High yield from repeated testing for tuberculosis among high-risk citizens in Denmark

Staerke, Nina Breinholt; Smidt-Hansen, Torben; Oldenborg, Leni; Jensen, Torben Tranborg; Weinreich, Ulla Møller; Shakar, Shakil; Wejse, Christian; Hilberg, Ole; Fløe, Andreas

Published in:
International Journal of Infectious Diseases

DOI (link to publication from Publisher):
10.1016/j.ijid.2020.10.076

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

International Journal of Infectious Diseases 102 (2021) 352–356

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

High yield from repeated testing for tuberculosis among high-risk citizens in Denmark

Nina Breinholt Staerke[a,b,*], Torben Smidt-Hansen[c], Leni Oldenborg[c], Torben Tranborg Jensen[d], Ulla Møller Weinreich[e], Shakil Shakar[e,f], Christian Wejse[a,g], Ole Hilberg[h,i], Andreas Fløe[c]

[a] Department of Infectious Diseases, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
[b] Department of Clinical Medicine, Aarhus University, Palle Juul-Jensens Boulevard 82, 8200 Aarhus N, Denmark
[c] Department of Pulmonary Medicine, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
[d] Department of Pulmonary Medicine, Sydvestjysk Sygehus, Finsensgade 35, 6700 Esbjerg, Denmark
[e] Department of Pulmonary Medicine, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark
[f] Department of Internal Medicine, North Denmark Regional Hospital, Bispensgade 37, 9800 Hjoerring, Denmark
[g] GloHAU, Center for Global Health, Department of Public Health, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
[h] Department of Internal Medicine, Sygehus Lillebælt, Beriderbakken 4, 7100 Vejle, Denmark
[i] Department of Regional Health Research, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

ARTICLE INFO

Article history:
Received 21 September 2020
Received in revised form 20 October 2020
Accepted 23 October 2020

Keywords:
Active case finding
Screening
Latent tuberculosis infection
Homeless
Socially marginalized

ABSTRACT

Background: Screening for TB (tuberculosis) among socially marginalized citizens has been implemented in many urban areas in countries with a low incidence of TB, including Denmark. This study aims to describe the findings of the screening programs for TB and latent tuberculosis (LTBI) used in the western part of Denmark in the period 2014–2019.
Methods: Data was collected retrospectively on test results from interferon-gamma release assays (IGRA), spot sputum tests and chest X-rays performed as part of TB and LTBI screening among 1024 socially marginalized citizens in urban areas of western Denmark in 2014–2019.
Results: The overall TB incidence was 2148/100.000 and number needed to screen to find one TB case was 39. The incidence of LTBI in the group screened using IGRA was 17.500/100.000. TB incidence when using spot sputum test was 2.5, while TB incidence when using IGRA as the primary screening test was 2.7. In total, 38.9% of TB diagnoses were obtained after the second or third round of screening.
Conclusion: We demonstrated a high incidence of TB and LTBI among socially marginalized citizens in Denmark. Screening with spot sputum testing and IGRA generated comparable results in diagnosing TB in this setting.

Introduction

In Denmark, as in many countries with low TB incidence, TB is to a large extent only seen in immigrants from countries with high TB incidence and in high-risk groups such as people with drug or alcohol addiction, and homeless people (ECDC, 2016; Gupta et al., 2018; Kruse et al. 2018; Lillebaek et al., 2012; WHO, 2015). Focus should be on these groups when TB prevention and eradication strategies are planned (ECDC, 2016; Gupta et al., 2018; Kruse et al., 2018; Lönnroth et al., 2015; de Vriers et al., 2014). A study from the Copenhagen area in Denmark found a TB prevalence of 2233/100.000 among socially marginalized people screened with a single sputum test (Jensen et al., 2015), while a study from Aarhus, Denmark found 0.8% with TB and 13% with LTBI in screening at a homeless shelter in 2014 (Staerke et al., 2016). Similar TB incidence has been reported from screening among socially marginalized persons in cities across low-incidence countries such as France, Spain, United Kingdom, United States and Germany (Badiaga et al., 2009; Bernard et al., 2012; Goetsch et al., 2012; Jimenez-Fuentes et al., 2014; Miller et al., 2006; Story et al., 2012; de Vries et al., 2007). These studies provide evidence of an ongoing problem with TB in the vulnerable, socially marginalized citizens. Due to these findings, TB screening among users of homeless shelters, drop-in centers and street clinics has been set up in several large cities of Denmark in recent years.

