Tuberculosis outbreak in Eastern Norway

BACKGROUND Tuberculosis is a rare disease in Norway, especially among Norwegian-born inhabitants. Contact tracing for cases of pulmonary tuberculosis is essential to find others who are ill or infected, and to prevent further transmission. This article describes the investigation of an outbreak in which many of those infected or ill were Norwegian adolescents.

MATERIAL AND METHOD Nine persons directly or indirectly associated with the same educational institution were diagnosed with tuberculosis in 2013. Genetic testing of tuberculosis bacteria linked a further 13 cases of the disease reported in Eastern Norway during the period 2009–2013 to the outbreak. Information from the Norwegian Surveillance System for Communicable Diseases (MSIS) was used to investigate the outbreak, and information was also retrieved on exposure and contact networks.

RESULTS The first patient at the educational institution had long-term symptoms before diagnosis. Contact tracing for this case included 319 persons, of whom eight were ill, 49 infected and 37 received preventive therapy. The extent of contact tracing for the remaining 21 cases varied and included a total of 313 persons, of whom two were found to be ill (included in the 21 cases), 30 were infected and 12 received preventive therapy.

INTERPRETATION Delayed diagnosis led to a tuberculosis outbreak that was unusually large in a Norwegian context. The extent of contact tracing varied with no obvious relation to the infectiousness of the index patient. The outbreak demonstrates the importance of continued vigilance with regard to tuberculosis as a differential diagnosis, also among Norwegian-born patients.

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MAIN MESSAGE

Altogether 22 cases of tuberculosis in the period 2009–2013 were linked to a single outbreak in Eastern Norway.

Delayed diagnosis contributed to an uncommonly large outbreak of tuberculosis.

As expected, the proportion of infected persons among the reported contacts of the first patient at the educational institution was highest among those who were assumed to have been most exposed.

Contact tracing can be extremely resource-intensive and needs to be targeted in order to reach those who are most exposed.

While the prevalence of tuberculosis in recent years has declined globally, it has increased in Norway. The number of new cases of tuberculosis reported to the National Surveillance System for Communicable Diseases (MSIS) has increased from 201 in 1996 to 401 in 2013 (1). This notwithstanding, Norway still has one of the lowest prevalence figures for tuberculosis in the world, especially among the Norwegian-born.

It is assumed that approximately one-third of the world's population are infected by *Mycobacterium tuberculosis*, but without any illness or ability to infect others (2). Of those who are infected, only a small minority, perhaps only 5–10 per cent, will develop active tuberculosis at some stage in life, and in approximately one-half of these it happens within the first two years after the initial infection (3, 4). In Norway, the IGRA test (Interferon-Gamma Release Assay) is used as an indicator of infection with tuberculosis, with or without a prior Mantoux skin test (5).

The risk of infected people falling ill with tuberculosis can be reduced through preventive treatment (3). A positive IGRA test provides no information on the time of infection, the test may remain positive even after treatment, and people with immune deficiency can obtain a false-negative result. Those who are found to be IGRA-positive by contact tracing are nevertheless considered newly infected in practice and are therefore commonly offered preventive treatment (5).

Of the 401 cases of tuberculosis that were reported in Norway in 2013, a total of 318 (79 %) were confirmed by culturing (1). Each strain of cultured mycobacteria is sent to the reference laboratory at the Norwegian Institute of Public Health, where it is screened for resistance and examined genetically. Approximately three-fourths of the patients had unique strains that had not been detected in Norway previously. The explanation is that most of those who fall ill with tuberculosis in this country have not contracted the infection here, but in a high-endemic country of origin (1, 6).

Tuberculosis is transmitted by droplet nuclei. In practice, only culture-positive, untreated pulmonary tuberculosis is infectious (7). For each case of pulmonary tuberculosis, the district medical officer shall consider initiation of contact tracing. The appropriate scope will depend on the contagiousness and contact network of the index patient and the vulnerability of the contacts (7).

