 86 close contacts referred to SHS between them, and 9 of the TB patients had close contacts that had received treatment (8 close contacts). There were two TB patients that

had one more IGRA tested close contact then total number of close contacts. For 14 other TB patients there was registered more IGRA-positive patient then there were IGRA tested close contacts (21 positive IGRA tests).

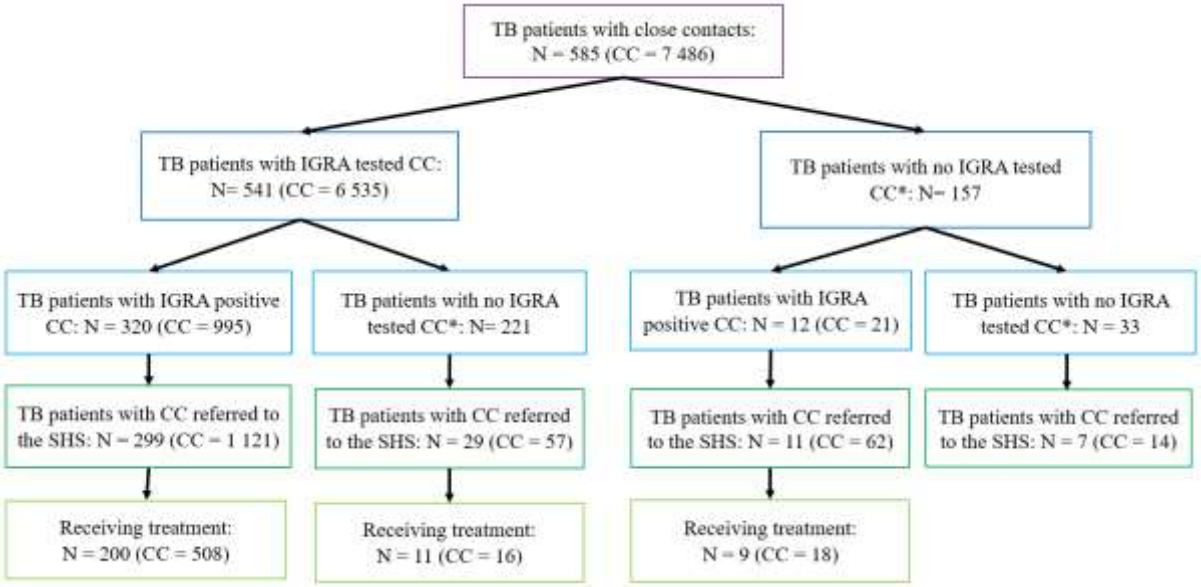

Figure 3.Total number of TB patients included in this study and their close contacts (CC) on each stage of the contact tracing. Data is from TB patients registered in 2016-2021 in MSIS. *The TB patient have zero close contacts in a specific category. The right side of the figure illustrates that the TB patients have close contacts that have positive IGRA tests, close contacts referred to SHS and close contacts received treatment, even if there is no registration of a IGRA test or a positive IGRA test.

3.3 Univariable and multivariate analysis

For study question 3, we performed analyses for six outcome variables, using selected sub-populations for each separate analyses. Each of the coloured boxes in Figure 4 represents the sub-population used for these analyses.

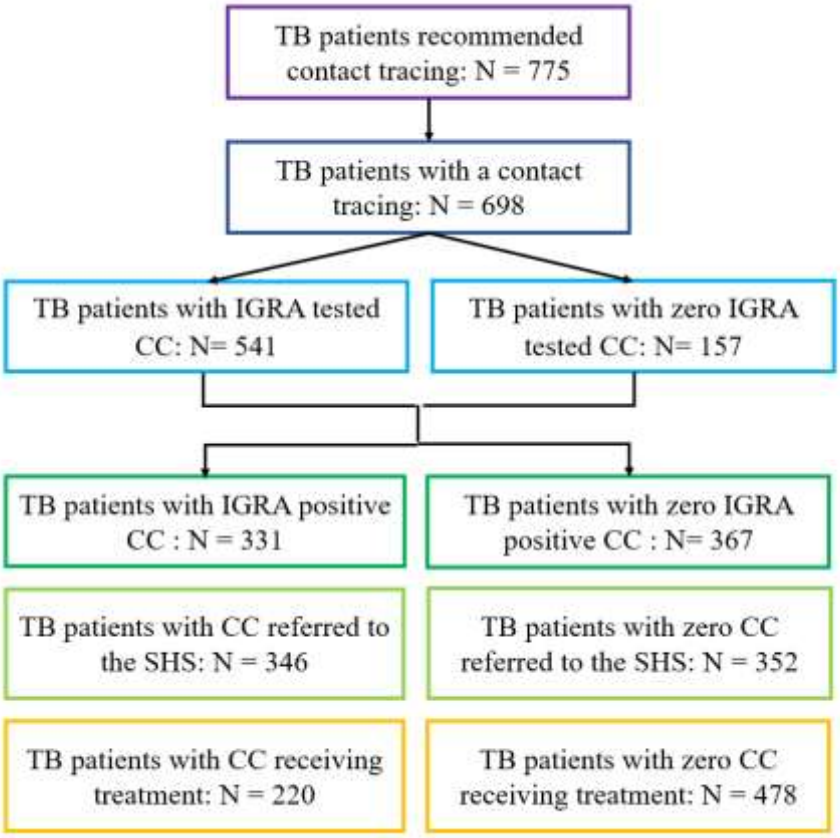

Figure 4. Number (N) of TB patients that have close contacts in the different stages of contact tracing, between 2016-2021. The colours of the boxes represent the study population for the study questions (SQ). Purple box = SQ 2a , Dark blue box = SQ 2b, light blue boxes = SQ 2c, dark green boxes = SQ 2d, light green boxes = SQ 2e, orange boxes = SQ 2f.

3.3.1 Characterics associatited with contact tracing

In this section we present the results related to **study question 3a**: Are the characteristics of the TB patient associated with the likelihood of being registered with contact tracing? For these analyses we included all TB patients (purple box in Figure 4), with the outcome variable being "contact tracing" and using TB patients without contact tracing as reference (N = 77, 9.9 % of population).

Based on the univariable analyses, age, municipality size, immigration status, positive test from respiratory sample and the type of organ affected were all statistically significantly associated with contacts tracing (for all details on univariable analysis see appendix 5, table 1). Compared to those 15-years and younger, those older were around 20% more likely to have a contact tracing reported: with risk ratios (RR) of 1.23 for those aged 15-30 years, 1.24 for those aged 31-60 years and 1.18 for those 60 year and older (Table 3). TB patients living in municipalities with under 20 000 population had a 26 % lower probability of having contact tracing reported (Table 3). Work immigrant status was associated with a slightly higher probability of having contact tracing (RR = 1.08) compared to being born in Norway. Additionally, TB patients with lung as infected organ (RR = 1.81, 95 % CI: 1.22-2.71) or lung involvement along with other organs (RR = 1.86, 95 % CI: 1.25-2.78) had a higher probability of being contact traced compared to those with other organs affected. In line with this, TB patients with a positive test from the respiratory system (RR = 1.10) had a higher probability of undergoing contact tracing compared to those without.

Based on these results, we included the following variables in the multivariable analysis: age, sex, municipality size, immigration status, and positive airway results. Results from the multivariable model show that age and municipality size were associated with contact tracing after adjusting for potential confounders (Table 3). TB patients from municipalities with smaller population (<20 000 and between 20 000-100 000) had a lower probability of being contact traced (RRR = 0.54 and 0.18, respectively) compared to municipalities with over 100 thousand population. Further, individuals aged 16-30 years and 31-60 years had around three times higher probability of being contact traced compared to those aged 15 years and below, with RRR of 3.29 and 2.71 respectively.

Table 3. Univariable and multivariable analysis of the association between characteristics of TB patents and if there is registered contact tracing, among 775 TB patients in Norway registered in MSIS between 2016-2021.

	Univariable analysis **RR (95% CI)***	***p-value***	Multivariable analysis **RRR (95% CI)^**	***p-value***
Total				
Age groups!				
0-15 years	Reference			
16-30	**1.23 (1.07-1.42)**	**0.003**	**3.29 (1.44-7.53)**	**0.005**
31-60	**1.24 (1.08-1.42)**	**0.003**	**2.71 (1.16-6.33)**	**0.022**
61+	**1.18 (1.02-1.38)**	**0.027**	1.34 (0.53-3.35)	0.535
Sex (775)				
Male	Reference		Reference	
Female	1.03 (0.99-1.08)	0.172	1.29 (0.73-2.26)	0.376
Municipality size!				
> 100 000	Reference		Reference	
20 000 – 100 000	0.96 (0.92-1.01)	0.096	**0.54 (0.24-1.22)**	0.139
< 20 000	**0.84 (079-0.90)**	**< 0.001**	**0.18 (0.09-0.38)**	**< 0.001**
Immigration status!				
Norwegian	Reference		Reference	
Other	0.99 (0.92-1.07)	0.836	0.78 (0.41-1.5)	0.453
Work immigrant	**1.08 (1.01-1.15)**	**0.018**	3.35 (0.97-11.57)	0.056
Immigrant/asylum seeker	0.98 (0.91-1.05)	0.538	1.26 (0.57-2.76)	0.571
Positive test from respiratory!				
No	Reference		Reference	
Yes	**1.1 (1.02-1.19)**	**0.009**	1.66 (0.87-3.16)	0.124

*Relative risk (RR) and 95 % confidence interval.
^Relative risk ratio (RRR) 95 % confidence interval.
! Variables have been changed or made especially for analysis, see variable dictionary in appendix 2 for details.

3.3.2 Characterics associatited with number of close contacts

In this section we present the results related to **study question 3b**: Are the characteristics of the TB patient associated with the number of close contacts identified during contact tracing? For these analysis we included 698 TB cased (dark blue boxes in Figure 4), with the outcome variable being "number of close contacts" and using TB patients with 0 to 2 close contacts as reference group (N= 245, 35.1% of the population). Additionally, contact tracing identified 224 (32.1 %) TB-patients with 3-7 contacts, 134 (19.2 %) with 8-20 contact and 95 (13.6 %) with more than 20 contacts.

Based on both the uni- and multivariable analysis, at-risk workplace, healthcare region, immigration status, period lived in Norway, foreign born parents, clinical symptoms, positive test from respiratory sample and they were all statistically significantly associated with the number of close contacts found through contact tracing (Table 4). Some of the results from univariable analysis that was not included in multivariable analysis was type of infected organ, and indication for examination. TB patients with lung involvement along with other organs had lower risk of having 3-7 close contacts and over 20 close contacts, compared to

having only lung as infected organ (RRR = 0.63, 95% CI: 0.42-0.95 and RRR = 0.38, 95% CI: 0.21-0.71, respectively). Having routine investigation as reason for examination had a lower probability of having over 8-20 and over 20 close contacts (RRR = 0.31, 95 % CI: 0.18-0.55 and RRR = 0.48, 95 % CI: 0.22-1.03, respectively), when compared to having symptoms and signs as indication for examination (See appendix 5, table 2 for details).

Further, TB patients working in education and healthcare had a two to three times higher risk of having over 20 close contacts compared to those not registered with an at-risk workplace (RRR = 2.15 and RRR = 3.04, respectably). Regarding geographical variables, living in Norway's central health region was associated with a lower risk of having over 20 close contacts (RRR = 0.26), compared to the South-eastern health region. Conversely, living in the Western health region was associated with an increased risk (Table 4). In terms of duration of residence, TB patients who had lived in Norway for less than 1 year had a lower risk of having 8 to 20 close contacts and having over 20 close contacts compared to the Norwegian TB patients (RRR = 0.49 and RRR = 0.36, respectively). There was an increased risk of having between 3 and 7 close contacts when having loved in Norway for over 10 years with a RR of 2.16 (Table 4). Work immigrant status and being Norwegian had a two times higher probability of having 8-20 close contacts (RRR = 2.86 and RRR = 2.39, respectively), when compared to the reference group (Table 4). Additionally, TB patients showing clinical symptoms had two times higher risk of having between 8 to 20 close contacts and having over 20 close contacts, compared to not having clinical symptoms (RR = 2.53 and RR = 2.66, respectively). Moreover, as the number of close contacts increased so did the corresponding risk when having a positive test from the respiratory system (Table 4).

In the multivariable analysis we included the following variables in the multivariable analysis: age, sex, at-risk workplace, hospital region, period lived in Norway, immigration status, clinical symptoms, and positive airway results. Results from the multivariable model show that at-risk workplace and having lived in Norway for under 1 year, no longer had an association with the number of close contacts found through contact tracing (Table 4). In the univariable analysis, age and sex did not show a significant association with the number of close contacts among TB patients (Table 4). However, in the multivariable model, we found that individuals 16-30 years had a 61 % lower probability of having 3-7 close contacts (RRR = 0.39), and that female TB patients had a 67 % increased probability of having 8-20 close contacts (RRR = 1.67).

The health region of residence was still associated with the number of close contacts, with living in Central Norway showing a reduced probability of having over 20 contact (RRR=0.27) and living in Western health region with higher probability of having 20 contacts (RRR=2.08) compared to South-eastern health region. (Table 4). Having the status as work immigrant and Norwegian was also associated with an increased risk of having 8 to 20 close contacts (RRR = 2.23 and RRR = 6.24, respectively) after adjusting for other variables. The association found in the univariable analyses related to having clinical symptoms and having a positive test from respiratory sample are similar in the multivariable analyses (Table 4).

Table 4. Uni- and multivariable analysis of TB patients' characteristics association to the number of close contacts found, among 698 TB patients in Norway registered in MSIS between 2016-2021.

Category	3-7 close contacts, RRR (95% CI)		8-20 close contacts, RRR (95% CI)		Over 20 close contacts, RRR (95% CI)	
Analysis	**Univariable**	**Multivariate**	**Univariable**	**Multivariate**	**Univariable**	**Multivariate**
Age groups[!]						
0-15	Reference	Reference	Reference	Reference	Reference	Reference
15-30	0.66 (0.33-1.32)	**0.39 (0.17-0.86)***	1.18 (0.48-2.86)	0.59 (0.21-1.68)	1.88 (0.67-5.32)	0.57 (0.17-1.95)
31+	1.12 (0.57-2.17)	0.47 (0.21-1.04)	1.59 (0.67-3.79)	0.5 (0.17-1.41)	1.36 (0.48-3.84)	0.32 (0.09-1.12)
Sex						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.3 (0.9-1.87)	1.38 (0.92-2.06)	1.4 (0.92-2.14)	**1.67 (1.03-2.69)***	1.2 (0.74-1.94)	1.18 (0.68-2.03)
At-risk workplace[!]						
Unknown/not at-risk	Reference	Reference	Reference	Reference	Reference	Reference
Other at-risk	**1.81 (1.16-2.81)***	1.2 (0.71-2)	**2.34 (1.42-3.85)***	1.52 (0.84-2.76)	1.06 (0.54-2.07)	0.95 (0.44-2.04)
Education	0.9 (0.52-1.56)	0.99 (0.54-1.82)	1.05 (0.55-2.01)	1.22 (0.59-2.5)	**2.15 (1.16-3.96)***	1.98 (0.97-4.04)
Healthcare	0.72 (0.27-1.88)	0.46 (0.16-1.27)	0.76 (0.24-2.46)	0.42 (0.12-1.45)	**3.04 (1.25-7.34)***	1.89 (0.68-5.26)
Heath region[!]						
South-eastern	Reference	Reference	Reference	Reference	Reference	Reference
Northern	0.6 (0.31-1.16)	0.91 (0.44-1.88)	0.45 (0.19-1.08)	0.75 (0.29-1.93)	0.91 (0.42-1.98)	0.92 (0.37-2.25)
Central Norway	1.06 (0.6-1.85)	1.24 (0.69-2.24)	0.94 (0.48-1.84)	1.06 (0.51-2.21)	**0.26 (0.08-0.9)***	**0.27 (0.08-0.95)***
Western	1.28 (0.77-2.11)	1.6 (0.94-2.73)	1.67 (0.96-2.88)	**2.42 (1.33-4.39)***	**1.83 (1.01-3.31)***	**2.08 (1.08-4.01)***
Period in Norway[!]						
Norwegian	Reference	Reference	Reference	Reference	Reference	Reference
Under 1 year	0.95 (0.54-1.67)	1.81 (0.71-4.6)	**0.49 (0.26-0.91)***	2.48 (0.65-9.46)	**0.36 (0.16-0.8)***	0.34 (0.11-1.04)
1-4 years	0.82 (0.42-1.58)	1.8 (0.66-4.88)	0.55 (0.27-1.12)	2.49 (0.62-10.01)	1.3 (0.61-2.75)	1.05 (0.35-3.14)
5-9 years	0.94 (0.48-1.85)	1.93 (0.68-5.44)	0.5 (0.23-1.08)	2.26 (0.54-9.56)	0.82 (0.35-1.92)	0.81 (0.24-2.68)
10 + years	**2.16 (1.1-4.26)***	**4.35(1.54-12.31)***	1.39 (0.68-2.86)	**6.28(1.52-25.93)***	1.27 (0.54-3.01)	1.36 (0.4-4.54)
Unknown[?]	0.56 (0.21-1.49)	-	**0.3 (0.09-0.99)***	-	0.93 (0.32-2.67)	-
Immigration status[!]						
Immigrant/asylum seeker	Reference	Reference	Reference	Reference	Reference	Reference
Other	**1.79 (1.13-2.82)***	1.47 (0.88-2.46)	1.31 (0.74-2.3)	1.08 (0.57-2.05)	1.05 (0.59-1.87)	1.16 (0.6-2.24)
Work immigrant	2.92 (1.72-4.94)	**2.3 (1.23-4.29)***	**2.86 (1.56-5.25)***	**2.23 (1.07-4.65)***	0.78 (0.35-1.72)	0.88 (0.35-2.22)
Norwegian	1.52 (0.86-2.69)	2.78 (0.96-8.08)	**2.39 (1.29-4.4)***	**6.24(1.48-26.26)***	1.25 (0.63-2.47)	1.15 (0.34-3.86)
Clinical symptoms						
No (208)	Reference	Reference	Reference	Reference	Reference	Reference
Yes (490)	1.13 (0.77-1.65)	1.15 (0.75-1.77)	**2.53 (1.53-4.2)***	**2.77 (1.56-4.92)***	**2.66 (1.48-4.78)***	**2.47 (1.27-4.8)***
Positive airway result[!]						
No (128)	Reference	Reference	Reference	Reference	Reference	Reference
Yes (570)	**2.29 (1.46-3.6)***	**2.55 (1.51-4.3)***	**3.64 (1.96-6.75)***	**4.08 (2-8.32)***	**(2.64-15.04)***	**1.70 (3.27-23.15)***

*P value <0.05, of the relative risk ratio (RRR) and 95 % confidence interval.