* Corresponding author at: Department of Infectious Diseases, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: ninase@rm.dk (N.B. Staerke).

https://doi.org/10.1016/j.ijid.2020.10.076

The incidence of TB in Denmark was 5.0/100.000 in 2018 (SSI, 2019) placing the country in the low-incidence category. While a quarter of the global population is estimated to have LTBI (Cohen et al., 2019; Houben and Dodd, 2016) the prevalence of LTBI is estimated to be as low as 1.2–4.2% in Denmark (Houben and Dodd, 2016); however, data on the prevalence of LTBI in high-risk groups is limited. The aim of this study is to describe the findings of systematic consecutive screening for TB and LTBI among socially marginalized persons in urban areas of Denmark, and to assess the yield of using spot sputum testing versus IGRA and chest X-ray. This study presents the results from TB screenings among homeless and other socially marginalized high-risk citizens in the cities of Aarhus, Aalborg and Esbjerg through the years 2014–2019.

Methods

Materials and study population

Data from TB screenings performed in Esbjerg (2014–2019), Aalborg (2016–2019) and Aarhus (2017–2019) was collected retrospectively for this study. These three cities are the largest cities in the Danish region of Jutland. Data was drawn from local databases and electronic patient records and anonymized.

Screening was carried out approximately once per year, with a team of nurses and doctors visiting the screening sites and offering testing to everyone present. Testing was offered at homeless shelters, temporary housing facilities and drop-in centers; the target group being users of these facilities. The screening rounds were planned in collaboration with the municipalities and announced to users of the facilities in advance in order to increase attendance. Data was collected from local databases and patient records, including: results from any screening tests applied (IGRA, spot sputum testing and chest X-ray); data on previously diagnosed TB or LTBI; and data on age and gender of screening participants.

Testing strategies

Two different testing strategies were used in the screening programs during the study period. At some screening rounds an IGRA test was used as the primary screening test for TB naive subjects, targeting both LTBI and TB, and an X-ray used as the primary screening test for persons who had previously had LTBI or TB. In other screening rounds a single spot sputum test was used as the primary test exclusively targeting TB (Figure 1). These two methods where applied at different time points in the three cities depending on factors such as practical conditions e.g., allowing for blood sampling, resources and the opinion of the local doctors responsible for the screening program.

IGRA tests used were either QuantiFERON®-TB Gold Plus (QIAGEN GmbH, QIAGEN Strasse 1, 40724 Hilden, Germany) or T-SPOT®.TB (Oxford Immunotec Global PLC, 143 Park Drive, Milton Park, Abingdon, Oxfordshire, United Kingdom). Both were used according to the instructions and analyzed at licensed laboratories at Statens Serum Institut, Artillerivej 5, 2300 København S., Denmark, or the Research Laboratory at the Department of Pulmonary Diseases at Aarhus University Hospital, Nørrebrogade 23B, 8000 Aarhus C.

All sputum samples were analyzed at the Department for Tuberculosis and Mycobacteria at Statens Serum Institut, Artillerivej 5, 2300 København S, Denmark. All samples underwent microscopy for acid-fast bacilli, and culture for mycobacteria for 56 days. PCR-testing for *Mycobacterium tuberculosis* complex was performed only on request from the physician.

Statistics

Data were analyzed using Microsoft Excel and Stata, version 14 (StataCorp, College Station, TX). Data are presented as proportions and percentages. Prevalence of TB and LTBI was calculated using the results of each person's first test result, divided by the total number of subjects. The effect of screening for TB and LTBI are expressed as percentage of positive test results using each test strategy, and by number needed to screen (NNS). Proportions were compared using student's chi-square test, applying a significance level of 0.05.