Infectiousness is assessed through direct microscopy of respiratory secretions. If acid-fast bacilli (microscopy-positive) are detected, the patient is considered «definitely contagious», in case of culture-positive, microscopy-negative tests, the patient is «low-level contagious». A rough rule of thumb says that those who have been «within speaking distance» indoors (at a distance where they can converse comfortably) for more than eight hours in the company of someone defined as «definitely contagious» or for more than 40

hours with someone who is «low-level contagious» are to be considered as contacts exposed to infection (5, 7).

In April 2013, a case of tuberculosis was reported in a student at an educational institution in Eastern Norway. This education involves close physical contact and a large amount of physical activity over time. In the following months, eight of this student's contacts, whereof six were students at the same educational institution, fell ill with tuberculosis. After subsequent analyses of bacterial DNA, another 13 tuberculosis patients were linked to the same outbreak, which consisted of 22 cases as of May 2014 (1).

The objective of this article is to describe this unusual outbreak of tuberculosis in Norway and how it was investigated, and to discuss various control measures that might have prevented it from assuming such proportions.

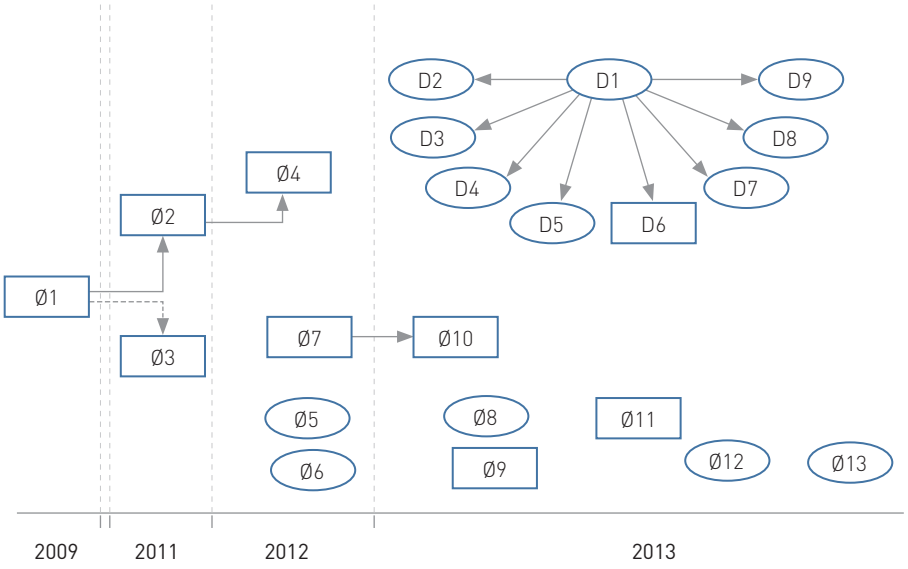

Figure 1 *Overview of cases included in the outbreak, by year. The D group: The index patient and his contacts. The Ø group: The remaining patients. Arrows: Likely infection contact. Rectangles: Parents from a high-endemic country. Ovals: Parents from Norway or another low-endemic country*

Material and method

The investigation of the tuberculosis outbreak made use of a number of information sources, including data that are routinely reported to and registered in MSIS, as well as information that was collected specifically in the context of handling the outbreak by those who undertook the contact tracing locally.

The Norwegian Institute of Public Health coordinated the investigation of the outbreak in collaboration with district medical officers, community health nurses, tuberculosis coordinators, clinicians responsible for treatment and microbiological laboratories. Issues pertaining to contact tracing were discussed in meetings, telephone conferences and follow-up calls.

MSIS contains information on each case of reported active tuberculosis, each identified strain of mycobacteria, preventive therapies initiated and contact tracings implemented. The registry is based on reports from clinicians, municipal health officers and laboratories. It contains no information on persons who are infected with tuberculosis but receive no preventive treatment, since a positive IGRA test alone is not a notifiable condition.

Since 2011, the reference laboratory has used the MIRU-VNTR method (mycobacterial interspersed repetitive unit – variable nucleotide tandem repeat) (8) for genetic determination of submitted isolates. The bacterial genome is studied in 24 loci, and the findings provide a «MIRU code». A cluster is defined as tests from patients that have an identical MIRU code. An identical MIRU code may indicate, but not confirm, an association between the infections (9). When investigating outbreaks such as this one, strains identified prior to 2011 may also be examined with a MIRU-VNTR test.