! Details on variables can be found in the variable dictionary in appendix 2.

?Omitted: not included in the multivariable model, because it has no explanatory effect on the outcome.

3.3.3 Characterics associatited with having IGRA tested close contacts

In this section we present the results related to **study question 2c**: Are the characteristics of the TB patient associated with having IGRA tested close contacts? We conducted a multivariable analysis including 698 TB cased (light blue boxes in Figure 4), with the outcome variable being "Having IGRA tested close contacts" and using TB patients with zero IGRA tested close contacts as reference group (N= 157, 22.5 % of the population).

The following variables were included in the final model: age groups, sex, hospital region, period lived in Norway, indication for examination, and positive airway results. In addition, we included the following variables: number of close contacts (grouped), TB patients with IGRA positive close contacts, TB patients with close contacts referred to SHS, and TB patients with close contacts that have received treatment or diagnosis (Table 5). Having IGRA tested close contacts had an association to having lived in Norway for over 10 years (RRR = 4.09), having a positive respiratory test (RRR = 3.28), and an eight times higher probability of having IGRA positive close contacts compared to not having IGRA positive close contacts (RRR = 8.52). But there was no association to the size of the contact tracing, having close contacts referred to SHS, or close contacts receiving treatment or diagnosis (Table 5).

3.3.4 Characterics associatited with having IGRA tested close contacts

To answer **study question 2d**: Are the characteristics of the TB patient associated with having IGRA positive close contacts? We conducted a multivariable analysis including 698 TB cased (dark green boxes in Figure 4), with the outcome variable being "Having IGRA positive close contacts" and using TB patients with zero IGRA positive close contacts as reference group (N= 367, 52.6 % of the population).

The following variables were included in the final model: age groups, sex, period lived in Norway, hospital region, positive airway results, number of close contacts (grouped), TB patients with CC referred to SHS, and TB patients with CC that have received treatment (Table 5). We found that having IGRA positive CC was associated with a two times higher risk when living in the Central Norway, compared to South-east hospital region (RRR = 3.1), and a higher risk of having both CC referred to SHS and receiving treatment (Table 5). Being female was associated with a lower risk of having an IGRA positive test compared to the male population (RRR = 0.48, CI: 0.26-0.89). There was no risk difference for period lived in Norway or if the TB patient had a positive airway result (Table 5).

Table 5. The relative risk ratio (RRR) of characteristics associated with TB patients having contacts who received an IGRA test and with TB patients having contacts who tested positive on IGRA among 698 TB patients in Norway registered in MSIS between 2016-2021.

	TB-patients with CC that have taken an IGRA test, RRR (95% CI)[!]	TB-patients with CC that have a positive IGRA test, RRR (95 % CI)[?]
Age groups[!]		
0-15 years	Reference	Reference
16-30	0.64 (0.16-2.63)	0.91 (0.2-4.16)
31+	0.88 (0.22-3.45)	0.52 (0.12-2.28)
Sex		
Male	Reference	Reference
Female	1.82 (0.9-3.66)	**0.48 (0.26-0.89)***
Period in Norway[!]		
Norwegian	Reference	Reference
Under 1 year	0.94 (0.31-2.79)	2.42 (0.91-6.44)
1-4 years	1.01 (0.34-2.97)	0.8 (0.27-2.35)
5-9 years	1.79 (0.53-6.03)	1.38 (0.41-4.65)
10 + years	**4.09 (1.02-16.35)***	1.45 (0.5-4.24)
Unknown	0.78 (0.14-4.31)	3.77 (0.62-22.88)
Indication for examination[!]		
Symptoms and signs	Reference	-
Other	1.49 (0.3-7.31)	-
Immunodeficiency	3.18 (0.37-27.23)	-
Contact tracing	3.1 (0.38-25.28)	-
Routine investigation of immigrant	1.45 (0.54-3.9)	-
Hospital region[!]		
South-eastern	Reference	Reference
Northern	6.19 (0.64-59.67)	1.66 (0.45-6.13)
Central Norway	0.9 (0.31-2.64)	**3.1 (1.14-8.42)***
Western	1.78 (0.47-6.71)	1.3 (0.59-2.86)
Positive test from respiratory[!]		
No	Reference	Reference
Yes	**3.28 (1.4-7.71)***	1.53 (0.57-4.11)
Number of close contacts[!]		
0 to 2 CC	Reference	Reference
3 to 7 CC	1.81 (0.8-4.06)	1.35 (0.66-2.75)
8 to 20 CC	1.64 (0.57-4.75)	1.93 (0.83-4.51)
21 + CC	1.05 (0.28-3.94)	**10.05 (2.56-39.42)***
Have IGRA positive close contacts[!]		
No	Reference	-
Yes	**8.53 (2.69-27.02)***	-
Have CC referred to SHS		
No	Reference	Reference
Yes	0.45 (0.16-1.29)	**57.75 (27.29-122.19)***
Have close contacts received treatment[!]		
No	Reference	Reference
Yes	0.88 (0.3-2.55)	**3.45 (1.59-7.46)***

*P value <0.05, of the relative risk ratio (RRR) and 95 % confidence interval.

! Details on variable is described in the variable dictionary in appendix 2.

3.3.5 Characterics associatited with having close contacts reffered to special healthcare services

In this section we present the results related to **study question 2e**: Are the characteristics of the TB patient associated with having CC referred to special healthcare services? For these analysis we included 698 TB patients (light green boxes in Figure 4), with the outcome variable being "Having close contacts referred to SHS" and using TB patients with zero close contacts referred to SHS as reference group (N= 352, 50.4 % of the population).

In the univariable analysis, living in small municipalities (<20 000) was associated with a lower risk of having close contacts referred to SHS (RR = 0.82). While having known exposure, a positive airway result and different characteristics indicating a foreign background had a higher probability of having close contacts referred to SHS. Being born outside of Norway and having been in a high incidence country for over three months had a higher risk of having CC referred to SHS (RR = 1.57, 95 % CI: 1.2-2.05 and RR = 2.16, 95 % CI: 1.24-3.77, respectively) (see appendix 5, table 3 details).

In the multivariable model the following variables were included: age groups, sex, municipality size, health region, period lived in Norway, clinical symptoms, positive airway results, number of CC (grouped), having IGRA tested CC, and having CC received treatment (Table 6). In the multivariate model, municipality size, clinical symptoms, and positive airway results no longer showed an association with having CC referred to SHS. However, living in Norway for 1-4 years and 5-9 years still had an increased probability of having CC referred to SHS compared to being Norwegian (RRR= 5.63 and RRR = 4.34, respectively). Furthermore, living in Central Norway healthcare region exhibited a lower risk (RRR = 0.29) of having CC referred to SHS compared to those living in the South-eastern region. Additionally, TB patients' number of CCs, having IGRA positive CC and having CC receiving treatment was highly associated with having CC referred to SHS (Table 6).

Table 6. Univariable and multivariable analysis of characteristics associated with TB patients having contacts who referred to SHS, among 698 TB patients in Norway registered in MSIS between 2016-2021.

Category (total number)	TB patients with CC referred to SHS	
Analysis	**Univariable, RR (95% CI)**	**Multivariate, RRR (95% CI)**
Age groups[!]		
0-15	Reference	Reference
15-30	1.01 (0.77-1.34)	0.51 (0.11-2.48)
31+	0.88 (0.66-1.15)	0.52 (0.11-2.46)
Sex		
Male	Reference	Reference
Female	1.04 (0.89-1.21)	0.87 (0.43-1.74)
Municipality size[!]		
> 100 000	Reference	Reference
20 000 – 100 000	0.92 (0.78-1.1)	0.48 (0.22-1.08)
< 20 000	**0.82 (0.68-0.99)***	0.47 (0.2-1.11)
Hospital region[!]		
South-eastern	Reference	Reference
Northern	0.89 (0.67-1.19)	0.61 (0.17-2.23)
Central Norway	0.79 (0.6-1.06)	**0.29 (0.09-0.92)***
Western	1.05 (0.88-1.26)	0.54 (0.21-1.41)
Period in Norway[!]		
Norwegian	Reference	Reference
Under 1 year	**1.45 (1.08-1.95)***	**1.97 (0.65-5.97)***
1-4 years	**1.75 (1.29-2.36)***	**5.63 (1.67-18.9)***
5-9 years	**1.66 (1.21-2.28)***	**4.34 (1.27-14.8)***
10 + years	**1.78 (1.32-2.41)***	2.67 (0.81-8.77)
Unknown	1.21 (0.75-1.96)	0.93 (0.14-6.07)
Clinical symptoms		
No	Reference	Reference
Yes	**1.28 (1.07-1.54)***	1.46 (0.66-3.25)
Positive airway result[!]		
No	Reference	Reference
Yes	**1.72 (1.31-2.25)***	0.61 (0.25-1.52)
Number of close contacts[!]		
0 to 2 CC	Reference	Reference
3 to 7 CC	**2.77 (2.07-3.72)***	**2.24 (1-5)***
8 to 20 CC	**4.14 (3.13-5.49)***	**8.04 (2.99-21.62)***
21 + CC	**4.87 (3.71-6.4)***	**5.43 (1.37-21.51)***
Have IGRA positive close contacts[!]		
No	Reference	Reference
Yes	**9.55 (6.99-13.04)***	**64.87 (30.22-139.22)***
Have close contacts received treatment[!]		
No	Reference	Reference
Yes	**3.65 (3.15-4.24)***	**61.85 (16.5-231.91)****

*P value <0.05, of the relative risk (RR) and relative risk ratio (RRR), with 95 % confidence interval.
! Details on variable is described in the variable dictionary in appendix 2.

3.3.6 Characterics associatited with having close contacts reciving treatment

In this section we present the results related to **study question 2f**: Are the characteristics of the TB patient associated with having CC treatment? In these analysis we included 698 TB patients (orange boxes in Figure 4), with the outcome variable being "Having close contacts receiving treatment" and using TB patients with zero close contacts receiving treatment as reference group (N= 478, 68.5 % of the population).

As in the univariable analysis of TB patients with CC referred to SHS, several demographic variables indicating a foreign background exhibited increased risk of with having CC that received treatment or diagnosis (see appendix 5, table 3). In addition to characteristics such as having a known exposure (RR = 1.61, 95 % CI: 1.1-2.36), being female was associated with an increased risk, compared to the reference groups (Table 7). Having lung and other effected organs had a decreased risk of having close contacts receiving treatment, when compared to only having lung as effected organ (RR = 0.67, 95 % CI: 0.50-0.89).

Number of close contacts, having IGRA tested and IGRA positive close contacts and having close contacts referred to SHS, all had an increased probability of having close contacts receiving treatment (see appendix 5, table 3). Having close contacts received treatment had an exponential high correlation to having close contacts referred to SHS (RR = 73.59, Table 7).

In the multivariable model, period lived in Norway, positive airway result, and number of CC were no longer associated with CC receiving treatment or diagnosis. In comparison to the univariable model, age, sex and not having MDR-TB showed an association with TB patients having CC receiving treatment or diagnosis (Table 7).

Being between 16-30 years and over 30 years exhibited a lower risk (RRR = 0.25 and RRR = 0.20, respectively) compared to those aged below 16 years. Female TB patient, TB patients without MDR-TB and TB patients living in small municipalities showed an increased risk of having CC receiving treatment, compared to respective reference group (Table 7).

Among the other outcome variables used in this study, TB patients with IGRA positive CC had a four times as high probability of having CC receiving treatment or diagnosis compared to those without IGRA positive CC (RRR = 3.84). Furthermore, having CC referred to SHS was associated with a particularly increased probability of also having CC receiving treatment (RRR = 83.32).

Table 7. Uni- and multivariable analysis of characteristics associated with TB patients having contacts receiving treatment, among 698 TB patients in Norway registered in MSIS between 2016-2021.

Characteristic		
Analysis	**Univariable, RR (95% CI)**	**Multivariate, RRR (95% CI)**
Age groups[!]		
0-15	Reference	Reference
15-30	0.88 (0.61-1.28)	**0.25 (0.07-0.92)***
31+	0.7 (0.48-1.02)	**0.2 (0.06-0.74)***
Sex		
Male	Reference	Reference
Female	**1.4 (1.13-1.74)***	**2.82 (1.71-4.66)***
Municipality size[!]		
> 100 000	Reference	Reference
20 000 – 100 000	1.02 (0.79-1.33)	1.44 (0.81-2.54)
< 20 000	0.98 (0.75-1.28)	**2.02 (1.07-3.81)***
Period in Norway[!]		
Norwegian	Reference	Reference
Under 1 year	1.38 (0.92-2.07)	0.64 (0.26-1.57)
1-4 years	**1.76 (1.16-2.66)***	0.93 (0.36-2.37)
5-9 years	1.5 (0.96-2.36)	0.78 (0.29-2.08)
10 + years	**1.77 (1.17-2.68)***	1.14 (0.44-2.98)
Unknown	1.05 (0.52-2.12)	0.39 (0.1-1.48)
Positive airway result[!]		
No	Reference	Reference
Yes	**2.38 (1.55-3.65)***	2.16 (0.81-5.73)
MDR TB[!]		
No	Reference	Reference
Yes	2.37 (0.95-5.89)	**4.49 (1.24-16.22)***
Unknown	0.69 (0.23-2.12)	0.87 (0.13-5.68)
Number of close contacts [!]		
0 to 2 CC	Reference	Reference
3 to 7 CC	**2.96 (1.98-4.42)***	1.13 (0.53-2.42)
8 to 20 CC	**3.93 (2.62-5.89)***	0.77 (0.36-1.68)
21 + CC	**5.92 (4.03-8.7)***	1.41 (0.61-3.29)
Have IGRA positive close contacts [!]		
No	Reference	Reference
Yes	**15.15 (9.17-25.05)***	**3.84 (1.76-8.38)***
Have close contacts referred to SHS[!]		
No	Reference	Reference
Yes	**73.59 (23.79-227.66)***	**88.32 (22.49-308.66)***

*P value <0.05, of Relative risk (RR) and relative risk ratio (RRR), with 95 % confidence interval.
! Details on variable is described in the variable dictionary in appendix 2.

4 Discussion

This is a retrospective cohort study of TB patients registered in MSIS, between 2016-2021. The study sought out to see if contact tracing was done according to regulations and recommendations, and to identify TB patient's demographic and medical characteristics associated with the results of the contact tracing.

4.1 Main findings

In this study, we found that contact tracing is performed and reported in a high proportion, 90%, of TB cases who are recommended for contact tracing. The proportion with contact tracing was higher among infectious pulmonary TB patients above 15 years (91.6 %) than among patients aged 15 years and below (66.2%). Additionally, contact tracing was not reported for the majority of TB patients (91.5%) where contact tracing is not recommended by regulations. Analysing the close contacts data demonstrated that vulnerability and exposure level influenced contact tracing outcomes, with higher follow-up as well as infection and treatment among those most at risk.