Results

In total, 1024 persons were tested in one or more screening rounds, yielding a total of 1399 screening tests. Uptake was

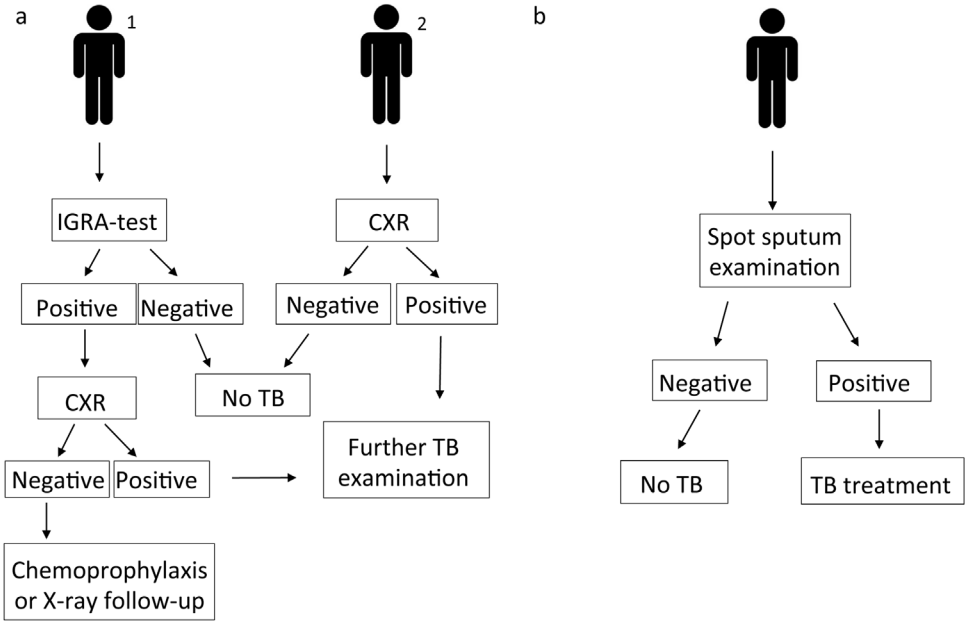

Figure 1. Flow chart of screening procedures. (a) Person 1 is TB naive, person 2 has previous TB or LTBI. TB examination includes microscopy, PCR and culture of relevant material (sputum, bronchoalveolar lavage fluid, gastric lavage fluid etc.) and physical exam. (b) Spot sputum examination includes microscopy, PCR and culture.

estimated to be 1/4 of the eligible population as 1172 persons were homeless in the three cities combined in 2019 (Benjaminsen, 2019) and in a sample of the persons screened in Aarhus, Aalborg and Esbjerg 28% were homeless (data not yet published). Assuming that the proportion of homelessness is the same in the untested population the eligible population would be 4186 persons.

Overall, 8.1% (113/1399) of tests resulted in a diagnosis of either TB or LTBI. 67.7% of the screened population were men and there was a mean age of 50 (range 15–87). Spot sputum testing was performed as the primary test in 758 persons (54.2%), while 469 (33.5%) and 172 (12.2%) were tested with IGRA or X-ray, respectively (Table 1).

Active tuberculosis

A total of 36 cases of TB were found through screening. Overall, the yield of TB screening was 2.6% (36/1399) and the NNS to find one case of TB was 39. The prevalence of TB, calculated from first screening instance, was 22/1024 (2.15%) or 2.148/100.000. In total, 241 persons completed two or more screening rounds and 14/36 (38.9%) of the TB diagnoses were made at second or third screening (Table 2). Only 51 persons completed four or more screening rounds and no additional TB cases were found among these. In total, 19/36 cases of TB (52.8%) were found using spot sputum testing, while 8/36 cases (22.2%) were found with the IGRA test and 9/36 with X-ray (25%). Combining IGRA for TB naïve subjects with X-ray for those with previous TB or LTBI revealed a TB rate of 2.7% and NNS of 38, while spot sputum testing had a positive rate of 2.5% and NNS of 40 (p = 0.86).

All TB cases were confirmed with sputum samples evaluated using culture and microscopy. PCR for mycobacterium tuberculosis was carried out in 27/36 cases (75%) and in 10 cases (37%) the PCR test was positive. In 20 cases (55.6%) the sputum samples were culture positive for TB but smear negative. When using spot sputum tests as the primary screening test, 10/19 samples that were culture positive for TB (52.6%) were smear negative. Of 17 culture-positive TB cases the 17 cultures that were positive for TB that were found using primary IGRA screening, 10 (58.8%) were smear negative (p = 0.84) (Table 1).

Table 1
Demography of the population screened for TB.