We considered as included in this outbreak those tuberculosis patients who had been reported to MSIS and were culture-positive and had an identical MIRU code, or who were culture-negative and thus had no MIRU code but had been found through contact tracing from an included case.

A summary report on every contact tracing undertaken must be routinely submitted to the Norwegian Institute of Public Health. In the context of the outbreak at the educational institution, the institute also prepared a template for contact information (line list) to help organise collection of information on contacts that the district medical officer in the municipality would normally collect, but not forward to NIPH. This line list was distributed to the medical officers who were responsible for local contact tracing. The doctors could decide for themselves whether they found this list suitable for their purposes. In cases where the contact tracing had already been completed, the line list remained largely unused.

The line list contained fields for entering the relationship between the infection contact and the patient, as well as results from the Mantoux test, the IGRA test and chest x-ray, including the conclusion drawn from the examination. The examining doctor was also asked to estimate the approximate time of exposure at speaking distance to the patient in the period during which he/she had symptoms, in one of six categories: less than 8 hours (no exposure to infection), approximately 8–39 hours (occasional contact), approximately 40–99 hours (established contact), approximately 100–250 hours (close/household contact) or > 250 hours (especially close contact).

In this article, healthy contact persons are defined as «infected» if the IGRA test came out positive, as «not infected» if the Mantoux or IGRA tests came out negative at least eight weeks after the last known exposure, and as «inconclusive» if the Mantoux test had not been confirmed by an IGRA test or if no adequate test results were available.

The investigation of the outbreak was submitted to the Regional Committee for Medical and Health Research Ethics, which determined that a separate application was not called for. Consent to publication of the medical history of the first person to contract tuberculosis at the educational institution (D1) has been obtained. The article was submitted to the data protection officer at the Norwegian Institute of Public Health, who had no objections to publishing.

Results

The part of the outbreak linked to the educational institution

A young, socially active man (D1) who had grown up in Norway in a Norwegian family had been coughing for two years and felt unwell over the last year, but had succeeded in completing his physically demanding full-time studies. He reported to have contacted various doctors, to have been given various diagnoses and to have been treated with asthma and cough medication, and to have been recommended to quit smoking. A chest x-ray taken 14 months prior to the time of diagnosis showed negative. When acutely hospitalised with suspected pulmonary tuberculosis he was febrile, had lost 20 kg of

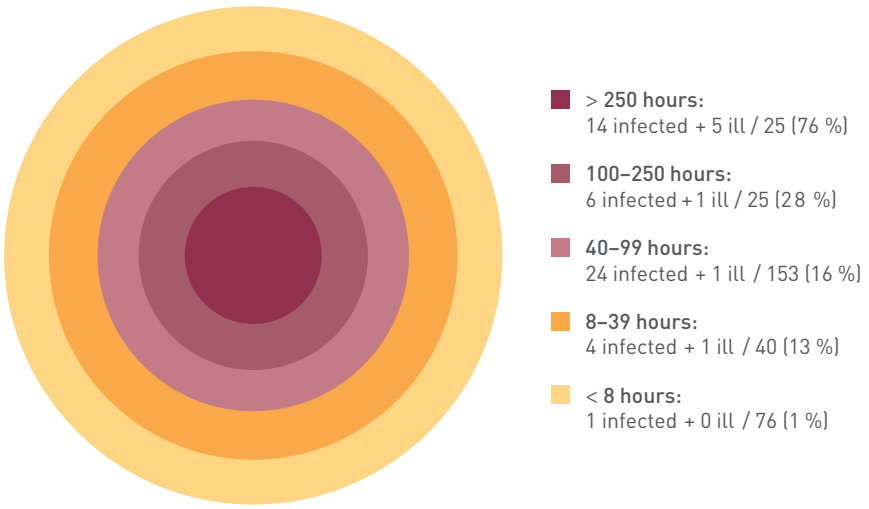

Figure 2 *Proportion of infected and ill persons (%) found in the contact tracing around the first case of tuberculosis at the educational institution, by estimated time of exposure. For 34 of the 319 examined persons no conclusive infection status was established*

weight and was coughing up blood. A chest x-ray showed caverns, and direct microscopy of sputum showed an abundance of acid-fast bacilli. This indicated that he was definitely contagious and most likely had been so for a long period.

