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Chest x-ray findings in tuberculosis patients identified by passive and active case finding: A retrospective study

Ema Rastoder[a,*], Saher Burhan Shaker[a], Matiullah Naqibullah[a], Mathilde Marie Winkler Wille[b], Mette Lund[b], Jon Torgny Wilcke[a], Niels Seersholm[a], Sidse Graff Jensen[a]

[a] Department of Respiratory Medicine, Gentofte Hospital, Kildegaardsvej 28, 2900 Hellerup, Copenhagen, Denmark
[b] Department of Radiology, Hillerød Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark

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ABSTRACT

Background: Chest x-ray is central in screening and diagnosis of tuberculosis. However, sputum culture remains gold standard for diagnosis.
Aim: To establish the rate of normal chest x-rays in tuberculosis patients found by spot sputum culture screening, and compare them to a group identified through passive case finding.
Method: Chest x-rays from 39 culture-positive patients, identified by spot sputum culture screening in Copenhagen from 2012 to 2014, were included in the study (spot sputum culture group(SSC)). 39 normal chest x-rays from persons screened by mobile x-ray, and 39 chest x-rays from tuberculosis-patients identified through passive case finding(PCF) were anonymised and randomised. Two respiratory physicians and two radiologists assessed the chest x-rays.
Results: The normal chest x-ray rate was higher in the non-tuberculosis control group (median = 32 (82.1%), range = 74.4% – 100%), compared to the SSC group (median = 7 (17.9%), range = 10.3% – 33.3%), and the PCF controls (median = 3(7.7%), range = 2.6% – 15.4%). In the SSC group 14 (35.9%) were categorized as normal by at least one study participant.
Conclusion: A substantial minority of patients diagnosed with tuberculosis by spot sputum culture screening, and through passive case finding would not have been identified with chest x-ray alone, highlighting that a normal chest x-ray does not exclude pulmonary tuberculosis.

1. Introduction

In 2016 the tuberculosis(TB) incidence rate in Denmark was 5.7/100,000 [1], but the incidence rate is not decreasing as it is seen in our neighboring countries: Finland, Norway and Sweden [2]. As in other low incidence countries, TB is most common in high-risk groups in Denmark. Limited access to the health care system may cause ongoing transmission among alcoholics, drug users, immigrants and homeless people. Thus, active screening among TB high-risk groups is pivotal in gaining TB control.

Several studies using chest x-ray (CXR) to screen for TB have been published, describing the method as effective with immediate results [3–8]. From September 2012 through June 2014 seven screening rounds, using spot sputum, were performed at 11 locations in Copenhagen. The participants with positive sputum smear microscopy, -culture or -nucleic acid amplification tests (NAAT) were referred to further investigation including CXR screening.

Results from this retrospective study were published in 2015. In total 1075 participants were screened and 36(3.35%) TB patients identified. The physicians assessing the chest x-rays had not been blinded to the fact that the patients had participated in the project. They concluded that 22.2% of TB patients found by spot sputum screening did not have CXR changes suggestive of TB [9].

The aim of this study was, in a blinded setting, to establish the rate of normal CXRs in tuberculosis patients found by spot sputum culture screening, and to compare the rate of CXR changes in this group, to a group of tuberculosis patients identified through passive case finding.

2. Methods

2.1. Patients and controls

Spot Sputum Culture (SSC) group: 39 TB-patients identified by spot sputum screening in eight screening rounds from September 2012 to

* Corresponding author.
E-mail address: ema.rastoder@regionh.dk (E. Rastoder).

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Table 1
Population characteristics at baseline, in the three patient/control groups: Patients found by spot sputum culture screening (SSC group); Patients identified by passive case finding (PCF controls); Participants who were screened by mobile chest x-ray and did not have tuberculosis (non-TB controls).