Various factors were associated to the contact tracing outcomes. Living in municipalities with lower population numbers (< 20 000) was associated with a low risk of being contact traced but an increased risk of having close contacts receiving treatment. Living in Central Norway health region lowered the risk of having over 20 close contacts and increased the risk of having IGRA positive close contacts, while living in the Western health region correlated with an increased risk of having over 7 close contacts.

Females had an increased risk of having close contacts who tested positive on IGRA , and who received treatment. TB patients aged 16-30 and above 30 years had higher probability of being contact traced, but a lower risk of having close contacts who received treatment. Young adults (16-30) had an increased risk of having 3-7 close contacts. TB patients who are a work immigrant or Norwegian had an increased the risk of having 8-20 close contacts. Residing in Norway for over 10 years increased the risk of having close contacts who received an IGRA test. Those TB patient with a foreign background were correlated with having close contacts referred to SHS and close contacts receiving treatment.

TB patients with MDR-TB had a lower likelihood of having close contacts receiving treatment, but there was no association to the other outcomes. Clinical symptoms and positive airway results increased the risk of having more close contacts, having close contacts referred to SHS and close contacts receiving treatment. TB patient who had close contacts referred to SHS showed a strong association with having close contacts receiving treatment. Having IGRA positive close contacts correlated with having over 20 close contacts, close contacts referred to SHS and close contacts receiving treatment. Having IGRA tested close contacts had no association to having close contacts referred to SHS or receiving treatment.

4.2 Contact tracing

It is legally required that contact tracing should be conducted around all cases of notifiable pulmonary TB to identify contacts who may have been exposed (79). In addition, limited contact tracing of household members should be done for children with TB, regardless of type, with the aim of identifying the source of infection (84). We show that in a very high proportion of these TB patients contact tracing is performed. However, contact tracing was not reported for all TB patients who fit the criteria for contact tracing. In addition, not all close contacts received the appropriate follow-up when it comes to being registered with having received preventive treatment of TB diagnosis. The proportion of TB patients where contact tracing was reported was higher among the pulmonary TB patients above 15 years than among children (≤15 years). The recommendations do not specify the age of the children where contact tracing should be performed, which could explain why the proportion is lower for the children. Due to the low numbers of children with TB, we were not able to perform sub-analyses to investigate this, but more specific studies around contact tracing in children should be performed,

The final goal of contact tracing in Norway is tuberculosis elimination. Contact tracing of risk groups is used as an important tool to achieve this goal, by actively seeking out and testing exposed individuals and treating those infected. When looking at the contact tracing data from 2016 to 2021, 15.5 % of the close contacts had a positive IGRA test among close contact who were IGRA. However, when we look at the particularly exposed contacts the proportion who tested positive on IGRA was 26 % in vulnerable contacts and 28.8 % in not vulnerable contacts. Similarly, Studies have found that screening large numbers of contacts does not yield many extra infected contacts, since usually the closest contacts of a TB patients are those who gets infected (55, 83). The number of vulnerable and exposed close contacts seems

to be in line with the guidelines, since they recommend starting with the closest contacts and testing them before expanding the search to other contacts, if the patient appears to be particularly contagious (84). At the same time, the number of close contacts in total are larger than necessary, since only 15.5 % of those tested end up with a positive test.

Our results show that 52.9% of all contacts who tested positive with IGRA received preventive treatment (45.7%) or were diagnosed with active TB disease (7.2%) and likely received treatment for this. In theory when a close contacts is newly infected, the risk of the infection to evolve into TB disease is highest the first two years (64). Close contacts who are at risk for being infected should be tested with IGRA, and those with a positive IGRA test should have received either preventive treatment (LTBI) or a TB diagnosis when there are no counter indications to receive treatment. When looking at previous studies from low and middle incidence countries, there are a lot of similar results. The proportion of LTBI patients who receive, and complete treatment varies from 54 to 67 % (54, 59, 115). A retrospective cohort study from Spain found that after 5 years of follow-up, 54.4 % of the close contacts with LTBI completed treatment, 7.3 % of the LTBI cases did not comply with treatment, treatment was not prescribed for 25 % of the LTBI cases, and that 13.1 % treatment information was not available (116). For this study we did not have the information on why some close contacts did not receive treatment nor if they completed their treatment. As treating LTBI cases is an important element of reducing and eliminating TB in Norway, it would be important to investigate why almost half of those who tested positive were not reported with treatment and determine the adherence to treatment. Potentially the contact tracing forms are submitted prior to all information regarding treatment being registered and we could be underestimating the number of contacts receiving proper follow-up.

When comparing the proportion of close contacts receiving treatment with close contacts referrals to SHS, it is reasonable to assume that a significant portion of those identified during contact tracing also received subsequent follow-up. At the same time, when looking specifically at the close contacts categorized as especially vulnerable, more close contacts have received preventive treatment or a TB diagnosis, than the number of close contacts with a positive test. But the number of close contacts referred to SHS is higher, indicating that not all who needs preventive or regular treatment is IGRA tested. Moreover, certain factors contribute to the lack of treatment or eligibility for treatment for specific population groups, including a lack of follow-up, age-related considerations, and medical circumstances. Medical conditions such as liver or kidney disease, certain autoimmune disorders, drug interactions,

and allergies can complicate the administration of TB medications or necessitate modifications to the treatment plan (41, 84). As found in this study, in cases of MDR-TB, conventional treatment regimens may prove less effective (36, 39) and therefore, the close contacts of MDR-TB patients have a lower likelihood receiving treatment, prompting alternative treatment options.

It is important to acknowledge the potential for inaccuracies in these figures due to the inherent reporting dynamics associated with close contacts via contact tracing forms. Further, if during the contact tracing no relevant contacts were identified, it is possible that no information on contact tracing was submitted in the forms. Consequently, an important facet in evaluating the efficacy of TB contact tracing in Norway is to consider the proportion of close contacts who were referred to SHS. The discrepancy between referrals to SHS and positive IGRA tests could be attributed to various factors including the medical circumstances of the close contacts and their clinical symptoms. At the same time the low number of close contacts receiving preventive treatment indicate that not all who are tested and infected get treated, finish their treatment plan, or are not reported.

4.3 TB patients' characteristics in relation to contact tracing.

According to the TB contact tracing recommendations a TB patients' infectiousness is a pillar in the contact tracing process. TB diagnosis, infected organ, different positive tests, CT, and symptoms should be taken into account to evaluate the infectiousness of the TB patient (84). It is stated that in some cases extrapulmonary TB can be infections and even in cases where it is not infectious limited contact tracing may still be applicable in cases of extrapulmonary tuberculosis, primarily to identify sources of infection or associated cases. In line with this, we show that TB patients with lung as infected organ or lung along with other organs had over 80 % increased probability of being contact traced compared to other organs in the univariate analysis. Further, having only lung as infected organ increased the risk of having more close contacts, when compared to having lung and other organs. We can speculate that the reason for why the TB patients with lung and other infected organs have less contacts is that these patients had symptoms and main infection in other organs then lung, and that the patients with only lung as infected organ had infectious pulmonary TB and therefore had a higher risk of transmitting the infection to others and therefore a more thorough contact tracing was performed.

As stated in the recommendations, having a positive test from the pulmonary system, positive test from cultivation result and having clinical symptoms had an association to some of the study outcomes. A positive test from the respiratory system had a 10 % increased probability of being contact traced, an 72 % increased risk of having close contacts referred to SHS and 238 % increased risk of having close contacts receiving treatment, but only in the univariate analysis. A positive test also gave an increased risk of having contacts IGRA tested and as well as having IGRA positive close contacts in the multivariable analysis. Indicating that when a TB patient is considered more infectious the contacts have been tested more often as well as were infected more often than TB patients with a negative test.

In line with the results from this study, multiple register-based studies have found an association between the TB patients' infectiousness and contact tracing (57, 58, 60, 61, 115, 117, 118). Mulder et al. found that smear positive and culture positive TB patients was more often contact traced compared to having negative tests (58). Reicher at al. found that close contacts exposed to patients with both a smear-positive and cavitary disease diagnosed by chest radiograph were more likely to have TB infection or disease than those with one or neither characteristic (61). Borraccino et al. found higher rates of TB infection in contacts who were exposed to sputum-smear-positive or culture-positive index cases and index patients who lived in the same household (60). Having a positive test from the respiratory system, also called a smear positive case, have shown to be more infectious than smear negative cases in many epidemiological studies (66, 119-127). We cannot directly compare the results from this study to all these studies because of difference in outcome and focus. However, our results show the same tendency as those reported previously. All in all, our results suggest that the TB patient's infectiousness increases the chance of contact tracing, and related follow-up, as well as the risk of finding infected contacts. This is in line with national recommendations (84) and is important to reduce further transmission.

In the TB recommendations from NIPH some conditions are related to exposure, as TB is transmitted through droplet nuclei, and the quantity of bacteria in the air will vary significantly based on ventilation, light, and distance between the patient and contact (84). It was not possible to analyse the association between the contact point where the TB patient met the close contacts, because no information on contact point was available. The recommendations also highlight the location of exposure, including workplace, school, or childcare facility. The data from the MSIS register used in this study included information regarding at-risk professions and workplaces. Our results show that recommendations

regarding location of exposure are followed in the contact tracing process. Contact tracing was done for all patients working in healthcare, and for 86.6 % and 91.3% of patients working in education and other at-risk workplaces respectively. In the univariate analysis, a higher number of close contacts was associated with at-risk work environment of the TB patient. TB patients working in education and healthcare had an increased risk of having over 20 close contacts, compared to no registration of at-risk workplace. In the multivariable model at-risk workplaces did not have an association to the number of close contacts but was still associated to the infectiousness of the patient. It seems likely that the workplaces mentioned in the recommendations have an association to the number of contacts found through contact tracing, but that the infectiousness of the patient is more important when looking at the results of the trace (if the TB patient has close contacts referred and treated). Similarly, Duarte et al. found that contact tracing procedures that included workplace and home was more effective for finding at-risk contacts then only finding contacts through interviewing (62).

The recommendations also take the duration of exposure into account. If the patient has both a negative culture and microscopy test, the public health officer in collaboration with a specialist should decide to what extent contact tracing should take place, and if only household members should be included. In this study we had no information about the relationship to the close contacts. There was information on the close contacts grade of exposure, but no specific analysis was done to look at the TB patients' characteristics and the different type of close contacts exposures.

The results from our study and previous research indicates the importance of contact tracing children with TB. We found that age had an association to whether contact tracing of the TB patient was dose, and that the age groups 16-30 and above 30 years had a lower probability of having close contacts receiving treatment compared to the 0-15 years age group. In accordance with the results of this study, three other studies found an association between childhood TB cases and the detection of close contacts (63-65). Morris et al. found that over 70 % of childhood cases had a close contact with TB infection or TB disease, often within family or living arrangements (63). The studies from Erkens et al. and Gafar et al. found that over 40 % of children diagnosed with TB were detected through contact tracing (64, 65). Sloot et al. found that close contacts screened for LTBI was associated with the TB patient being younger, and close contacts of smear negative patients had a lower risk of being screened for and diagnosed with LTBI (115). The study of Sloot et al. did the multivariable analysis on the close contacts characteristics and not the TB patient like in this study, so the

results cannot be compared directly. But the aim of doing contact tracing among children is to identify the source and this is in line with contacts of children having a higher risk of receiving treatment.

When it comes to sex, men are usually more affected of TB than woman, biological mechanisms can account for a parts of this difference seen (128). In this study the male population stood for 57.8 % of the TB patients, but there was no difference in risk for being contact traced. Female TB patients had an increased risk of having IGRA positive close contacts, and close contacts receiving treatment or diagnosis compared to the male TB patient.

Further, this study found that the probability of contact tracing was not associated with immigration status. Characteristics associated with a foreign background had no significant correlation in the multivariable analysis, except from being a work immigrant. Having immigration status as work immigrant had an increased probability of being contact traced. Further, having a foreign background had an association to having close contacts referred to SHS and close contacts receiving treatment in the univariable analysis. Patients who had lived in Norway 10 years and more had an increased risk of having IGRA tested close contacts and contacts receiving treatment. In comparison, two studies from the Netherlands found that patients with immigration status was negatively associated to being contact traced, and that close contacts and casual contacts of immigrant TB patients were less likely to be examined for LTBI. The possible explanation for this difference is that almost all TB cases in Norway are born outside of Norway in countries with a higher TB incidence. Previous studies and recommendations highlight the importance of screening for TB when staying in high TB countries for over three months or when immigrating to Norway (68, 80, 129). At the same time previous studies have found that most TB outbreaks are caused by M.tb strains circuiting in Norway for many years, that many immigrants are infected upon arrival and in addition that some immigrant groups have shown to not get infected before 7-years after immigrating (68, 70, 73). This could explain why this study founds a higher risk of having more close contacts when being Norwegian-born or having lived in the country for over 10 years. Along with the high TB incidence in the foreign-born population, the results from our analysis indicate that TB patients with immigration status get the same or in some cases better follow-up than Norwegian born patients.

In this study we also found geographical differences in contact tracing yield. The results indicate that smaller municipalities are less likely to register numerous contacts in one single contact tracing. Which is expected in a low-density population. However, when it comes to if TB patients close contacts receives treatment, those in smaller areas are more likely to ensure that their close contacts receive treatment when compared to municipalises with over 100 thousand population. Norway comprises of over 300 municipalities, with the top 100 most populated ones house about 80% of the population as of January 2021 (130). All these municipalities are responsible for managing the contact tracing process for TB patients within their boundaries (79). Therefore, it is reasonable to think that some municipalities are better equipped than others to conduct thorough and comprehensive contact tracing due to their previous experience and greater resources. Additionally, we observed that residing in the western health region of Norway increases the chances of having more close contacts compared to the South-eastern health region. While we do not have a definitive explanation for this, we can speculate that differences in contact tracing procedures might play a role. Furthermore, the Western health region houses two of the largest municipalities in Norway, which also have substantial immigrant populations and major universities. In contrast, the Central Norway health region consists of numerous smaller municipalities and lower population density per square mile (131). Previous studies have shown that TB patients in urban settings played a larger role in TB transmission (56, 69, 74).

4.4 The studies methodological approach

To quality assess the information found through the contact tracing data and to see what influences the results from contact tracing in Norway, a retrospective study design was chosen. This study design was chosen mainly to analyse the information that was already gathered and allow for quick analyses and recommendations.

Limits of a register-based cohort study should be considered when interpreting the results, as the data was not collected for the purpose of our study. Because of the retrospective study design, there is no control of the data selection, and the results are more susceptible to bias and confounding variables. In a prospective study you have more control of data collection, the exposure of the surroundings and follow-up. On the other hand, the retrospective design is cost-effective and do not require as much time and resources as a prospective study would. And even though the data is collected retrospectively, it can cover a long period of time,

enabling the examination of long-term outcomes and trends and allows for a broader analysis of trends and information. By looking at already collected data this study found that certain changes can be made when collecting different characteristics and variables as mentioned previously.

By using a multivariable analysis approach, we tried to acknowledge the potential influence the TB patients' different characteristics have, address confounding effects, and provide a more nuanced understanding of the relationships between the TB patients characteristics and the study outcomes. Variables that may seem insignificant in isolation can collectively contribute to the over outcome patterns when considered within a multivariable model. By using an approach that considers multiple factors simultaneously, there is a possibility of capturing some of the complex interactions between the factors that can impact contact tracing yield (132). The decision to incorporate sex, age, and the different outcome variables as confounders in the multivariable analysis was to help ensure that the observed effects are not biased by these factors. While these variables may not exhibit significant associations on their own, they could still confound the true relationships between the independent variables and the outcomes of interest (105). The reason for adjusting for sex and age in infectious disease research is mainly because of how the body is affected by the intercity and prevalence of infections caused microbiological agents (133, 134). Further, the multivariable model with "number of close contacts" as outcome showed that both age and sex were associated to the outcome, which was not seen in the univariate model. The inclusion of outcome variables from other analyses in the multivariable model was to explore potential confounding effects between the different stages of contact tracing. It is well-established that certain variables can act as confounders and we tried to adjust for those know, but residual confounding could still be presented (135).

4.5 Limitations and Implications

Despite the insights gained, this study has limitations, including its retrospective nature and potential unaccounted-for external influences on contact tracing outcomes. In this study we did not have any personal information on the close contacts, which limited the study's capacity to determine if the right close contacts were found and treated. This is also the reason why this study focused on the TB patients' characteristics influence on contact tracing yield and whether the patient had close contacts in the different stages of contact tracing. Further,

this study could not account for marginalized factors, time-to and grade of exposure variables that could have influenced the contact tracing outcomes.