Over the course of nine months in 2013, altogether eight of his contacts, hereafter referred to as D2–D9, fell ill with tuberculosis (Figure 1). D2–D6 were hospitalised after approximately one month. In the second half of the year, active tuberculosis was detected in three further contacts at the institution (D7–D9). These had already been identified as infected, and preventive treatment had been planned. A MIRU code identical to the one in D1 was identified in all of these, with the exception of one from whom a bacteriological sample was not collected.

Including D1, seven of the patients were students at the same educational institution. The nine patients had an average age of 21 years, while the median age was 22 years. Six of them were women. Eight of nine had grown up in Norway with Norwegian parents.

Other cases that could be linked to the outbreak by DNA analyses

The same MIRU code as in eight of the patients in the D1–D9 group was detected in 12 other patients from Eastern Norway. The strains belonged to the Beijing family of *M. tuberculosis*. A 13th case, for which the sample was culture-negative and thus had no MIRU code, was included because the patient had been found through contact tracing for one of the included patients. These 13 will hereafter be referred to as Ø1–Ø13.

The first case (Ø1) was reported in 2009, Ø2-Ø3 were reported in 2011, Ø4-Ø7 in 2012 and Ø8-Ø13 in 2013 (Figure 1). The average age of these 13 was 35 years, while the median age was 30 years. Eight of these 13 had been born outside Norway, in five different countries of origin.

Ø1-Ø4 shared the same country background and lived in the same area of Eastern Norway at the same time. For one of these cases, no known contact with any of the other three cases had been found. To check whether the findings of the same strain of bacteria reflected that this was a common strain in their country of origin, the resistance pattern for all cases of tuberculosis reported with the same country background as Ø1-Ø4 since 2001 were collated. Five had the same resistance pattern as the strain in question, but none of the five had the relevant MIRU-VNTR code.

Ø7 and Ø10 were close acquaintances. For the remaining seven no known contact was found, beyond the fact that they all had been staying within a limited area of Eastern Norway and that all of them were diagnosed in the course of 2012 and 2013.

Six of these 13 were reported to MSIS by clinicians as presumably infected abroad, five as infected in Norway and two with an unknown country of infection.

Of a total of 22 ill patients, sixteen had received the BCG vaccine (registered in SYSVAK, had a visible scar or were assumed to have been vaccinated because of their age and having spent their adolescence in Norway), while the remaining six had an unknown vaccination status.

Contact tracing around D1

The contact tracing around D1 was quickly initiated and comprehensive. The medical officer in charge chose to complete the line list systematically from the outset.

The closest contacts (from the same household or class) were examined during the same week with chest x-ray and an IGRA test. The other students at the school were quickly informed and offered an initial examination with a Mantoux test undertaken at the school's premises. If the result was positive an IGRA test was taken, and if this showed positive, the student was referred to preventive therapy. If the test was negative, it was repeated eight weeks after the last exposure to infection. Those who failed to report for the test received a reminder by letter or telephone.

A total of 319 contacts around D1 were examined (Figure 2). Altogether eight ill and 49 infected persons were found, whereof 37 (75 %) received preventive therapy. Thirty-four contacts who had taken the initial Mantoux test, whereof 15 showed positive, did not take the IGRA test or a new Mantoux test at least eight weeks after the last contact, and no conclusion was therefore drawn regarding their infection status.

The proportion of infected and ill persons co-varied with the estimated time of exposure (Figure 2), from 19 of 25 (76 %) contacts with a time of exposure of more than 250 hours to one of 76 (1 %) in contacts with a time of exposure shorter than eight hours. Five of the eight contacts who had fallen ill as of May 2014 were in the category with the highest exposure.