	Screened population (n = 1399)	TB cases (n = 36)
Age, years, mean (range)	50 (15–87)	48 (29–60)
Sex		
Female	452 (32.3%)	12 (33.3%)
Male	947 (67.7%)	24 (66.7%)
City		
Aarhus	565 (40.4%)	6 (1.1%)
Esbjerg	409 (29.2%)	19 (4.6%)
Aalborg	425 (30.4%)	11 (2.6%)
Total	1399 (100%)	36 (2.6%)
Primary test		
Sputum	758 (54.2%)	19 (2.5%)
IGRA or X-ray	641 (45.8%)	17 (2.7%)
IGRA	469 (33.5%)	8 (2.0%)
X-ray[a]	172 (12.3%)	9 (5.2%)
Sputum results		
Positive microscopy		14 (38.9%)
Positive PCR		10 (37.0%[b])
Positive microscopy or PCR		16 (44.4%)
Positive culture		36 (100%)

[a] Persons with previous LTBI or TB.
[b] PCR was performed in 27 cases.

Table 2
Results from consecutive TB screening tests. Screened population and number of TB cases identified by number of screening rounds completed.

Number of screening rounds completed	Screened population	TB cases (%)
1	1024	22 (2.15%)
2	241	11 (4.6%)
3	83	3 (3.6%)
4–7	51	0

Latent tuberculosis

In 469 instances, an IGRA test was used as the primary-test was used as the primary test. Hereof, 98 were positive, whereof 77 subjects were diagnosed with latent tuberculosis, 8 with active tuberculosis, 12 were inconclusive due to loss to follow-up and 1 had previous active TB Figure 2). Calculated at the first instance of IGRA-testing, we found an LTBI incidence of 70/400 (17.5%) or 17.500/100.000 was identified. Of the patients diagnosed with LTBI 34 (44%) received chemoprophylaxis while 43 (56%) either declined treatment, were lost to follow-up, or were deemed not eligible for treatment by the treating physician (Table 3).

Discussion

In this study, high rates of TB and LTBI were identified among socially marginalized persons tested in screening programs. Furthermore, detection rates of active TB stayed high for subjects tested at up to three consecutive screening rounds. Additionally, similar detection rates for TB using two different screening strategies – spot sputum testing and IGRA supplemented with X-ray – were identified.

The high incidence of active and latent TB identified underlines the importance of active case finding focused on the vulnerable group of socially marginalized citizens. A systematic review of active case finding strategies among the homeless describes a yield from 0 to 3.1% for TB (Hamilton et al., 2018) placing the screening programs described in this study in the high end of the spectrum

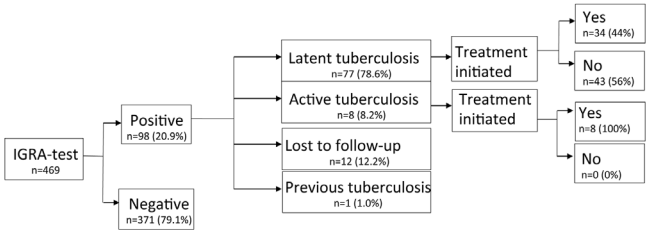

Figure 2. Results from IGRA-testing.

Table 3
Demography of the population screened for LTBI.

	Screened population (n = 469)	LTBI (n = 77)
Age, years, mean (range)	51 (15–81)	53 (20–71)
Sex		
Female	170 (36.2%)	18 (23.4%)
Male	299 (63.8%)	59 (76.6%)
City		
Aarhus	124 (26.4%)	17 (13.7%)
Esbjerg	237 (50.5%)	43 (18.1%)
Aalborg	108 (23.1%)	17 (15.7%)
Total	469 (100%)	77 (16.4%)
Prophylactic treatment initiated	NA	34 (44.2%)

with an overall yield of 2.6% (36/1399). Notably the TB incidence identified is similar to that seen in Copenhagen (Jensen et al., 2015) suggesting that TB transmission among the socially marginalized is a country-wide issue in Denmark.