During data cleaning, we observed discrepancies in the number of close contacts per observation. Some TB patients had more IGRA-positive contacts than IGRA-tested close contacts, suggesting potential issues in data recording. In some cases, the values were also missing for certain variables, making it hard to distinguish between true missing values and zero. These discrepancies can have different origins, where one reason could be the way contact tracing information is collected. The municipal medical officer in the index TB patient's municipality of residence is responsible for carrying out contact tracing and must compile all the results after completion of contact tracing including gathering information from other municipalities, health trusts, asylum centres, and similar institutions. In some cases, this results in a very long time prior to sending the results to MSIS through the contact tracing forms. In addition, the forms have boxes where you can both fill in the number of close contacts that fit different categories in the stages as also the total per stage (Appendix X). A summary of the findings and results from treatment must be submitted to MSIS using the contact tracing form. Therefore, another possible reason for discrepancies in the numbers could be caused by the format of the contact tracing form. If there were zero registrations in one specific contact group, the person responsible for the trace may have only filled out the total box and left the box for the specific group empty, or vice versa. As of 2023 the contact tracing forms must be manually filled in either in PDF document or by hand before submitting it to MSIS. In the PDF-programme the total boxes will be filled in automatically, but not if submitted by hand. Further, there is a possibility for the people filling in the form to just fill in the total number and not the different categories and the opposite. Further, the data from the contact tracing forms is manually put into MSIS.

The discrepancies mentioned above could introduce uncertainty into our results and conclusions, highlighting the need for cautious interpretation. The study's findings are specific to the period and geographic location under investigation. The limited scope of our study may restrict the generalizability of our results to different populations or regions with distinct characteristics.

However, our findings provide valuable information for optimizing TB control efforts. The associations between demographic, medical, and contact tracing characteristics offer opportunities for targeted interventions. A key strength of this study lies in its use of

multivariable analysis. By accounting for potential confounding factors and exploring interactions among variables, the findings presented a nuanced understanding of the relationship between the TB patients characteristics and the contact tracing outcomes. Further, a wide range of demographic, medical, and environmental characteristics was used, providing a holistic view of the contact tracing process. By addressing the potential discrepancies transparently, this study ensures that the potential impact on our findings is recognized and considered.

5 Conclusion

In conclusion, our study revealed a relatively high contact tracing rate (91.6%) among infectious pulmonary TB patients above 15 years of age, indicating a strong adherence to legal requirements and recommendations. However, a lower contact tracing rate (66.2%) among paediatric TB patients underscores the need for targeted strategies to ensure comprehensive follow-up for this vulnerable group. Addressing preventive treatment for positively tested contacts remains suboptimal, even after accounting for influencing factors. This highlights the necessity for more precise guidelines on reporting contact tracing involving children, IGRA-test utilization, and provision of preventive treatment. The contacts vulnerability and exposure level were found to influence the success of contact tracing efforts,

Our findings emphasize that contact tracing success is influenced by the contacts vulnerability and exposure level, and the TB patients age, gender, geography, foreign background, period lived in Norway, and infectiousness, which is consistence with the guidelines. Accurate data recording and reporting are crucial to address challenges and ensure reliable information. Digital data collection mechanisms are warranted to rectify disparities in close contact counts.

The link between infectiousness and contact tracing outcomes underscores the importance of precise assessment before and during contact tracing. Future research should target specific aspects, such as paediatric TB challenges, regional disparities, and the reasons behind age and gender differences. Additionally, research that examines long-term follow-up and treatment outcomes for contacts can contribute to refining preventive treatment strategies and ensuring successful treatment completion.

By addressing the identified gaps and building upon the study's insights, public health authorities can optimize contact tracing practices, minimize disparities, and contribute to the overall reduction of TB transmission and incidence. In addition to its local implications, our study holds potential for significant global impact. By shedding light on the challenges and successes of TB contact tracing, our findings offer valuable insights that can inform not only Norway's efforts but also those of other countries striving to eliminate tuberculosis.

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Appendices

Appendix 1: Illustration of medical, treatment and contact tracing reports sent to MSIS (Illustrations in Norwegian).

Appendix 2: Variable dictionary.

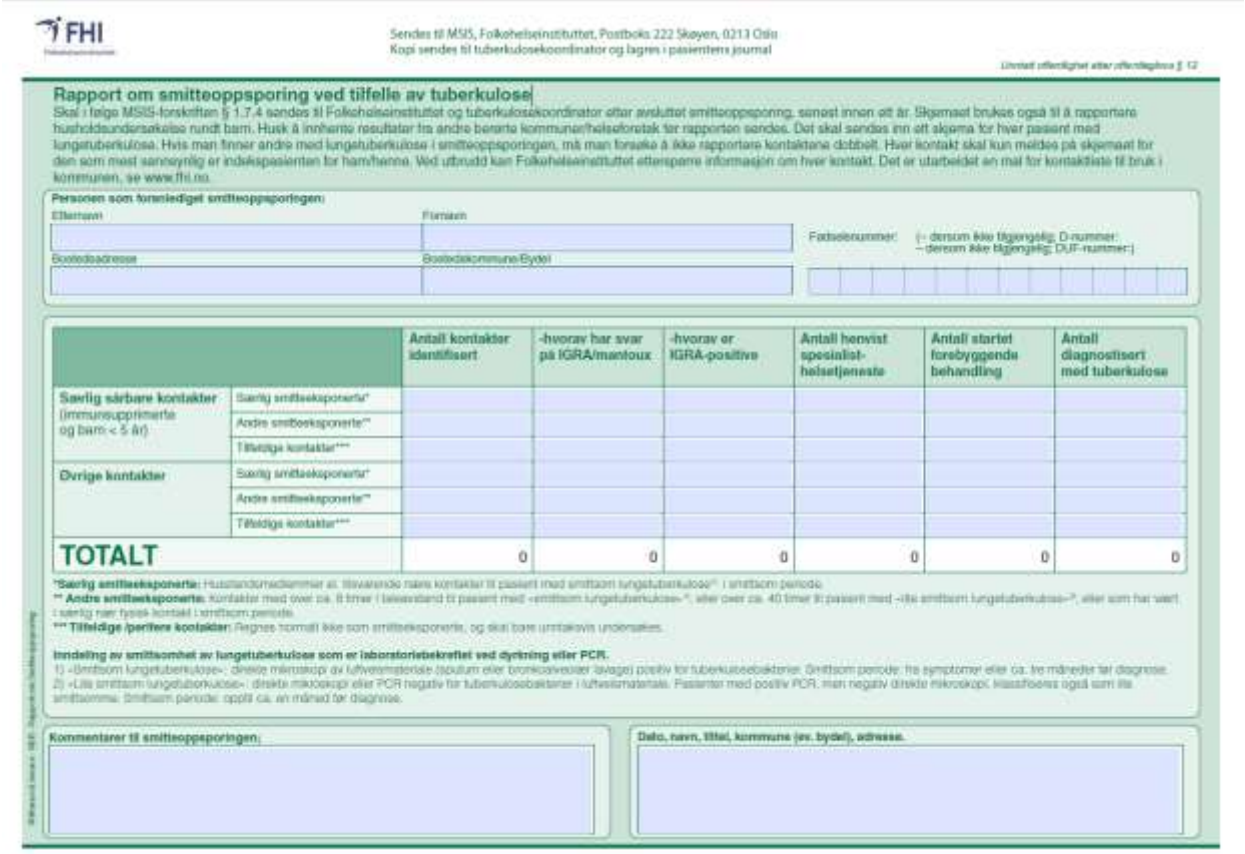
Appendix 3: Letter from the Regional Committee for Medical Research Ethics (REK) regarding application number 536821 (Text in Norwegian).

Appendix 4: Decision regarding exemption from confidentiality obligation and accessibility of health information regarding reference number H-191 (Text in Norwegian).

Appendix 5: Tables of all uni- and multivariable analysis done for answering study question 2a & 2b, and tables of all statistically significant univariable analysis of study questions 2f and 2e.

Illustration of medical, treatment and contact tracing reports that is sent in to MSIS.

Here the close contacting form submitted from the municipalities after they finalize the contact tracing is illustrated, together with the medical report and treatment report that is submitted by clinicians to MSIS. To access original documents please refer to NIPH websites.



FHI

Sendes til MSIS, Folkehelseinstituttet, Postboks 222 Skøyen, 0213 Oslo
Kopi sendes til tuberkulosekoordinator og lagres i pasientens journal

Unntatt offentlighet etter offentlighetsloven § 13

Rapport om smitteoppsporing ved tilfelle av tuberkulose

Skal i følge MSIS-forskriften § 1.7.4 sendes til Folkehelseinstituttet og tuberkulosekoordinator ofte avsluttet smitteoppsporing, senest innen ett år. Skjemaet brukes også til å rapportere husholdsundersøkelse rundt barn. Husk å innhente resultater fra andre berørte kommuner/helseforetak før rapporten sendes. Det skal sendes inn ett skjema for hver pasient med lungetuberkulose. Hvis man finner andre med lungetuberkulose i smitteoppsporingen, må man forsøke å ikke rapportere kontaktene dobbelt. Hvor kontakt skal kun meldes på skjemaet for den som mest sannsynlig er indekspasienten for hans/henne. Ved utbrudd kan Folkehelseinstituttet etterspørre informasjon om hver kontakt. Det er utarbeidet en mal for kontaktliste til bruk i kommunen, se www.fhi.no.

Personen som forestår smitteoppsporingen:

Etternavn | Fornavn | Fødselsnummer: (= dersom ikke tilgjengelig; D-nummer: = dersom ikke tilgjengelig; DUF-nummer:)

Bostedsadresse | Bostedskommune/-Bydel

		Antall kontakter identifisert	-hvorav har svar på IGRA/mantoux	-hvorav er IGRA-positive	Antall henvist spesialist-helsetjeneste	Antall startet forebyggende behandling	Antall diagnostisert med tuberkulose
Særlig sårbare kontakter (immunsupprimerte og barn < 5 år)	Særlig smitteeksponerte*						
	Andre smitteeksponerte**						
	Tilfeldige kontakter***						
Øvrige kontakter	Særlig smitteeksponerte*						
	Andre smitteeksponerte**						
	Tilfeldige kontakter***						
TOTALT		0	0	0	0	0	0

***Særlig smitteeksponerte:** Husstandsmedlemmer el. tilsvarende nære kontakter til pasient med smittsom lungetuberkulose[1] i smittsom periode.
****Andre smitteeksponerte:** Kontakter med over ca. 8 timer i tilsvarende til pasient med «smittsom lungetuberkulose», eller over ca. 40 timer til pasient med «lite smittsom lungetuberkulose», eller som har vært i særlig nær fysisk kontakt i smittsom periode.
*****Tilfeldige /perifere kontakter:** Regnes normalt ikke som smitteeksponerte, og skal bare unntaksvis undersøkes.

Inndeling av smittsomhet av lungetuberkulose som er laboratoriebekreftet ved dyrkning eller PCR.
1) «Smittsom lungetuberkulose»: direkte mikroskopi av luftveismateriale (sputum eller bronkialvesker /lavage) positiv for tuberkulosebakterier. Smittsom periode: fra symptomer eller ca. fire måneder før diagnose.
2) «Lite smittsom lungetuberkulose»: direkte mikroskopi eller PCR negativ for tuberkulosebakterier i luftveismaterialet. Pasienter med positiv PCR, men negativ direkte mikroskopi, klassifiseres også som lite smittsomme. Smittsom periode: opptil ca. en måned før diagnose.

Kommentarer til smitteoppsporingen:

Dato, navn, tittel, kommune (ev. bydel), adresse.

FHI
Folkehelseinstituttet

Sendes til MSIS, Folkehelseinstituttet, Postboks 222 Skøyen, 0213 Oslo
Kopi sendes til tuberkulosekoordinator, kommuneoverlegen og ev. bydelsoverlegen der pasienten bor
Lagres i pasientens journal

Unntatt offentlighet etter offentleglova § 13

MSIS-melding om: ☐ Tuberkulosesykdom ☐ Forebyggende behandling for latent tuberkulose

Personopplysninger

Etternavn

Fornavn

Fødselsnummer | Evt. D-nummer/DUF.nr.

Adresse

Mann ☐ Kvinne ☐ Yrke

Arbeidsplass/skole/barnehage

Bokommune/bydel | Fødeland

Mors fødeland | Fars fødeland

For utenlandsfødte

Dato for ankomst til Norge Dag ☐☐ Md. ☐☐ År ☐☐☐☐

Botid i Norge

Årsak til opphold i Norge:

- ☐ Asylsøker/flyktning
- ☐ Familiegjenforening
- ☐ Adopsjon
- ☐ Arbeidsinnvandring
- ☐ Annet midlertidig opphold
- ☐ Midl. opphold (< 3 md)
- ☐ Annet

For norskfødte

Lengre opphold (> 3 md) i land med høy forekomst av TB?

☐ Nei ☐ Ja, land

Årsak til tuberkuloseundersøkelsen (Flere kryss er mulig)

- ☐ Ankomstscreening
- ☐ Immunsvekkende tilstand/behandling
- ☐ Arbeid med pasienter eller barn
- ☐ Symptomer/tegn fra ☐☐ md ☐☐ år
- ☐ Obduksjon, dødsdato
- ☐ Smitteoppsporing rundt følgende pasient:

(skal ikke utleveres til pasienten)

Navn

Personnummer

☐ Annet

Fritekst

Grunnlag for oppstart av behandling

Hvis flere mate ialer er undersøkt med samme metode, før inn kun positivt svar. Bruk evt. fritekstfeltet.

	Pos	Neg	Ikke undersøkt	Prøvemateriale/funn, evt. "inkonklusiv", "usikker" el. "avventer"
IGRA (QFT/T-spot)	☐	☐	☐	titer
Mantoux-test	☐	☐	☐	mm
Mikroskopi luftveismat.	☐	☐	☐	funn
Direkte PCR	☐	☐	☐	mat.
Dyrking	☐	☐	☐	mat.
Histologi	☐	☐	☐	mat.
CT	☐	☐	☐	funn
Lungerøntgen	☐	☐	☐	funn
TB-symptomer	☐	☐	☐	
Sikker eksponering	☐	☐	☐	
Hiv-status	☐	☐	☐	

☐ Annen immunsvekkelse

☐ Annet

BCG-vaksinert

☐ Ja ☐ Nei ☐ Ukjent

(Hvis arr eller dokumentasjon krysses av som "Ja")

Dato for behandlingsstart: Dag ☐☐ Md. ☐☐ År ☐☐☐☐

Behandlingskombinasjon ved oppstart:

- ☐ Isoniazid + Rifampicin i 3 md. (latent TB)
- ☐ Isoniazid + Rifapentine i 12 ukentlige doser (latent TB)
- ☐ Isoniazid i 6 md. (latent TB)
- ☐ Isoniazid + Rifampicin + Pyrazinamid + Etambutol
- ☐ Annen:

Kun for tuberkulosesykdom

Kategori

- ☐ Tuberkulose for første gang
- ☐ Tuberkulose for første gang, tidligere forebyggende behandling
- ☐ Tidligere tuberkulose, ikke medikamentelt behandlet
- ☐ Tidligere tuberkulose, medikamentelt behandlet
- ☐ Tilflyttet under pågående behandling for tuberkulose
- ☐ Usikker

Organ(er) rammet

- ☐ Lunge
- ☐ Pleura
- ☐ Columna/ben/ledd
- ☐ Buk/tarm
- ☐ Uro-genital
- ☐ Lymfe/hilusglandler
- ☐ Meninger/CNS
- ☐ Miliær/disseminert
- ☐ Annet:

Melders navn, adresse og telefonnummer

Navn: Telefon:

Sykehus: Avdeling:

Dato: Signatur:

Wiltsuten & Jensen - 837427 - Endret 07.18

Fastsatt av Helse- og omsorgsdepartementet desember 2013. NB! Husk gjennomskrift. Bruk kulepenn og skriv hardt.

FHI

Sendes til MSIS, Folkehelseinstituttet, Postboks 222 Skøyen, 0213 Oslo
Kopi sendes til tuberkulosekoordinator, kommuneoverlegen og ev. bydelsoverlegen der pasienten bor
Lagres i pasientens journal

Unntatt offentlighet etter offentleglova § 13

MSIS-melding: Behandlingsresultat tuberkulose

Personopplysninger

Etternavn | Fornavn | Fødselsnummer/ Evt. D-nummer/DUF.nr.