Contact tracing around the 21 other cases

The contact tracing around the 21 other cases encompassed a total of 313 persons, whereof 30 had been infected. Twelve of these (40 %) had been referred to preventive therapy.

Among the cases D2–D9, five had pulmonary tuberculosis. Only one of these was definitely contagious (directly microscopy-positive), three were not very contagious (culture-positive, microscopy-negative), and in one case no microscopy had been undertaken. Three had extra-pulmonary tuberculosis (in the pleura) and were non-infectious. The contact tracing around D2-D9 included between two and 26 contacts (Figure 3). A total of 89 persons were examined. whereof five were infected and none were ill.

Of the 13 cases Ø1-Ø13, eleven had culture-positive pulmonary tuberculosis. Eight were microscopy-positive, meaning that they were definitely infectious. Contact tracing around these eight included between zero and 109 persons, and four of the contact tracings included fewer than four contacts (Figure 3). The first case (Ø1) was identified in 2009 under a routine examination of immigrants upon arrival. The contact tracing for this person included three persons but failed to cap-

ture Ø2, who later reported to have been in contact with Ø1.

Around Ø7 a total of 28 contacts were examined, one of whom proved to have tuberculosis (Ø10).

In the telephone follow-up of the persons in charge of each contact tracing and in telephone conferences held for purposes of coordination, it transpired that a number of the contact tracings around the Ø cases in particular were difficult to implement. The reasons were that the patients refused to divulge information about their contacts, that the contacts could not be found, and partly also that those summoned for a control examination failed to show up. In some of the contact tracings, and around the D cases in particular, the opposite problem was encountered – there were more people who wanted to be examined than medical reasons would indicate.

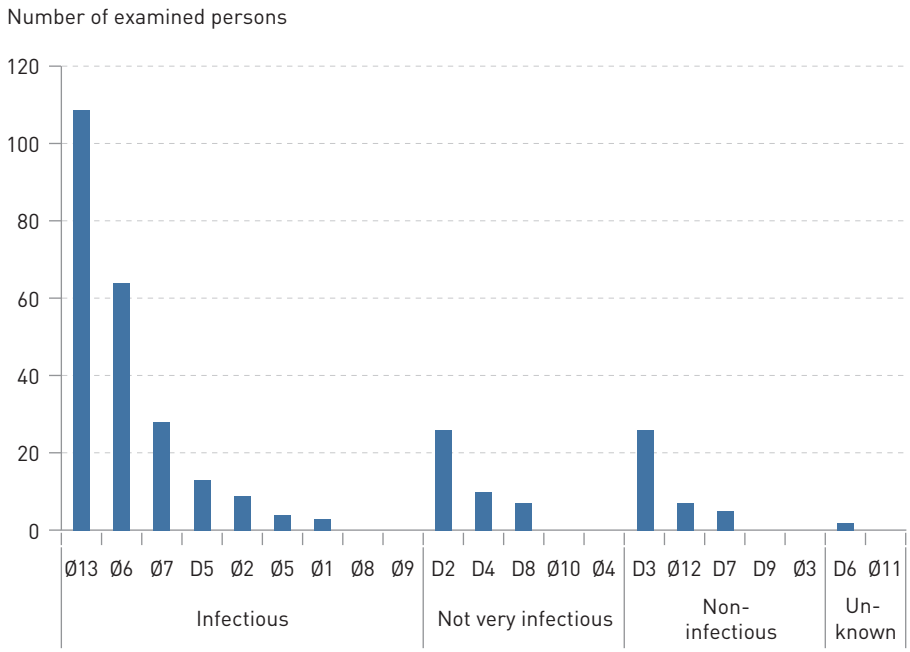

Figure 3 *Number of persons examined in each contact tracing in relation to the infectiousness of the index patient. The D group: The index patient and his contacts. The Ø group: The remaining patients*

Discussion

We have described an outbreak consisting of nine cases of active tuberculosis with known contact with a highly infectious case and 13 other cases of illness that we assume to be linked to these. A total of 632 persons were examined in the course of the contact tracing around the 22 tuberculosis patients, ten ill persons were found through contact tracing (included in the 22 cases), and 79 were found to have been infected. This outbreak is uncommonly large in a Norwegian context.