The high TB prevalence shows that the screening programs reach a relevant population, however, it may also suggest that testing is too limited resulting in cases going undetected. From our estimate as many as 3/4 of those eligible for screening did not attend; the rate of TB in the untested group is unknown. A Swiss study reporting results from TB screening among the homeless found that attending screening was associated with male gender, age below 25 years and homelessness for less than 12 months (Janssens et al., 2017). A study from Atlanta, USA, found that returning for reading ofa reading of a tuberculin skin test was more likely for those who knew someone with TB, did not misuse drugs or alcohol, had completed high-school and had attended screening before (Bock et al., 1999). These findings are ambiguous as to whether the untested population can be expected to be at high risk for TB, as substance misuse, homelessness and having close contacts with TB are all known risk factors for developing TB. However, it is evident that a large proportion of the eligible population opt out of screening and efforts should be made to increase attendance to the screening programs, possibly through offering incentives, which has been shown to be effective (Hamilton et al., 2018).

The study was not able to determine whether one of the two test strategies is superior to the other in detecting TB as both the yield and the rate of smear test negative cases in the two strategies were almost equal. The use of the spot sputum test for TB screening was evaluated in a similar setting by Jensen et al. (2015) where a comparable yield was described. A major issue with using the currently available IGRAs for TB screening is the suboptimal sensitivity described by Whitworth et al. (2019). According to their findings combinations with newly discovered *M. tuberculosis* antigens may increase sensitivity and when new generations of IGRAs are developed these should be evaluated for screening use. The spot sputum test is simple to retrieve but is unable to diagnose LTBI and thereby be useful in the prevention of TB transmission through chemoprophylaxis or close follow-up of patients with LTBI. The choice of test strategy should be based on a careful evaluation of the subset of the population that the particular screening round is targeting. Some parts of the population may be easier to access for prophylactic treatment and close follow-up, in these cases using an IGRA test either as the primary screening test or in combination with another test could be an advantage.

All TB cases identified in this study were culture-positive This reflects that a sputum culture test was used either as the only test performed, or as the confirmation test following a positive IGRA or an X-ray suggestive of TB. It is well known that a significant proportion of TB cases found during passive case finding are culture-negative for TB, hence the diagnosis is reached by clinical and radiological investigations without microbiological evidence. Cases may therefore have been missed that would have been judged culture-negative for TB in a more comprehensive investigation. However, in a screening for TB, the objective is to detect TB cases among those not presenting for clinical evaluation due to characteristic symptoms. A full clinical and radiological evaluation is neither feasible, nor ethical, in this context. One could view culture-positivity as the threshold accepted as the lower level of detection under these circumstances. According to Frascella et al. (2020) 50.4% of microbiologically confirmed TB cases found through national surveys were subclinical which supports the use of a microbiological method as opposed to symptom screening in TB screening programs. Furthermore, repeated testing of high-risk groups may to some extent compensate for missing culture-negative cases; for example, some of the cases detected at the second or third screening round may have been detected initially in a conventional diagnostic setup, applying, for example, CT scans and bronchoscopy sampling.

PCR for *M. tuberculosis* complex was performed on 27/36 (75%) of the culture confirmed samples and in 10 of 27 cases (37%) the test was positive suggesting a lower sensitivity of PCR as opposed to culture. Nevertheless, PCR has the advantage of a faster result, and hence, when positive, will lead to earlier treatment which favors its routine use in this setting.

Different rates of TB where found in the three cities which probably reflects a difference in demography of the population of socially marginalized people between the cities with regards to risk factors such as ethnic origin in a country with high TB prevalence or substance abuse, but may also reflect differences in how widely screening was offered.

The material in this study was collected retrospectively which entails a limitation to the comparison of the test strategies as the subjects were not randomized and there were no considerations regarding clustering of cases. As the information obtained for this study was anonymized the amount of information about the individual subjects is very limited including individual risk factors such as homelessness, substance abuse and country of origin; this is also a limitation to this study.

In conclusion, this study demonstrated a high rate of TB and LTBI among socially marginalized citizens in Denmark, with comparable yield using two different screening strategies. A large number of TB cases were found to be sputum smear-negative, possibly reflecting an early disease stage and a low risk of disease transmission. These findings provide new knowledge about screening and management of TB and LTBI among socially marginalized citizens and may build on the experience necessary to reduce the number of new TB cases and the spread of the disease in this vulnerable high-risk population and ultimately reach the goal of TB elimination.