Adresse | Bokommune/-bydel

Siste behandlingsdag (dato)

Behandlingskombinasjon i fortsettelsesfasen av behandlingen:

☐ Rifampicin og isoniazid ☐ Annet, spesifiser:

Resultat av behandlingen

(Kryss bare av for det som beskriver første hendelse. Ved behandlingsavbrudd over 2 måneder, se E)

☐ **A. Fullført behandling med negativ dyrkning.** Pasient med dyrkningspositiv lungetuberkulose som har fullført behandlingen, med negativ dyrkning av prøver tatt ved avsluttet behandling og ved minst ett tidligere tidspunkt. Definert som «helbredet» i WHO's statistikk.

☐ **B. Fullført behandling uten negativ dyrkning.** Pasient med tuberkulose som har fullført behandlingen, men som ikke fyller kriteriene for punkt A. (Summen av A og B utgjør «Vellykket behandling» i nasjonal og WHO-statistikk.

☐ **C. Død før eller under behandling.** Død dato:

Dødsårsak: ☐ **Tuberkulose** ☐ **TB medvirkende** ☐ **Annen årsak** ☐ **Ukjent årsak**

☐ **D. Avsluttet på grunn av bivirkninger.**

☐ **E. Forsvunnet fra behandling eller avbrutt av annen årsak.** Pasient som er forsvunnet fra behandling i 2 måneder eller mer. Hvis pasienten kommer tilbake og fullfører behandlingen, vil resultatet fortsatt være «forsvunnet». Dersom ny behandling startes opp, skal det meldes til MSIS som nytt tuberkulose-tilfelle i kategorien "Tidligere tuberkulose, medikamentelt behandlet".

☐ **F. Pasienten flyttet ut av landet før avsluttet behandling.**

Reist ut av landet: ☐ **Reist frivillig** ☐ **Bortvist fra landet**

Dato for flytting: | Hvor: | Oppfølgingsansvar overført til:

☐ **G. Fortsatt under behandling.** Pasienten er fortsatt under behandling på grunn av behandlingsavbrudd, resistens eller annen årsak.

Angi årsak: | Behandling forventes avsluttet dato:

☐ **H. Feil diagnose. Tuberkulosediagnosen er avkreftet.**

☐ **I. Annet, spesifiser:**

Utfyllende opplysninger:

Melders navn | adresse

Sted/ Dato | tlf. | Underskrift

Wittusen & Jensen - MSIS-melding: Behandlingsresultat tuberkulose - 08.17

Fastsatt av Helse- og omsorgsdepartementet august 2017.

Variable dictionary

Here all the variables that was included in the study "Does tuberculosis contact tracing work as intended in Norway? A retrospective register-based cohort study of tuberculosis patients and contact tracing data from 2016 to 2021." are presented. The table gives information on what the variables are used as, in addition to the definition and content. Some of the variables that are listed are the original variables in MSIS, where some have been further used to make new variables to serve the study questions.

Variable	Value (coding)[?]		Description[!]	Definition
Id	10001-20070	Numeric	Original MSIS variable	Individual specific running number giving each patient a unique observation.
Number of registrations	1-2	Numeric	Used for inclusion process.	Showing the number of registrations, a patient had in the years between 2016-2021. Based on the variable "Id".
Age	0-96	Numeric	Original MSIS variable	Calculated through test date/registration date minus birthdate.
Age group 1	<= 15 16-30 >31	Categorical	Independent variable in all analysis except for answering study question 2a.	Grouped the variable Age into three different age groups.
Age group 2	<= 15 16-30 31-60 > 60	Categorical	Independent variable in study question 2a.	Grouped the variable Age into four different age groups.
Sex	1 = female 2 = male	Categorical	Independent variable	The patients genetical sex.
Pulmonary TB	0 = No 1 = Yes	Categorical	Independent variable	If a TB patient has pulmonary TB defined as having lung as affected organ.

TB category (original)	a: TB first time, previously received preventive treatment. b: Previous TB with chemotherapy. c: Previous Tb not treated d: TB first time e: TB unsure category	Categorical	Original MSIS variable	Variable indication if a patient had tuberculosis for the first time or had prior tuberculosis.
TB category (used for analysis)	1 = First time 2 = Previous TB 3 = Unsure category	Categorical	Independent variable	Made from the original "TB category" variable where the value 1 = a & d, the value 2 = b & c, the value 3 = e
Contact tracing	0 = No 1 = Yes	Categorical	Independent variable	If a TB patient was registered to have a contact tracing
Exposure	1 = No 2 = Yes 3 = Not examined	Categorical	Independent variable	If a Tb patient has known exposure to someone effected with TB. Original MSIS variable used.
Indication for examination (original)	A: other indication, B: working with patients or children, C: Immunosuppressed, D: autopsied, E: routine investigation of immigrant, F: Routine investigation, not specified, G: routine investigation for hospital stay, H: contact tracing, I: Symptoms and signs, J: random find.	Categorical	Original MSIS variable	The indication or reason why the TB patient was examined at the hospital.

Indication for examination	1 = Symptoms and signs 2 = Other 3 = Immunodeficiency 4 =Contact tracing 5 = Routine investigation of immigrant		Independent variable	Made from the original Indication for examination variable. 1 = I 2 = A, B, D, F, G & J 3 = C 4 = E
Organ	47 unique values	String	Original MSIS variable	What organ(s) that was affected by TB disease.
Organ other	28 unique values	String	Original MSIS variable	Free text variable to fill in if the organ was other then what was presented in the patient form.
Subtype (original)	A: africum, M. B: Bovis, M. C: M tub complex D: Tuberculosis, M.	String	Original MSIS variable	If the TB disease was caused by a specific subtype of M.tb.
Subtype (for analysis)	1: Tuberculosis, M. 0 = other subtypes	Categorical	Independent variable	Made from the original subtype variable. Where A, B and C = 0, and D = 1.
Treatment result[!]	11 unique values	String	Original MSIS variable	What kind of treatment outcome the TB patient had. Firstly, if the patient finished treatment, and different reasons why the patient did not finish treatment. Some values indicating reasons for the TB patient passing, or if the patient was still under treatment.
Rifampicin resistance	I: sensitive. II: reduced sensitivity (low-grade resistance), III: resistance	Categorical	Original MSIS variable	The results from test showing if the TB patient has TB bacteria that is resistant to the drug rifampicin
Isoniazid resistance	a: sensitive. b: not examined, c: reduced sensitivity (low-grade resistance), d: resistance	Categorical	Original MSIS variable	The results from test showing if the TB patient has TB bacteria that is resistant to the drug isoniazid
MDR-TB	0= No 1 = Yes	Categorical	Independent variable	Made from the variables “Rifampicin resistance” “Isoniazid resistance”.

				0 = 1, a & b. 1 = II, III, c & d.
Time of registration	01.01.2016-31-01.2021	Numeric	Original MSIS variable	Date the MSIS from is filled out with patient information.
Diagnosis	Active TB disease	String	Original MSIS variable	Variable indication what diagnosis a patient has in MSIS.
VNTR 1	541 unique values	String	Original MSIS variable	Variable number tandem repeats (VNTRs) are short nucleotide sequences (20–100 bp). This variable was used prior to 2019 in MSIS.
VNTR 2	19 unique values	String	Original MSIS variable	VNTR number used after 2019 in MSIS.
WGS number	37 unique values	String	Original MSIS variable	A whole genome sequencing number that refers to a special group of M.TB with under 5 bp apart.
Outbreak number (original)	32 unique values	String	Original MSIS variable	An internal outbreak number used by the laboratory prior to 2019.
Outbreak number (used for analysis)	0= No 1 = Yes	Categorical	Independent variable	The variable was med using the variables “VNTR 1”, “VNTR 2”, WGS number” and “outbreak number”. The value = 1 if any of the mentioned variables above was not empty. The value = 0 if all the variables mentioned where empty.
Workplace	I: Other, II: Kindergarten, III: primary and secondary school, IV: health institution other, V: university, VI: nursing home, VII: hospital.	String	Original MSIS variable	Registration of where the patient worked. The categories are based on those most at risk for infection. The alternative òther` indicate workplaces not at risk.
Profession	a: Other, b: Au pair, c: children in kindergarten, d: kindergarten personnel, e: healthcare personnel, f: food personnel, g: transport personnel, h:	String	Original MSIS variable	Registration of the patients work professions. The categories are based on those most at risk for infection. The alternative òther` indicate professions not at risk.

	students, i: unknown and j: teaching personnel.			
At-risk workplace	1 = Unknown/not at-risk 2 = Other at-risk 3 = Education 4 = Healthcare	Categorical	Independent variable	Patients registered under the variables “Workplace” and Profession” was grouped to make one variable. 1 = I & A, i. 2 = B, F, G. 3 = II, III, V, c, d, h & j. 4 = IV, VI, VII, e. *No values had contradicting meaning.
Municipality	322 unique values	String	Original MSIS variable	The municipality the TB patient lived in at the time of registration.
Municipality number	0101-5444	Numeric	Original MSIS variable	The municipality number of the municipality the TB patient lived in at the time of registration.
Municipality size	1 = <100 000 2 = 20 000-100 000 3 = 0-19 999	Categorical	Independent variable	Population data from SSB (99) was used to find the population that lived in the different municipalities. The population sizes were made into categories based on median and interquartile range of the municipalities in the dataset.
County	27 unique values	String	Original MSIS variable	The county the TB patient lived in at the time of registration.
County number	01-54	Numeric	Original MSIS variable	The county number of the county the TB patient lived in at the time of registration.
Hospital region	1 = South-eastern health region 2 = Central Norway 3 = Northern health region 4 = Western health region	Categorical	Independent variable	The variable “county” is used to make health regions based on the list of counties included in the different health regions provided on the Norwegian governments website (100).
Foreign born	Central Norway	Categorical	Independent variable	
Country of birth	Northern	String	Original MSIS variable	The country where the TB patient was born.
Fathers’ country of birth	Western	String	Original MSIS variable	The country where the father of the TB patient was born.

Mothers' country of birth	68 unique values	String	Original MSIS variable	The country where the mother of the TB patient was born.
Parents foreign born	0 = none 1 = one or both parents	Categorical	Independent variable	If one or both parents have country of birth other, then Norway the value = 1. In both parents is born in Norway the value = 0. (Variables used: Fathers and mothers' country of birth)
High incidence country <3 months	0 = No 1 = Yes	Categorical	Independent variable	If a Tb patient have been to a high incidence country for over three months.
High incidence country[l]	18 unique variables	String	Original MSIS variable	Indicating what high incidence country, the TB patient had been to. The Tb patient had to have been there for over three months.
Reason for residence	11 unique values: a: adopted, b:other, c: work immigrant, d: asylum seeker, e: family reunion, f: immigrant, g: temporary residence (<3 moths), h: Norwegian, i: Norwegian born with foreign born parents, j: unknown, k: Foreign-born with temporary residence.	String	Original MSIS variable	The reason for residence in Norway with different categories indication why residing in Norway.
Immigration status	1 = Norwegian 2 = Other 3 = Work immigrant 4 = immigrant or asylum seeker	Categorical	Independent	Made by using the variable "reason for residence". What the values includes is listed under: 1 = h & i, 2 = a, b, e, g, j & k 3 = c, 4 = d & f.
Date of passing[l]	33 unique values	Date	Original MSIS variable	The registered date of passing provided by medical personnel.
Deceased	0 = No 1 = Yes	Categorical	Independent variable	The variable "date of passing" was used to make this variable. 0= If the value was missing and 1 = if there was a date of passing.

Period lived in Norway (original)	A: 1-2 years b: 1-5 months c: >= 10 years d: 3-4 years e: 5-9 years f: 6-11 months g: unknown h: <1 month	Categorical	Original MSIS variable	The variable indicates how long the patient had lived in Norway. Only applicable for not Norwegian born patients.
Period lived in Norway (used for analysis)	1 = Norwegian 2 = Under 1 year 3 = 1-4 years 4 = 5-9 years 5= 10 + years 6 = Unknown	Categorical	Independent variable	Was made using the original variable “period lived in Norway” and the variable “country of birth”. 1= if country of birth was Norway. 2 = b, f & h 3 = a & d 4 = e 5 = c 6 = g & if not born in Norway.
Contact traced	Yes = 1 No = 0		Dependent variable	If the TB patient is registered with contact tracing and contact tracing information is available.
IGRA-test (original)	a: threshold value, b: not examined, c: inconclusive, d: negative, e: positive	Categorical	Original MSIS variable	Results from Interferon-gamma Release Assays (IGRA) test.
IGRA-test (used for analysis)	1 = Positive 0 = negative	Categorical	Independent variable	Made from the original IGRA-test variable, where the value 0 = b, c & d, and 1 = a & e.
CT scan (original)	a: not examined, b: negative, c: positive from cavern, d: positive other	Categorical	Original MSIS variable	Results from Computed Tomography (CT).

CT scan (used for analysis)	1 = positive 0 = negative	Categorical	Independent variable	Made from the original CT variable, where value 0 = a & b, and 1 = c & d.
Culture result[l]	Positive, Negative, Not examined	Categorical	Original MSIS variable	
Culture material	36 unique values	String	Original MSIS variable	Indicating what type of material was used for laboratory testing. Culture is a test that examines different tissue for bacteria and other organisms.
Direct microscopy	Positive, Negative, Not examined	Categorical	Original MSIS variable	Test results from a microscopy test prior to 2019.
Direct microscopy (2)	Positive, Negative, Not examined	Categorical	Original MSIS variable	Test results from a microscopy test from 2019.
Culture from airways	0 = No 1 = Yes	Categorical	Independent variable	Positive cultivation result of lung biopsy. Made from the variable "culture material" and "culture result". If culture result = positive and culture material included materials from lung, the value = 1.
Direct microscopy material[l]	10 unique values	String	Original MSIS variable	Indicating what type of material (tissue) was used for the microscopy test.
Positive test from respiratory	0 = No 1 = Yes	Categorical	Independent variable	Made by the variables: "Direct microscopy material", Direct microscopy" (1 & 2) and culture from airways. The value is 1 if the culture is from the respiratory system and have a positive result eighter from microscopy result and material or culture result and material. The value is 0 for all other combinations.
Immunosuppressed	0 = No 1 = Yes	Categorical	Independent variable	The variable was made specifically from MSIS to be part of this analysis. The value = 1 if the TB patient is HIV positive, registered as immunodeficient, have a type of immunosuppressive state, or have event type as immunosuppressed. The value = 0 if the TB patient have none of the four above. Figure 1 gives an illustration of the process.
Tb patients total close contacts	0-253	Numeric	Dependent variable	The total number of close contacts the TB patient is registered with. Made from summarizing all the variables: total vulnerable

				and particularly exposed, total of vulnerable and other exposed, total of vulnerable and random exposed, total of regular and particularly exposed, total of regular and other exposed and regular and random exposed.
A TB patients total close contacts (grouped)	0-2 3-7 8-20 >=21	Categorical	Dependent and independent variable	Used the variable "total close contacts" to group the close contacts into four groups based on inter quartile range and what is recommended (84).
Vulnerable and particularly exposed	0-22	Numeric	Original MSIS variable	A TB patients total close contacts that is categorized as vulnerable and particularly exposed to infection.
Vulnerable and particularly exposed IGRA tested CC	0-22	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized vulnerable and particularly exposed to infection.
Vulnerable and particularly exposed IGRA positive CC	0-6	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized vulnerable and particularly exposed to infection.
Vulnerable and particularly exposed CC referred to SHS	0-19	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized vulnerable and particularly exposed to infection.
Vulnerable and particularly exposed CC receiving preventive treatment	0-7	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized vulnerable and particularly exposed to infection.
Vulnerable and particularly exposed CC receiving TB diagnosis	0-2	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized vulnerable and particularly exposed to infection.
Vulnerable and other exposed	0-103	Numeric	Original MSIS variable	A TB patients total contacts that is categorized as vulnerable and being
Vulnerable and other exposed IGRA tested CC	0-77	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized as other exposed (friends, colleges and so on)
Vulnerable and other exposed IGRA positive CC	0-4	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized as other exposed (friends, colleges and so on)

Vulnerable and other exposed CC referred to SHS	0-52	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized as other exposed (friends, colleges and so on)
Vulnerable and other exposed CC receiving preventive treatment	0-8	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized as other exposed (friends, colleges and so on)
Vulnerable and other exposed CC receiving TB diagnosis	0-1	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized as other exposed (friends, colleges and so on)
Vulnerable and random exposed	0-4	Numeric	Original MSIS variable	A TB patients total close contacts that is categorized as vulnerable and not particularly exposed to infection.
Vulnerable and random exposed IGRA tested CC	0-4	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized vulnerable and not particularly exposed to infection.
Vulnerable and random exposed IGRA positive CC	0	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized vulnerable and not particularly exposed to infection.
Vulnerable and random exposed CC referred to SHS	0-1	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized vulnerable and not particularly exposed to infection.
Vulnerable and random exposed CC receiving preventive treatment	0	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized vulnerable and not particularly exposed to infection.
Vulnerable and random exposed CC receiving TB diagnosis	0-1	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized vulnerable and not particularly exposed to infection.
Regular and particularly exposed	0-28	Numeric	Original MSIS variable	A TB patients total close contacts that is categorized as not vulnerable but particularly exposed to infection.
Regular and particularly exposed IGRA tested CC	0-28	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized as not vulnerable but particularly exposed to infection.