The same outbreak?

The assumption that Ø1-Ø13 belonged to the same outbreak as D1-D9 was made because they had all lived in the same town in Eastern Norway at the same time, and their bacterial strains (those that could be cultured) shared the same MIRU code. In comparison, most bacterial strains detected in Norway have only been found in single tuberculosis patients (1, 6).

Associated infections cannot be confirmed by the MIRU-VNTR method; associations can only be rejected if the bacterial strains are different or deemed likely when seen in light of epidemiological information (9). Ø1-Ø4 shared the same country background – an alternative explanation could be that they had been infected by the same strain there or while en route to Norway. However, Ø2 reported to have been in contact with Ø1 after having arrived in Norway, making this a more likely place of infection. The other persons had five different countries of origin between them, making it difficult to imagine a place of infection which is more likely than Eastern Norway, where they all had stayed during the same period.

Based on the medical history, patient D1 can be assumed to have infected his contacts at school, not the other way round, and that this patient was infected by one of the earlier cases of pulmonary tuberculosis. A planned full-genome sequencing may be able to provide further information on the infection pathway.

Many of the foreign-born patients had been reported as having been infected outside Norway, but the investigation of the outbreak has later indicated that they were most likely infected in this country. This is a reminder that even persons who originate in or have visited high-endemic countries may have been infected in Norway.

The association between exposure and infection

In the large-scale contact tracing around D1, the exposure time of each individual contact was systematically assessed in one of five categories. In the contact tracings around the other 21 cases, the degree of exposure was reported in varying ways or not reported at all. We will therefore focus on what was found with regard to D1.

In the category «especially close contact» – in which it was assumed that they had spent more than 250 hours within speaking distance of the infectious person – three-fourths (76 %) were either infected or ill. In the category «other close contacts», the proportion of infected and/or ill persons amounted to 28 %, then 16 % and finally 13 %. Of those examined who had been in the proximity of D1 for less than eight hours, and who according to the prevailing guidelines would normally not be included in a contact tracing, only one of 76, i.e. somewhat more than one per cent, was infected. We have no information on the proportion of infected persons in the general Norwegian population, but given the WHO estimates that one-third of the world's population is infected (2), the proportion of infected persons in the Norwegian population is most likely well over one per cent.

These findings are consistent with the findings made by another Norwegian study (10) and with the prevailing recommendations that persons with an exposure time of less than eight hours are commonly at little risk of infection (5). However, these findings may be fraught with uncertainty regarding the estimated exposure time and a varying scope of the contact tracing around each individual case.

The large proportion of infections among the close contacts of the infectious persons was more unusual. In comparison, a meta-analysis of 108 contact tracings from high-income countries found an average of 3.1 per cent ill persons among household contacts (11). It is therefore natural to ask whether there were any peculiarities in D1's medical history, in the conditions at the educational institution or in the bacterium that were conducive to the spread of infection.

Why did the outbreak assume such proportions?

The main single factor that caused the outbreak to assume such a magnitude was most

likely the delayed diagnosis of D1. The time elapsing from symptom onset to diagnosis and treatment is crucial for the spread of infection, irrespective of whether the delay is caused by the patient or the health services (7). In this case, no testing for tuberculosis was made, despite lengthy and strong respiratory symptoms and multiple consultations with doctors.

Moreover, properties of the tuberculosis bacterium may have had an effect. The tuberculosis strain in question belonged to the Beijing family, which may have an elevated virulence (12).

In addition, features of the surroundings may have had a contributory effect (7). The concentration of droplet nuclei depends on the air volume in which they are dispersed. The premises used by the educational institution at the time were low-ceilinged and with little ventilation and airing, resulting in a relatively small air volume per person

The characteristics of the education programme may also have had an effect. Major physical exertion causes inhalation of larger volumes of air, and close physical contact with the source of infection accounts for a higher concentration of droplet nuclei in the air inhaled.