	SSC group *n* (%)	PCF controls *n* (%)	Non-TB controls *n* (%)	Total *n* (%)	*P value*[*]
Patients screened	39 (33.33)	39 (33.33)	39 (33.33)	117	
Age, year, mean (SD)	50.19 (9.7)	50.28 (14.5)	50.25 (9.2)	50.24 (11.4)	0.4150
Sex					
Male	28 (71.8)	32 (82.1)	28 (71.8)	88 (75.2)	0.2824
Substance abuse[**]					
Alcohol abuse					
Yes	23 (58.97)	16 (41.03)	/NA	39 (33.3)	0.2739
Smoking					
Yes	28 (71.79)	18 (46.1%)	/NA	46 (39.3)	0.0706
Cannabis					
Yes	22 (56.41)	9 (23.08)	/NA	31 (26.5)	0.0108
Illicit drugs					
Yes	2 (5.13)	3 (7.69)	/NA	5 (4.3)	0.7444
Homeless[***]					0.0379
Yes	21 (53.85)	10 (25.64)	/NA	31 (26.5)	
No	17 (43.9)	24 (61.54)	/NA	41 (35.0)	
Other[****]	1 (2.56)	3 (7.69)	/NA	4 (3.4)	
Originating from high incidence country					0.1569
Yes	27 (69.3)	23 (59.0)	/NA	50 (42.7)	
No	10 (25.6)	16 (41.0)	/NA	26 (22.2)	
Unknown	2 (5.1)	0 (0)	/NA	2 (1.7)	
Greenlander					
Yes	19 (48.7)	8 (20.5)	/NA	27 (23.1)	0.0063
Culture samples					
Positive	38 (97.4)	30 (76.92)	/NA	68 (58.1)	0.0067

[*] *P* value between the SSC group and the PCF controls.
[**] Information about substance abuse was not available in 1 SSC case and in 2 PCF controls cases. These tree patients are categorized as having no substance abuse.
[***] Home status was not available in two cases in PCF controls; these two patients are not included in the analysis.
[****] These patients are in prison.

September 2014. The screened population were socially marginalised persons (homeless persons, alcoholics etc.). A sputum sample was collected from each patient on as many occasions as possible and sent for analysis. If the sputum sample was suggestive of TB (smear microscopy and/or culture positive) the participant was notified and referred for further investigations and treatment at the Department of Respiratory Medicine at Gentofte Hospital. A detailed description of the screening project has previously been published [9].

Passive case finding (PCF) controls: TB-patients identified after contacting the health care authorities due to symptoms suggestive of TB, 39 consecutive TB patients treated at the Department of Respiratory Medicine, Gentofte Hospital from May 1st 2012.

Non-TB controls: 39 consecutive persons from socially marginalised groups in Copenhagen screened by mobile chest x-ray (MCXR) from March 1st 2014, with a chest x-ray assessed to be normal, by a respiratory physician external to this study, were included in the control group. Bone fractures were not thought to influence the overall interpretation of the CXR and these images were therefore included.

All individuals with poor x-ray quality (anatomical inclusion, projection, rotation, inspiration/lung volume, penetration and artefacts) or individuals who had been diagnosed and treated at another hospital were excluded. Sixteen individuals from the PCF group were excluded, 13 because of missing CXRs, 1 because only CT of the chest was available, and 2 because of treatment initiation at another hospital. The investigator of the project decided which x-rays did not meet the standards listed above.

Participants were defined as TB patients if they had positive sputum culture or had positive sputum smear and/or nucleic acid amplification test with symptoms and/or CXR changes suggestive of TB.

2.2. Chest x-ray blinding and interpretation

In this project we used digital x-rays with 2 views. They were analysed on high resolution screens, and the readers had unlimited time to read the images. The images were anonymised, numbered from one to one hundred and seventeen, and put in random order to avoid recognition of the patient groups.

Four independent readers (two respiratory physicians and two radiologists) assessed the chest radiographs. The respiratory physicians have been in the profession for 26 and 21 years respectively, for the radiologists it is 11 and 20 years. They filled in questionnaires prepared for the study. Inspired by two papers [10, 11] CXRs were classified as normal, acute CXR changes and chronic CXR changes, followed by a sub-categorisation of the acute and chronic changes. Acute: (a) The suspicion of active TB is high, (b) CXR changes compatible with active TB, (c) Acute CXR changes not suggestive of active TB. In the tables a and b have been merged to the category, acute changes suggestive of tuberculosis. Chronic: (a) Rib fractures, (b) CXR changes typical of healed TB and (c) Chronic pulmonary changes of unknown origin [10, 11].