Regular and particularly exposed IGRA positive CC	0-12	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized as not vulnerable but particularly exposed to infection.
Regular and particularly exposed CC referred to SHS	0-16	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized as not vulnerable but particularly exposed to infection.
Regular and particularly exposed CC receiving preventive treatment	0-8	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized as not vulnerable but particularly exposed to infection.
Regular and particularly exposed CC receiving TB diagnosis	0-5	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized as not vulnerable but particularly exposed to infection.
Regular and other exposed	0-253	Numeric	Original MSIS variable	A TB patients total close contacts that is categorized as
Regular and other exposed IGRA tested CC	0-217	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized
Regular and other exposed IGRA positive CC	0-26	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized
Regular and other exposed CC referred to SHS	0-26	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized
Regular and other exposed CC receiving preventive treatment	0-18	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized
Regular and other exposed CC receiving TB diagnosis	**0-3**	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized
Regular and random exposed	**0-69**	Numeric	Original MSIS variable	A TB patients total close contacts that is categorized as not vulnerable and not particularly exposed to infection.
Regular and random exposed IGRA tested CC	**0-46**	Numeric	Original MSIS variable	A TB patient total IGRA tested close contacts that is categorized as not vulnerable and not particularly exposed to infection.

Regular and random exposed IGRA positive CC	0-16	Numeric	Original MSIS variable	A TB patient total IGRA positive close contacts that is categorized as not vulnerable and not particularly exposed to infection.
Regular and random exposed CC referred to SHS	**0-16**	Numeric	Original MSIS variable	A TB patients total close contacts that have been referred to special health care services and that is categorized as not vulnerable and not particularly exposed to infection.
Regular and random exposed CC receiving preventive treatment	0-4	Numeric	Original MSIS variable	A TB patients total close contacts that have received and finished preventive treatment and is categorized as not vulnerable and not particularly exposed to infection.
Regular and random exposed CC receiving TB diagnosis	0-2	Numeric	Original MSIS variable	A TB patients total close contacts that have received a TB diagnosis and is categorized as not vulnerable and not particularly exposed to infection.
Having IGRA tested close contacts	0 = No 1 = Yes		Independent and dependent variable	The value = 1 if a TB patient has IGRA tested close contacts, the value = 0 if the TB patient have zero IGRA tested close contacts.
Having IGRA positive close contacts	0 = No 1 = Yes		Independent and dependent variable	The value = 1 if a TB patient has IGRA positve close contacts, the value = 0 if the TB patient have zero IGRA positive close contacts.
Having close contacts referred to SHS	0 = No 1 = Yes		Independent and dependent variable	The value = 1 if a TB patient has close contacts referred to special healthcare services (SHS), the value = 0 if the TB patient have zero close contacts referred to SHS.
Close contact received treatment	0 = No 1 = Yes		Independent and dependent variable	The value = 1 if a TB patient has close contacts receiving preventive treatment of TB diagnosis (receiving treatment), the value = 0 if the TB patient have zero close contacts receiving treatment.

! For this variable the values are not provided. The reason for this is that some variables have to many values indicating free-text values or result into specific values that have under five registrations.

References:
1. SSB. 07459: Alders- og kjønnsfordeling i kommuner, fylker og hele landets befolkning (K) 1986 - 2023 Statistisk sentralbirå (SSB) [Available from: https://www.ssb.no/statbank/table/07459/.

2. Helse og omsorgsdepartementet. H-o. Oversikt over landets helseforetak regjeringen.no [updated 26.05.2021. Available from: https://www.regjeringen.no/no/tema/helse-og-omsorg/sykehus/innsikt/oversikt-over-landets-helseforetak/id485362/.

3. NIPH. Tuberkuloseveilederen. NIPH; 2022.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst B	Camilla Oppegård		16.11.2022	536821

Trude Margrete Margrete Arnesen

Prosjektsøknad: Smitteoppsporing av tuberkulose i Norge, en retrospektiv studie av registerdata og data fra helgenomsekvensering i perioden 2016 til 2021.
Søknadsnummer: 536821
Forskningsansvarlig institusjon: Folkehelseinstituttet
Samarbeidende forskningsansvarlige institusjoner: Norges teknisk-naturvitenskapelige universitet

REK avviser søknaden

Søkers beskrivelse

Formålet med denne studien er kvalitetssikring av smittesporingen rundt aktive tuberkulosetilfeller i Norge identifiserer de menneskene i samfunnet som har tuberkulose og om de mottar behandling, om smittesporingen bidrar til å stoppe spredningen av smitte, og om man får gitt de nysmittede forebyggende behandling. Dette gjennom å se på hvilke epidemiologiske likheter/forskjeller det er mellom de indekspasientene som det blir smittesporet rundt, grad av smittesporing rundt gitte pasienter, se på smittesporingsresultatene opp mot (1) klynger funnet gjennom helgenomsekvensering, og (2) meldinger om startet forebyggende behandling sendt inn til MSIS.

Populasjonen består av tuberkulosepasienter registrert i Meldingssystem for smittsomme infeksjonssykdommer (MSIS) og er basert på informasjon fra leger, laboratorier og reseptrapportering fra landets sykehusapotek. Dataene som skal tas i bruk er allerede registrert i registeret og vil ikke inneholde direkte personidentifiserbar informasjon.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst B) i møtet 26.10.2022. Vurderingen er gjort med hjemmel i helseforskningslovens § 10, jf. forskningsetikkloven § 10.

REKs vurdering

Formålet med prosjektet, slik komiteen forstår søknad og protokoll, er å kvalitetssikre smittesporingen rundt aktive tuberkulosetilfeller i Norge

Komiteen har vurdert søknaden og mener at formålet med prosjektet er utenfor helseforskningslovens virkeområde. Dette da hensikten med prosjektet er å kvalitetssikre smittesporing, og det vil dermed ikke skaffes ny kunnskap om sykdom og helse slik dette forstås iht. helseforskningsloven, jf. helseforskningsloven §§ 2 og 4 bokstav a.

Prosjektet kan gjennomføres uten godkjenning av REK innenfor de ordinære ordninger for helsetjenesten med hensyn til for eksempel regler for taushetsplikt og personvern. Søker bør derfor ta kontakt med enten forskerstøtteavdeling eller personvernombud for å avklare hvilke retningslinjer som er gjeldende.

Komiteen gjør oppmerksom på at det faktum at et prosjekt blir vurdert av REK til å være utenfor helseforskningslovens virkeområde ikke er til hinder for at resultater fra prosjektet kan publiseres.

Vedtak

Prosjektet faller utenfor helseforskningslovens virkeområde, jf. §§ 2 og 4 bokstav a. Det kreves ikke godkjenning fra REK for å gjennomføre prosjektet.

Det er institusjonens ansvar å sørge for at prosjektet gjennomføres på en forsvarlig måte med hensyn til for eksempel regler for taushetsplikt og personvern.

Komiteens avgjørelse var enstemmig.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Ragnhild Emblem
Professor, dr. med.
Leder REK sør-øst B

Marianne Bjørnerem
Rådgiver, REK sør-øst

Kopi til:

Folkehelseinstituttet
Norges teknisk-naturvitenskapelige universitet

Direktoratet for e-helse

Norges Teknisk-naturvitenskapelige universitet (NTNU)
Postboks 8900 Torgarden

Othelie Ree Harangen

Deres ref.:

Vår ref.: H-191
Saksbehandler: Unni J Trondsen
Dato: 09.05.2023

Vedtak om dispensasjon fra taushetsplikten og tilgjengeliggjøring av helseopplysninger

Direktoratet for e-helse viser til søknad mottatt den 12.04.2023 om dispensasjon fra taushetsplikten jfr. helseregisterloven § 19 e og tilgjengeliggjøring av helseopplysninger jfr. helseregisterloven § 19 a. I søknaden er det opplyst at NTNU ved prosjektleder Othelie Ree Harangen søker om helseopplysninger til prosjektet «Does tuberculosis contact tracing work as intended in Norway, a retrospective study of tuberculosis patients and contact tracing data from 2016 to 2021». Søker er Othelie Ree Harangen. Dataansvarlig er Folkehelseinstituttet ved øverste leder.

Direktoratet for e-helse har myndighet til å fatte vedtak om dispensasjon fra taushetsplikten og tilgjengeliggjøring av helseopplysninger jfr. forskrift om nasjonal løsning for tilgjengeliggjøring av helsedata §§ 4 og 7. Forskriften er fastsatt med hjemmel i helsepersonelloven § 29 sjette ledd og helseregisterloven § 19 e femte ledd og § 20.

Informasjon om prosjektet

Prosjektet er et samarbeid mellom FHI og NTNU. Hoveddelen av arbeidet og analysene skal gjøres av en masterstudent på NTNU. De analyser som ikke blir en del av masteroppgaven vil en ansatt fra FHI utføre. FHI har løpende ansvar for tuberkulosekontrollen i Norge. Dette prosjektet er satt opp for å se om det er deler av denne kontrollen som burde endres eller oppdateres til å være mer effektiv og samfunnsnyttig.

Formålet med denne studien er kvalitetssikring av smittesporingen rundt aktive tuberkulosetilfeller i Norge, om smittesporingen identifiserer de menneskene i samfunnet som har tuberkulose og om de mottar behandling, om smittesporingen bidrar til å stoppe spredningen av smitte, og om man får gitt de nysmittede forebyggende behandling.

Prosjektet skal bruke opplysningene til helseanalyse, kvalitetsforbedring, planlegging, styring og beredskap i helse- og omsorgsforvaltningen og helse- og omsorgstjenesten.

Det er fremlagt følgende dokumentasjon:

- REK-vedtak av 16.11.2022 med referanse 536821: Prosjektet kan gjennomføres uten godkjenning av REK, da det ikke er medisinsk eller helsefaglig forskning
- Forskningsprotokoll
- Masteravtale/Hovedoppgaveavtale
- Variabelliste

Behandlingsgrunnlag

Søker legger til grunn følgende som behandlingsgrunnlag for helseopplysningene i prosjektet:

- Artikkel 6 nr. 1 bokstav e)
- Artikkel 9 nr. 2 bokstav h)
- Supplerende rettsgrunnlag: Et vedtak om dispensasjon fra taushetsplikten etter helseregisterloven § 19 e og/eller helsepersonelloven § 29 kan være et gyldig supplerende rettslig grunnlag etter personvernforordningen artikkel 6 nr. 3.

Direktoratet for e-helse sin vurdering

Helseopplysninger fra helseregistre og/eller pasientjournaler og andre behandlingsrettede helseregistre kan brukes til et uttrykkelig angitt formål som er innenfor registerets/registrenes formål til statistikk, helseanalyser, forskning, kvalitetsforbedring, planlegging, styring eller beredskap i helse- og omsorgsforvaltningen for å fremme helse, forebygge sykdom og skade og gi bedre helse- og omsorgtjenester.

Dersom helseopplysninger skal tilgjengeliggjøres til søker, må enten de registrerte ha samtykket til tilgjengeliggjøringen, tilgjengeliggjøringen omfattes av særlig unntak i lov eller det må være gitt dispensasjon fra taushetsplikten.

Direktoratet for e-helse vurderer at omsøkte behandling er innenfor formålet til registeret prosjektet skal behandle opplysninger fra jfr. Forskrift om Meldingssystem for smittsomme sykdommer (MSIS-forskriften) §§ 1-3 og 4-1.

Det søkes om dispensasjon fra taushetsplikt for prosjektets behandling. Prosjektet oppgir at samtykke er vurdert til å ikke innhentes fordi det da må innhentes personopplysninger for å finne deltagere til utvalget, og fordi utvalget er stort. Det er vurdert mest hensiktsmessig å minimere risiko for at resultatene kan være personidentifiserbare på individnivå, enn å involvere de registrerte.

Av fremlagt søknad/protokoll fremgår det at behandlingen av opplysningene er av vesentlig interesse for samfunnet fordi prosjektet kan bidra til å bedre smitteoppsporing og oppfølging av ulike undergrupper med demografiske likheter.

Søkers beskrivelse: I Norge kan smitteoppsporingen bidra til å stoppe smittespredning på samfunnsnivå. Studien kan bidra til å finne mulige behov for forbedringer rundt smittesporingsarbeidet. Resultatene kan bidra til å se hvor det er behov for mer eller mindre ressurser i spesifikke deler av tuberkuloseomsorgen, samt se hvilke aspekter av smitteoppsporingene som fungerer optimalt og ikke. På et internasjonalt nivå kan resultatene fra studien gi litteraturbakgrunn om smitteoppsporing når andre land skal sette opp eller forbedre sin tuberkulosekontroll.

Ulempen/risikoen for pasientene/personene det behandles opplysninger om vurderes å være lav.

Søker har gjort rede for hvilke tekniske og organisatoriske tiltak som skal settes i verk for å ivareta grunnleggende rettigheter og interesser til personene som skal inngå i prosjektet. Partene vil bruke TSD til å dele data, inkludert personopplysninger, relevant i prosjektet. Bruk av TSD er dekket av gjeldende databehandleravtale mellom FHI og TSD. Dataen skal lagres avidentifisert på TSD, dvs. atskilt i en nøkkel- og en opplysningsfil. Prosjektmedarbeiderne skal ikke eksportere data ut av TSD og skal sikre at data ikke brukes urettmessig eller

kommer uberettigede i hende. For å opprettholde datasikkerhet har prosjektleder og prosjektmedarbeidere tidligere signert taushetserklæring, samt samarbeidsavtale. I samarbeidsavtalen er det spesifisert dato får når dataene skal være tilgjengelige for prosjektet. Videre vil datasettet kun være tilgjengelig på TSD.

Opplysningene kan bare tilgjengeliggjøres dersom det er ubetenkelig ut fra etiske, medisinske og helsefaglige hensyn. Det er ikke funnet hensyn til hinder for tilgjengeliggjøring.

Det skal ikke tilgjengeliggjøres flere opplysninger enn det som er nødvendig for formålet. Graden av personidentifikasjon skal ikke være større enn nødvendig for det aktuelle formålet. Prosjektet skal bare motta helseopplysninger som er *adekvate, relevante og begrenset til det som er nødvendig for å oppnå formålet med behandlingen (dataminimering).*

Vedtak
Direktoratet for e-helse har vurdert søknaden og finner grunnlag for å innvilge søknad om dispensasjon fra taushetsplikten etter helseregisterloven § 19 e for opplysninger fra følgende helseregister: Meldingssystem for smittsomme sykdommer (MSIS).

Dispensasjonen gis til dataansvarlig virksomhet for prosjektet «Does tuberculosis contact tracing work as intended in Norway, a retrospective study of tuberculosis patients and contact tracing data from 2016 to 2021» ved prosjektleder Trude Margrethe Arnesen. Prosje ktleder er ansvarlig for å føre en oppdatert liste over hvem som skal ha tilgang til helseopplysningene, som kan fremlegges ved forespørsel. Reglene om taushetsplikt gjelder tilsvarende for den som mottar opplysningene jfr. helseregisterloven § 17 og/eller helsepersonelloven § 21. Det skal tilgjengeliggjøres opplysninger i samsvar med dette vedtaket. Vi viser til helseregisterloven § 19 a, sjette ledd.

Dispensasjonen gjelder til 31.12.2024.

Det følger også av helseregisterloven § 19 a at det ikke skal tilgjengeliggjøres flere opplysninger enn det som er nødvendig for formålet.

Studiepopulasjonen er tuberkulosepasienter med aktiv og latent tuberkulose i alle aldre fra årene 2016 til 2021, med et forventet antall på 4731 individer.

Det tas sikte på tilgjengeliggjøring av følgende opplysninger fra MSIS for tuberkulosehendelser med prøvedato innenfor perioden 01.01.2016-31.12.2021, jfr variabelliste og Tilretteleggingsdokument:

- Datasett 1: Opplysninger for tilfeller med hendelsesType "Aktiv sykdom".
- Datasett 2: Opplysninger om smittesporing for tilfeller med HendelsesType "Aktiv sykdom".
- Datasett 3: Opplysninger for tilfeller med HendelsesType "Forebyggende behandling".