Are we looking where we should?

Whether a contact tracing should be undertaken and the breadth of its scope depend on multiple factors. The main deciding factor is the infectiousness of the index patient.

Figure 3 shows no clear association between the degree of infectiousness of the 22 cases and the scope of the contact tracing around them. For example, four contacts or fewer were investigated around four clearly infectious Ø cases, while 26 contacts were investigated around a non-infectious D case. The seeming absence of a clear association may also be due to varying size of the contact networks.

It is especially interesting to note that Ø2 had reported Ø1 as a contact, but still had not been captured by the contact tracing around Ø1. In Figure 1 we can see that the outbreak possibly could have been avoided if the contact tracing around Ø1 had succeeded in finding all the infected persons and referring them to preventive therapy before they fell ill.

The contact tracings around the D cases in this material were largely undertaken in resourceful and well-integrated environments, while the environments around the Ø cases were more varied and to some extent resource-deficient or with a loose affiliation to Norwegian society.

The personnel involved in the implementation of the different contact tracings had varying experiences. Some of them reported that the work was extremely challenging, in particular with regard to the tracing of some of the Ø cases. Some of the networks included many recently arrived immigrants, there was little trust in the health services, some did not have a permanent place of residence, did not read Norwegian or for various reasons failed to report to the right place at the right time, even after repeated attempts to establish contact and communicate information. Reaching out to those who do not want to be examined may be extremely resource-intensive or even practically impossible.

An additional feature that may have amplified the difference between these networks is that an examination for latent tuberculosis requires a fairly considerable effort on the part of the person to be examined. Until October 2014, a Mantoux test was required before the IGRA test was taken, meaning that the patient needed to attend on three occasions in order to be diagnosed with tuberculosis. Chest x-ray and an outpatient examination, if required, would need additional attendances. In this material we can see that despite the impressive efforts made in the resourceful environment around D1, altogether 34 persons who took the Mantoux test failed to take a repeat test at least eight weeks later or failed to take a conclusive IGRA test. We assume that if the IGRA test was the only one that needed to be taken, this might simplify the examination.

Preventive therapy and vaccination

The risk that latent tuberculosis will develop into active tuberculosis is at its highest immediately after exposure. At the same time, it is crucial that active tuberculosis is excluded before initiation of preventive therapy.

In this material, three of those who were ill had already been diagnosed with latent tuberculosis, but for various reasons no preventive therapy had been initiated. This may serve as an argument for the importance of quickly assessing preventive therapy for newly infected persons.

BCG vaccination was taken out of the vaccination programme in 2008/09. This change was introduced after most of those included in this outbreak had already received the vaccine.

Conclusion

Delayed diagnosis contributed to an uncommon outbreak of tuberculosis in nine young people in Eastern Norway in 2013, seven of whom were students at the same educational institution. As expected, we found an association between the exposure category and the number of ill and infected persons among the reported contacts with the first patient at the educational institution. Another 13 tuberculosis patients in Eastern Norway in the period 2009–2013 are considered as belonging to the same outbreak. The first of these was discovered during a routine screening of immigrants.

The scope of the contact tracings reflected the infectiousness of the index patients to a varying degree. This may be due to different contact networks, varying attendance for examination in the communities where the contact tracing is undertaken, or differences in the efforts undertaken by the personnel responsible for control of communicable diseases in the municipality.

Among those who were examined for latent tuberculosis, there were some who never received any answer as to whether they were infected. We assume that simplified diagnostics of latent tuberculosis may increase attendance for examination.

We wish to thank Ingunn Haakerud, Henriette Egebakken, Janne Oseberg Rønning, Camilla Rytterager Ingvaldsen, Hege S. Bjelkarøy and Irene Teslo for their contributions to the discussions, collection of data and analysis of samples at the initial stage, and Brita Winje, Bernardo Guzman, Einar Heldal and Karin Rønning for reviewing the manuscript and providing important comments.

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Received 11 June 2014, first revision submitted 19 December 2014, accepted 19 October 2015.
Editor: Siri Lunde Strømme.