Ethical statement

Data for this study was anonymized to ensure the privacy of the subjects. As the study used anonymized data informed consent was not possible. This study was supported financially by Aarhus University. The authors have no conflict of interest with regards to this study.

Acknowledgments

Nurses Vibeke Muff Sørensen and Tilde Ellingsgaard from Department of Pulmonary Medicine at Esbjerg Hospital and nurse Mette Christensen from Aalborg municipality made significant contributions to this study through their tireless work with tuberculosis screening.

References

Badiaga S, et al. Contribution of a shelter-based survey for screening respiratory diseases in the homeless. Eur J Public Health 2009;19(2):157–60.
Benjaminsen L. Hjemløshed i Danmark 2019 — National kortlægning. The Danish Center for Social Science Research — VIVE; 2019. https://www.vive.dk/media/pure/14218/3352843.
Bernard C, et al. Impact of a 14-year screening programme on tuberculosis transmission among the homeless in Paris. Int J Tuberc Lung Dis 2012;16(5):649–55.
Bock NN, et al. A tuberculin screening and isoniazid preventive therapy program in an inner-city population. Am J Respir Crit Care Med 1999;159(1):295–300.
Cohen A, et al. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J 2019;54(3).
de Vries G, et al. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. Am J Respir Crit Care Med 2007;176(2):201–7.
de Vries G, et al. Epidemiology of tuberculosis in big cities of the European Union and European Economic Area countries. Euro Surveill 2014;19(9).

European Center for Disease Prevention and Control. Guidance on tuberculosis control in vulnerable and hard-to-reach populations. Stockholm: ECDC; 2016. https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-vulnerable-groups.pdf.

Frascella B, et al. Subclinical tuberculosis disease — a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. Clin Infect Dis 2020;(September (16)) Online ahead of print.

Goetsch U, et al. Tuberculosis among drug users and homeless persons: impact of voluntary X-ray investigation on active case finding. Infection 2012;40(4):389–95.

Gupta RK, et al. Active case finding and treatment adherence in risk groups in the tuberculosis pre-elimination era. Int J Tuberc Lung Dis 2018;22(5):479–87.

Hamilton K, Tolfree R, Mytton J. A systematic review of active case-finding strategies for tuberculosis in homeless populations. Int J Tuberc Lung Dis 2018;22(10):1135–44.

Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016;13(10)e1002152.

Janssens JP, et al. Screening for tuberculosis in an urban shelter for homeless in Switzerland: a prospective study. BMC Infect Dis 2017;17(1):347.

Jensen SG, et al. Screening for TB by sputum culture in high-risk groups in Copenhagen, Denmark: a novel and promising approach. Thorax 2015;70(10):979–83.

Jimenez-Fuentes MA, et al. Screening for active tuberculosis in high-risk groups. Int J Tuberc Lung Dis 2014;18(12):1459–65.

Kruse A, et al. Tuberkulosebekæmpelse i Danmark. Et nationalt Tuberkuloseprogram. Danish Society of Respiratory Medicine; 2018. https://www.lungemedicin.dk/fagligt/faglige-dokumenter/klaringsrapporter-1/11-tb-nationalt-2018.html.

Lillebaek T, et al. Continued problems with tuberculosis among Danes and Greenlanders in Denmark and the need for reinforced control—a systematic review. Ugeskr Laeger 2012;174(44):2696–701.

Lönnroth K, et al. Towards tuberculosis elimination. An action framework for low-incidence countries. Eur Respir J 2015;45:928–52.

Miller TL, et al. Using cost and health impacts to prioritize the targeted testing of tuberculosis in the United States. Ann Epidemiol 2006;16(4):305–12.

Staerke NB, et al. Latent tuberculosis infection is prevalent among socially marginalised citizens in Aarhus, Denmark. Dan Med J 2016;63(7).

Statens Serum Institut. Tuberkulose — opgørelse over sygdomsforekomst 2018. SSI; 2019. https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/t/tuberkulose—opgoerelse-over-sygdomsforekomst-2018.

Story A, et al. Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. Int J Tuberc Lung Dis 2012;16(11):1461–7.

Whitworth HS, et al. Clinical utility of existing and second-generation interferon-gamma release assays for diagnostic evaluation of tuberculosis: an observational cohort study. Lancet Infect Dis 2019;19(2):193–202.

World Health Organization. The end TB strategy. WHO; 2015. https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1.