Det er avklart med prosjektet at opplysninger for sykdomshendelser med HendelseType= «Forebyggende behandling» ikke skal inngå i datasett 1, men heller leveres som et separat og aggregert datasett (datasett 3) da dette er tilstrekkelig for å svare ut prosjektets problemstillinger.

Omsøkte fritekstfelt utgår etter enighet med prosjektet fra datasettene som leveres fra MSIS. Fritekstfelt kan inneholde direkte identifiserende personopplysninger og må ev. gjennomgås før tilgjengeliggjøring. En manuell gjennomgang vil føre til forsinkelse av tilgjengeliggjøring, noe som prosjektet ikke ønsker på grunn av deres tidsramme.
Det er ikke nødvendig for prosjektet å hvite hvilken immunsvekkende tilstand pasienten har. I

stedet for å tilgjengeliggjøre variablene HivStatus, HarAnnenImmunsvekkelse og AnnenImmunsvekkelse inkluderes derfor en kategorisk samlevariabel HarImmunsvekkelse, som settes til 1 dersom minst ett av følgende kriterier er sanne:

- HivStatus er «Positiv»
- HarAnnenImmunsvekkelse er «Ja»
- Fritekstfeltet AnnenImmunsvekkelse er ikke tomt
- Indikasjon er «Immunsvekkende tilstand/behandling»

Datatilrettelegging

Data vil bli tilrettelagt av registerforvalter for omsøkt datakilde.

Betaling for tilgjengeliggjøring
Direktoratet for e-helse kan kreve betaling for behandling av søknader om dispensasjon fra taushetsplikten og/eller tilgjengeliggjøring av helseopplysninger jfr. forskrift om nasjonal løsning for tilgjengeliggjøring av helsedata § 8. Faktura vil bli ettersendt når Direktoratet for e-helse har vurdert søknaden.

Utgifter knyttet til tilgjengeliggjøring av opplysninger fra omsøkte datakilder håndteres av registerforvalter.

Frist for tilgjengeliggjøring

Opplysningene skal tilgjengeliggjøres innen 30 virkedager fra fullstendig søknad er mottatt. Dersom tilgjengeliggjøringen krever sammenstilling med opplysninger fra flere registre, er fristen 60 virkedager. Fristene går frem av helseregisterloven § 19 f.

Tilgjengeliggjøringen kan utsettes dersom særlige forhold gjør det uforholdsmessig vanskelig å overholde fristen.

Klageadgang
Vedtaket kan påklages jfr. forvaltningsloven §29. En eventuell klage sendes Direktoratet for e-helse ved Helsedataservice innen tre uker fra mottak av datasett og følgebrev, eventuelt vedtak om avslag.

Direktoratet vil vurdere om vedtaket skal omgjøres. Dersom vedtaket opprettholdes, vil klagen oversendes til klageinstans Nasjonalt klageorgan for helsetjenesten (Helseklage) for behandling.

Vilkår for tilgjengeliggjøring

- Dataansvarlig har ansvaret for at all behandling av personopplysninger er i samsvar med den til enhver tid gjeldende regelverk; herunder personopplysningsloven og personvernforordningen. Dette inkluderer å vurdere om gjennomføring av personvernkonsekvensvurdering (DPIA) er nødvendig før behandling av personopplysninger starter.
- Prosjektet må sørge for å informere den registrerte om behandlingen av opplysningene i samsvar med forordningens artikkel 14, unntak fra dette fremgår av artikkel 14 nr. 5 bokstav b. Vurderingstemaet som må vurderes av prosjektleder er blant annet om det er «umulig å gi nevnte informasjon eller det vil innebære en uforholdsmessig stor innsats».
- Dataansvarlig har ansvaret for å ha rettslig grunnlag for behandlingen av opplysningene i prosjektet før behandlingen starter.

- Dataansvarlig har vurdert og har ansvaret for at behandlingen av opplysningene vil være innenfor rammene av eventuelle samtykker og ikke i strid med eventuelle reservasjoner. Gyldig samtykke må være innhentet før databehandlingen starter.
- Opplysningene kan kun brukes til de formål som er oppgitt i søknaden.
- Dataansvarlig skal informere Direktoratet for e-helse om vesentlige endringer i prosjektet, som f.eks. endring av dataansvarlig institusjon, prosjektleder, antall personer som har tilgang til de tilgjengeliggjorte opplysningene eller endring i prosjektvarighet.
- Det forutsettes at prosjektleder har fullmakt fra dataansvarlig til å søke om og motta de omsøkte opplysninger fra Direktoratet for e-helse.
- Alle som behandler tilgjengeliggjorte opplysninger fra helseregistre har taushetsplikt i henhold til helseregisterloven § 17. Alle som behandler opplysninger fra pasientjournaler og andre behandlingsrettede helseregistre har taushetsplikt etter helsepersonelloven § 21. Vi minner om at dersom det er innvilget dispensasjon fra taushetsplikten, så er det prosjektleders ansvar å sørge for at alle medarbeidere som skal ha tilgang til datasettet har fått innvilget dispensasjon.
- Prosjektleder må sørge for at det til enhver tid foreligger en ajourført oversikt over hvilke personer som lovlig kan gis tilgang til de tilgjengeliggjorte opplysningene. Opplysningene skal ikke overlates til andre enn denne begrensede personkretsen.
- Prosjektleder er ansvarlig for at opplysningene oppbevares trygt og på en slik måte at uvedkommende ikke får tilgang til dem.
- Overføring av helseopplysninger til prosjektmedarbeidere utenfor EU/EØS kan bare skje dersom dette er tillatt etter personvernforordningen og personopplysningsloven.
- Prosjektleder er ansvarlig for at publisering og annen offentliggjøring gis en slik form at enkeltpersoner ikke kan identifiseres.
- Prosjektleder er ansvarlig for at Direktoratet for e-helse holdes orientert om publisering av materiale fra registeret/registrene ved at kopi av abstracts (aksepterte) og vitenskapelige arbeider sendes Direktoratet for e-helse.
- Ved publisering eller offentliggjøring skal kildenes offisielle navn eller forkortelse inngå i tittel eller sammendrag.
- Direktoratet for e-helse og registerforvalterne er ikke ansvarlig for tolkninger eller analyser av dataene som blir gjort av andre.
- **Prosjektleder er ansvarlig for at tilgjengeliggjorte opplysninger ikke behandles etter 31.12.2024.**
- **Prosjektleder er ansvarlig for at alle opplysninger blir slettet innen 31.12.2024.**
- Prosjektleder er kjent med at brudd på vilkårene kan straffes med fengsel og ileggelse av overtredelsesgebyr fra Datatilsynet etter personvernforordningen artikkel 83 og personopplysningsloven §§ 26 og 27 jfr. helseregisterloven §§ 29 og 30. Brudd på vilkårene kan også få betydning ved vurdering av fremtidige søknader.

Kontaktinformasjon

Ved spørsmål, ta kontakt via meldingstjenesten på «Min side» på Helsedata.no.

Vennlig hilsen

Øystein K. Johansen
Seksjonssjef
Helsedataservice

Unni J Trondsen
Rådgiver
Helsedataservice

Godkjent av: ØYSTEIN KYRRE JOHANSEN
Dato: 09.05.2023

Tables of all uni- and multivariable analysis used to answer study question 2a and 2b, and tables of all statistically significant univariate analysis of study question 2e and 2f.

In this attachment all results and variables that is included in the master's thesis is presented. Table 1includes all variables that was used in the uni- and multivariable analysis of answering study question 3a: "Are the characteristics of the TB patient associated with the likelihood of being registered with contact tracing?". Table 2. Includes all variables that was used in the uni- and multivariable analysis of answering study question 3b: "Are the characteristics of the TB patient associated with the number of close contacts identified during contact tracing?". Table 3 includes all variables that had a statistically significant association to having TB patients referred to special healthcare services (SHS) and having close contacts received preventive treatment or TB diagnosis (close contacts receiving treatment).

Table 1. The TB population characteristics, univariate and multivariate analysis of the association between demographic and medical characteristics and if there is done contact tracing.

	Univariate analysis		Multivariable analysis	
Tb patient characteristics (N)	**RR (95% CI)**	***p-value***	**RRR (95% CI)**	***p-value***
Age groups (775) [!]				
0-15 years	Reference			
16-30	**1.23 (1.07-1.42)**	**0.003**	**3.29 (1.44-7.53)**	**0.005**
31-60	**1.24 (1.08-1.42)**	**0.003**	**2.71 (1.16-6.33)**	**0.022**
61+	**1.18 (1.02-1.38)**	**0.027**	1.34 (0.53-3.35)	0.535
Sex (775)				
Male	Reference		Reference	
Female	1.03 (0.99-1.08)	0.172	1.29 (0.73-2.26)	0.376
At-risk Workplace[!]				
Unknown/not at-risk	Reference			
Other at-risk professions	1.02 (0.97-1.08)	0.494		
Education	0.97 (0.9-1.05)	0.41		
Healthcare	1			
Municipality size (770) [!]				
< 20 000	Reference		Reference	
20 000 – 100 000	**1.14 (1.07-1.22)**	**< 0.001**	**0.54 (0.24-1.22)**	0.139
> 100 000	**1.18 (1.11-1.26)**	**< 0.001**	**0.18 (0.09-0.38)**	**< 0.001**
Hospital region (628) [!]				
South-eastern	Reference			
Central Norway	0.93 (0.84-1.03)	0.142		
Northern	0.91 (0.83-1)	0.062		
Western	1 (0.95-1.06)	0.92		

Deceased[!]				
No	Reference			
Yes	0.74 (0.46-1.17)	0.197		
TB status (409)				
First time	Reference			
Previous TB	0.91 (0.81-1.02)	0.099		
Unsure category	0.92 (0.81-1.03)	0.15		
Foreign born (775) [!]				
No	Reference			
Yes	1 (0.94-1.07)	0.953		
Period in Norway (775) [!]				
Norwegian	Reference			
Under 1 year	1.02 (0.95-1.09)	0.604		
1-4 years	1 (0.92-1.08)	0.919		
5-9 years	1.07 (0.99-1.15)	0.089		
10 + years	1.04 (0.97-1.13)	0.258		
Parents foreign born (448) [!]				
One or Both	Reference			
No	1.01 (0.93-1.1)	0.776		
From a high incidence country (775) [!]				
No	Reference			
Yes	1.02 (0.91-1.14)	0.745		
Unknown	0.98 (0.91-1.05)	0.543		
Immigration status (768) [!]				
Norwegian	Reference		Reference	
Other	0.99 (0.92-1.07)	0.836	0.78 (0.41-1.5)	0.453
Work immigrant	**1.08 (1.01-1.15)**	**0.018**	3.35 (0.97-11.57)	0.056
Immigrant/asylum seeker	0.98 (0.91-1.05)	0.538	1.26 (0.57-2.76)	0.571
Indication for examination (771) [!]				
Other	Reference			
Symptoms and signs	1.02 (0.91-1.14)	0.699		
Immunodeficiency	1.01 (0.87-1.18)	0.872		
Contact tracing	0.89 (0.75-1.06)	0.2		
Routine investigation of immigrant	1.01 (0.9-1.14)	0.861		
Known exposure (666)				
Not examined	Reference			
Yes	1 (0.92-1.08)	0.989		
No	1.04 (0.97-1.12)	0.221		
Immunosuppressive (775) [!]				
No	Reference			
Yes	1.02 (0.96-1.09)	0.49		
Clinical symptoms (748)				
No	Reference			
Yes	1.03 (0.97-1.08)	0.361		
Treatment result (769) [!]				
Not finished	Reference			
Finished	0.98 (0.9-1.08)	0.708		
Deceased	0.94 (0.79-1.1)	0.430		
CT scan (775) [!]				
No	Reference			
Yes	1.01 (0.96-1.06)	0.703		
Culture result (733)				
Negative	Reference			
Positive	1.05 (0.95-1.16)	0.36		
IGRA (712)				
Positive	Reference			
Not done	1.03 (0.95-1.13)	0.46		
Inconclusive	1.04 (0.99-1.1)	0.141		
Direct microscopy (762)				

Negative	Reference			
Positive	1.05 (1-1.1)	0.054		
Culture result from respiratory (699)[!]				
No	Reference			
Yes	0.95 (0.87-1.04)	0.291		
Positive test from respiratory (699)[!]				
No	Reference		Reference	
Yes	**1.1 (1.02-1.19)**	**0.009**	1.66 (0.87-3.16)	0.124
MDR-TB[!]				
No	Reference			
Yes	1.02 (0.92-1.13)	0.674		
Organ (775)[!]				
Other	Reference			
Lunge	**1.81 (1.22-2.71)**	**0.004**		
Lunge and other	**1.86 (1.25-2.78)**	**0.002**		
Type of TB bacteria (698)[!]				
Other[&]	Reference			
Tuberculosis, M.	1.01 (0.91-1.11)	0.889		
Outbreak number (775)[!]				
No	Reference			
Yes	1.01 (0.96-1.06)	0.845		
Vaccinated (775)[!]				
No	Reference			
Yes	1.05 (1-1.1)	0.053		

*Relative risk and 95 % confidence interval.

^Relative risk ratio 95 % confidence interval.

! Variables have been changed or made especially for analysis, see appendix 2: variable dictionary for details.

Table 2. Uni- and multivariate analysis results of the association between a TB patients characteristics and the number of CC found through contact tracing, of 698 TB patients in Norway between 2016-2021.

Category (total number)	3-7 close contacts, RRR (95% CI)		8-20 close contacts, RRR (95% CI)		Over 20 close contacts, RRR (95% CI)	
Analysis	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Total, N (%)	224 (32.1)		134 (19.2)		95 (13.6)	
Age groups (698) [!]						
0-15 (53)	Reference	Reference	Reference	Reference	Reference	Reference
15-30 (271)	0.66 (0.33-1.32)	*0.39 (0.17-0.86)**	1.18 (0.48-2.86)	0.59 (0.21-1.68)	1.88 (0.67-5.32)	0.57 (0.17-1.95)
31+ (374)	1.12 (0.57-2.17)	0.47 (0.21-1.04)	1.59 (0.67-3.79)	0.5 (0.17-1.41)	1.36 (0.48-3.84)	0.32 (0.09-1.12)
Sex (698)						
Male (398)	Reference	Reference	Reference	Reference	Reference	Reference
Female (300)	1.3 (0.9-1.87)	1.38 (0.92-2.06)	1.4 (0.92-2.14)	**1.67 (1.03-2.69)***	1.2 (0.74-1.94)	1.18 (0.68-2.03)
At-risk Workplace (698) [!]						
Unknown/not at-risk (380)	Reference	Reference	Reference	Reference	Reference	Reference
Other at-risk (179)[¤]	**1.81 (1.16-2.81)***	1.2 (0.71-2)	**2.34 (1.42-3.85)***	1.52 (0.84-2.76)	1.06 (0.54-2.07)	0.95 (0.44-2.04)
Education (105)	0.9 (0.52-1.56)	0.99 (0.54-1.82)	1.05 (0.55-2.01)	1.22 (0.59-2.5)	**2.15 (1.16-3.96)***	1.98 (0.97-4.04)
Healthcare (34)	0.72 (0.27-1.88)	0.46 (0.16-1.27)	0.76 (0.24-2.46)	0.42 (0.12-1.45)	**3.04 (1.25-7.34)***	1.89 (0.68-5.26)
Municipality size (698) [!]						
> 100 000 (273)	Reference		Reference		Reference	
20 000 – 100 000 (217)	0.91 (0.59-1.41)		0.99 (0.6-1.65)		1.39 (0.79-2.45)	
< 20 000 (207)	0.77 (0.5-1.19)		0.81 (0.49-1.35)		0.91 (0.5-1.64)	
Healthcare region (698) [!]						
South-eastern (424)	Reference	Reference	Reference	Reference	Reference	Reference
Northern (62)	0.6 (0.31-1.16)	0.91 (0.44-1.88)	0.45 (0.19-1.08)	0.75 (0.29-1.93)	0.91 (0.42-1.98)	0.92 (0.37-2.25)
Central Norway (77)	1.06 (0.6-1.85)	1.24 (0.69-2.24)	0.94 (0.48-1.84)	1.06 (0.51-2.21)	**0.26 (0.08-0.9)***	**0.27 (0.08-0.95)***
Western (135)	1.28 (0.77-2.11)	1.6 (0.94-2.73)	1.67 (0.96-2.88)	**2.42 (1.33-4.39)***	**1.83 (1.01-3.31)***	**2.08 (1.08-4.01)***
TB status (698)						
First time (598)	Reference		Reference		Reference	
Previous TB (54)	0.77 (0.4-1.48)		0.85 (0.4-1.81)		0.31 (0.09-1.05)	
Unsure category (46)	0.66 (0.31-1.39)		0.84 (0.37-1.93)		0.75 (0.29-1.93)	
Foreign born (698)						
No (116)	Reference		Reference		Reference	
Yes (582)	1.11 (0.66-1.86)		0.62 (0.36-1.05)		0.76 (0.41-1.42)	
Period in Norway (698) [!]						
Norwegian (115)	Reference	Reference	Reference	Reference	Reference	Reference
Under 1 year (213)	0.95 (0.54-1.67)	1.81 (0.71-4.6)	**0.49 (0.26-0.91)***	2.48 (0.65-9.46)	**0.36 (0.16-0.8)***	0.34 (0.11-1.04)
1-4 years (123)	0.82 (0.42-1.58)	1.8 (0.66-4.88)	0.55 (0.27-1.12)	2.49 (0.62-10.01)	1.3 (0.61-2.75)	1.05 (0.35-3.14)
5-9 years (95)	0.94 (0.48-1.85)	1.93 (0.68-5.44)	0.5 (0.23-1.08)	2.26 (0.54-9.56)	0.82 (0.35-1.92)	0.81 (0.24-2.68)
10 + years (117)	**2.16 (1.1-4.26)***	**4.35(1.54-12.31)***	1.39 (0.68-2.86)	**6.28(1.52-25.93)***	1.27 (0.54-3.01)	1.36 (0.4-4.54)
Unknown (35)[?]	0.56 (0.21-1.49)	-	**0.3 (0.09-0.99)***	-	0.93 (0.32-2.67)	-
Parents foreign born (416) [!]						

One or Both (350)	Reference		Reference		Reference	
No (66)	1.42 (0.71-2.83)		*2.55 (1.26-5.19)**		0.88 (0.35-2.24)	
From a high incidence country (698) !						
No (67)	Reference		Reference		Reference	
Yes (29)	1.06 (0.32-3.45)		1.26 (0.38-4.17)		2.24 (0.62-7.99)	
Unknown (602)*	1.12 (0.59-2.12)		0.75 (0.38-2.12)		0.94 (0.42-2.12)	
Immigration status (693) !						
Immigrant/asylum seeker (245)	Reference	Reference	Reference	Reference	Reference	Reference
Other (197)[e]	**1.79 (1.13-2.82)***	1.47 (0.88-2.46)	1.31 (0.74-2.3)	1.08 (0.57-2.05)	1.05 (0.59-1.87)	1.16 (0.6-2.24)
Work immigrant (136)	2.92 (1.72-4.94)	**2.3 (1.23-4.29)***	**2.86 (1.56-5.25)***	**2.23 (1.07-4.65)***	0.78 (0.35-1.72)	0.88 (0.35-2.22)
Norwegian (115)	1.52 (0.86-2.69)	2.78 (0.96-8.08)	**2.39 (1.29-4.4)***	**6.24(1.48-26.26)***	1.25 (0.63-2.47)	1.15 (0.34-3.86)
Indic. for examination (698) !						
Symptoms and signs (419)	Reference		Reference		Reference	
Other (34)	1.22 (0.49-3.05)		1.1 (0.41-2.96)		1.4 (0.42-4.68)	
Immunodeficiency (29)	1.25 (0.56-2.78)		-		-	
Contact tracing (44)	0.79 (0.38-1.62)		0.39 (0.15-1.02)		0.52 (0.17-1.57)	
Routine investigation of immigrant (170)	0.75 (0.49-1.14)		**0.31 (0.18-0.55)***		**0.48 (0.22-1.03)***	
Known exposure (486) !						
No (280)	Reference		Reference		Reference	
Yes (206)	1.07 (0.70-1.65)		1.05 (0.63-1.77)		0.75 (0.41-1.36)	
Unknown (115)	0.74 (0.44-1.26)		0.94 (0.51-1.72)		0.57 (0.27-1.18)	
Immunosuppressive (698) !						
No (598)	Reference		Reference		Reference	
Yes (100)	0.88 (0.53-1.46)		0.72 (0.38-1.34)		0.84 (0.43-1.65)	
Clinical symptoms (698)						
No (208)	Reference	Reference	Reference	Reference	Reference	Reference
Yes (490)	1.13 (0.77-1.65)	1.15 (0.75-1.77)	**2.53 (1.53-4.2)***	**2.77 (1.56-4.92)***	**2.66 (1.48-4.78)***	**2.47 (1.27-4.8)***
Treatment result (693) !						
Finished (615)	Reference		Reference		Reference	
Not finished (56)	1.05 (0.55-2)		1.06 (0.5-2.23)		0.35 (0.1-1.19)	
Deceased (22)	1.98 (0.65-6.02)		1.85 (0.53-6.53)		1.45 (0.34-6.19)	
CT scan (698) !						
No (438)	Reference		Reference		Reference	
Yes (260)	1.24 (0.85-1.81)		1.1 (0.71-1.7)		1.03 (0.63-1.69)	
Culture result (666)						
Negative (54)	Reference		Reference		Reference	
Positive (612)	**2.77 (1.42-5.4)****		**4.43 (1.69-11.62)***		**8.15 (1.92-34.64)***	
IGRA (698)						
Positive (488)	Reference		Reference		Reference	
Not done (40)	0.96 (0.45-2.09)		0.66 (0.23-1.87)		1.38 (0.54-3.56)	
Inconclusive (119)	1.21 (0.73-1.99)		1.54 (0.88-2.68)		1.32 (0.68-2.54)	
Positive airway result (698) !						
No (128)	Reference	Reference	Reference	Reference	Reference	Reference
Yes (570)	**2.29 (1.46-3.6)***	**2.55 (1.51-4.3)***	**3.64 (1.96-6.75)***	**4.08 (2-8.32)***	**6.3 (2.64-15.04)**	**8.7 (3.27-23.15)***

Organ (686) !			
Lunge (509)	Reference	Reference	Reference
Lunge and other (177)	**0.63 (0.42-0.95)***	0.66 (0.41-1.06)	**0.38 (0.21-0.71)***
Type of TB bacteria (634) !			
Other[&] (38)	Reference	Reference	Reference
Tuberculosis, M. (596)	**2.15 (1.02-4.56)***	**2.98 (1.1-8.08)***	1
MDR TB (620)!			
No (593)	Reference	Reference	Reference
Yes (27)	1.09 (0.41-2.89)	0.79 (0.23-2.66)	1.66 (0.56-4.92)
Outbreak number (698) !			
No (482)	Reference	Reference	Reference
Yes (216)	1.03 (0.69-1.52)	0.88 (0.55-1.41)	1.41 (0.86-2.32)
Vaccinated (698)!			
No (518)	Reference	Reference	Reference
Yes (180)	0.98 (0.65-1.49)	1.13 (0.7-1.81)	1.05 (0.61-1.81)

*P value <0.05, of the relative risk (RR) or Relative risk ratio (RRR) and 95 % confidence interval.

! Details on variables can be found in appendix 2: variable dictionary.

?Omitted: not included in the multivariable model, because it has no explanatory effect on the outcome.

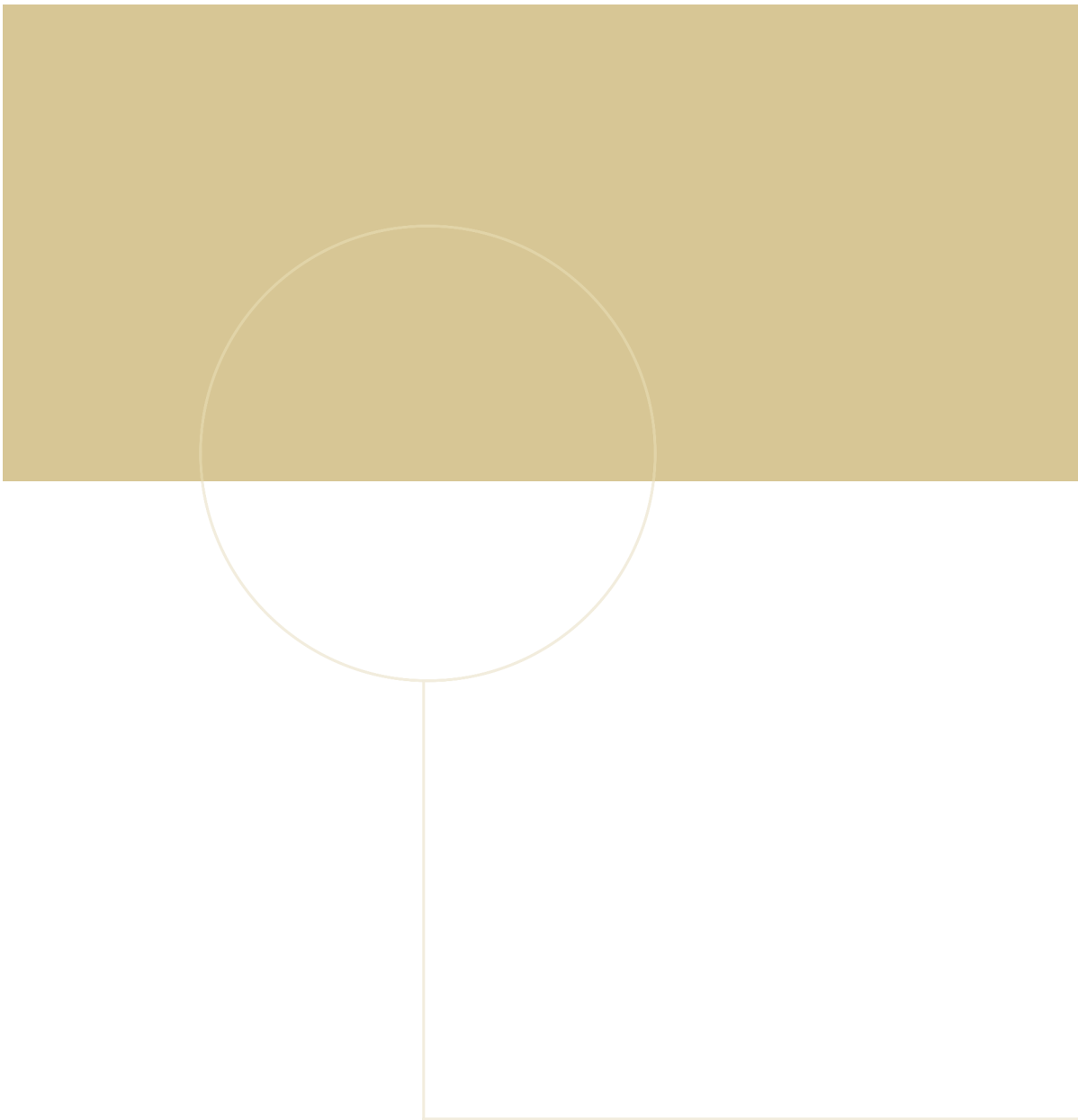
Table 3. Results from uni- and multivariate analysis of characteristics associated with TB patients having contacts referred to SHS and having close contacts receiving treatment, among 585 TB patients in Norway between 2016 and 2021.

Category (total number)	TB patients with CC referred to SHS, RRR (95% CI)		TB patients with CC received treatment and/or diagnosis, RRR (95% CI)	
Analysis	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Total, N = 585(%)	224 (32.1)	585	134 (19.2)	585
Age groups				
0-15	Reference	Reference	Reference	Reference
15-30	1.03 (0.57-1.85)	0.51 (0.11-2.48)	0.82 (0.45-1.51)	**0.25 (0.07-0.92)***
31+	0.77 (0.43-1.37)	0.52 (0.11-2.46)	0.59 (0.32-1.06)	**0.2 (0.06-0.74)***
Sex				
Male	Reference	Reference	Reference	Reference
Female	1.08 (0.8-1.46)	0.87 (0.43-1.74)	**1.64 (1.19-2.27)****	**2.82 (1.71-4.66)****
Municipality size				
> 100 000	Reference	Reference	Reference	Reference
20 000 – 100 000	0.85 (0.59-1.21)	0.48 (0.22-1.08)	1.04 (0.71-1.52)	1.44 (0.81-2.54)
< 20 000	**0.67 (0.47-0.97)***	0.47 (0.2-1.11)	0.97 (0.66-1.44)	**2.02 (1.07-3.81)***
Hospital region				
Southeast	Reference	Reference	Reference	-
North	0.8 (0.47-1.37)	0.61 (0.17-2.23)	0.96 (0.54-1.7)	-
Mid	0.66 (0.4-1.07)	*0.29 (0.09-0.92)**	0.71 (0.41-1.24)	-
West	1.11 (0.75-1.64)	0.54 (0.21-1.41)	1.19 (0.79-1.79)	-
Foreign born				
No	Reference	-	Reference	-
Yes	**2.2 (1.45-3.35)****	-	**1.83 (1.14-2.95)***	-
Period in Norway				
Norwegian	Reference	Reference	Reference	Reference
Under 1 year	**1.86 (1.16-2.99)***	1.97 (0.65-5.97)	1.55 (0.91-2.63)	0.64 (0.26-1.57)
1-4 years	**2.77 (1.63-4.69)****	**5.63 (1.67-18.9)****	**2.23 (1.25-3.95)***	0.93 (0.36-2.37)
5-9 years	**2.45 (1.4-4.29)****	**4.34 (1.27-14.8)***	1.74 (0.94-3.23)	0.78 (0.29-2.08)
10 + years	**2.91 (1.71-4.98)****	2.67 (0.81-8.77)	**2.25 (1.26-4.01)***	1.14 (0.44-2.98)
Unknown	1.35 (0.62-2.95)	0.93 (0.14-6.07)	1.07 (0.43-2.64)	0.39 (0.1-1.48)
Parents foreign born				
One or Both	Reference	-	Reference	-
No	**0.26 (0.14-0.47)****	-	**0.33 (0.16-0.66)****	-
From a high incidence country¤				
Yes	Reference	-	Reference	-
No	**0.29 (0.12-0.73)***	-	**0.33 (0.12-0.92)***	-
Unknown	1.02 (0.49-2.16)	-	0.95 (0.43-2.07)	-
Indication for examination				
Symptoms and signs	Reference	-	-	-

Other	**0.41 (0.19-0.86)***	-	-	-
Immunodeficiency	**0.45 (0.2-0.99)***	-	-	-
Contact tracing	*0.85 (0.46-1.59)*	-	-	-
Routine investigation of immigrant	*0.71 (0.49-1.01)*	-	-	-
Known exposure				
No	Reference	-	Reference	-
Yes	**1.67 (1.05-2.65)***	-	**1.96 (1.16-3.3)***	-
Unknown	1.18 (0.76-1.83)	-	1.35 (0.81-2.24)	-
Clinical symptoms				
No	Reference	Reference	-	-
Yes	**1.6 (1.16-2.23)****	1.46 (0.66-3.25)	-	-
Positive airway result[s]				
No	Reference	Reference	Reference	Reference
Yes	**2.55 (1.7-3.84)****	0.61 (0.25-1.52)	**3.12 (1.86-5.24)***	2.16 (0.81-5.73)
Organ [+]				
Lunge	-	-	Reference	-
Lunge and other	-	-	**0.57 (0.38-0.84)***	-
MDR TB[^]				
Yes	-	-	Reference	Reference
No	-	-	**3.11 (1.06-9.1)***	**4.49 (1.24-16.22)***
Unknown	-	-	0.66 (0.18-2.39)	0.87 (0.13-5.68)
Size of contact trace (Nr of CC)				
0 to 2 CC	Reference	Reference	Reference	Reference
3 to 7 CC	**4.61 (3.04-6.98)***	**2.24 (1-5)***	**3.9 (2.4-6.36)***	1.13 (0.53-2.42)
8 to 20 CC	**14.17 (8.49-23.64)***	**8.04 (2.99-21.62)***	**6.16 (3.64-10.43)***	0.77 (0.36-1.68)
21 + CC	**37.78 (18.19-78.45)***	**5.43 (1.37-21.51)***	**15.17 (8.48-27.14)***	1.41 (0.61-3.29)
Have IGRA tested CC				
No	Reference	-	Reference	-
Yes	**2.22 (1.19-4.16)***	-	**2.49 (1.17-5.28)***	-
Have IGRA positive CC				
No	Reference	Reference	Reference	Reference
Yes	**135.73 (77.53-237.62)***	**64.87 (30.22-139.22)***	**38.18 (21.76-67)***	**3.84 (1.76-8.38)***
Have CC referred to SHS				
No	-	-	Reference	Reference
Yes	-	-	**195.69 (61.52-622.46)***	**83.32 (22.49-308.66)***
Have CC received treatment or diagnosis				
No	Reference	Reference	-	-
Yes		**61.85 (16.5-231.91)***	-	-

*P value <0.05, of the relative risk (RR) and relative risk ratio (RRR), with 95 % confidence interval.

! Details on variable is described in appendix 2: the variable dictionary.



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