2.3. Analyses of data

Data in the article is presented using median and range calculated among the four readers.

The Chi-squared test was used to compare CXRs in the SSC group and the PCF control group.

We used the kappa statistics to assess agreement among physicians and radiologists. In this study strength of agreement is defined as follows:

Kappa-value < 0.20 = Poor
Kappa-value 0.21–0.40 = Fair
Kappa-value 0.41–0.60 = Moderate
Kappa-value 0.61–0.80 = Good
Kappa-value 0.81–1.00 = Very good

Sensitivity was calculated using the x-ray results of culture positive patients from the SSC and the PCF group; and specificity was calculated using the x-ray results of non-TB patients examined by mobile CXR. The

sensitivities and the specificities reported are the means of the sensitivity and the specificities of the readers (respiratory physicians and radiologists).

2.4. Ethics

The study was a cross-sectional register study as confirmed by the Central Ethics Committee of Denmark (protocol no. H-15007396). Permission to access and process data was given by the Danish Data Protection Agency (j.nr.: 2007 – 58 – 0015).

3. Results

We analysed 2 × 39 CXRs from patients diagnosed with TB, and 39 from persons without TB. Table 1 shows the three groups, and their baseline characteristics. 1(2.6%) patient in the SSC group and 9(23.1%) patients in the PCF group were culture negative. Patients in the SSC group were significantly more likely to be homeless compared to the PCF controls (p value = 0.0379), and they were significantly more likely to have a cannabis abuse (p value = 0.0108). 48.7% in the SSC group were Greenlanders compared to, 20.5% in the PCF controls (p value = 0.0063). There was no statistically significant difference in the age and sex distribution among the three groups

Table 2 shows the x-ray results of the SSC group and the PCF controls. As expected, the rate of normal CXRs was highest in the non-TB control group (median = 32 (82.1%) and range = 74.4% – 100%) compared to the SSC group (median = 7 (17.9%), range = 10.3% – 33.3%) and the PCF controls (median = 3 (7.7%), range = 2.6%–15.4%). In the SSC group 14 (35.9%) were categorized as normal by at least one reader.

In Table 3 the results from patients with culture-negative TB have been excluded, thus, solely including results from patients with culture verified tuberculosis. The rate of normal CXRs in the SSC group was higher (median = 6 (15.8%), range 10.5%–31.6%) compared to the PCF controls (median = 1 (3.3%), range = 0%–10%).

The overall level of agreement for diagnosing x-rays as normal among the four readers was good (kappa-value = 0.67). Respiratory physicians were more likely to agree on acute changes (0.61) compared to the radiologists (0.54). Radiologists on the other hand were more likely to agree on changes suggestive of TB (0.67) compared to the respiratory physicians (0.56) (Table 4).

The sensitivity of the radiologists was higher (0.91) compared to the respiratory physicians (0.85). In contrast the specificity of the respiratory physicians (0.93) was higher compared to the radiologists (0.79).

4. Discussion

In this blinded study we established that in the SSC group of TB-patients 17.9% had CXRs categorized as normal, furthermore 35.9% of the CXRs in this group were categorized as normal by at least one of the participating respiratory physicians and/or radiologists. This highlights the fact that a normal CXR does not exclude active TB. We found a higher percentage of normal CXRs in the SSC group (17.9%), compared to the PCF controls (7.7%). Our results support the findings of Jensen et al. study from 2015, where 22.2% of TB patients found by spot sputum screening had no CXR changes suggestive of TB [9].

The respiratory physicians and radiologists participating in this study were presented with nothing except a CXR of each patient, whereas in the study by Jensen et al physicians were aware of the patients' symptoms and their positive spot sputum samples or positive microscopy. A study published in 2012 by Van't Hoog et al. showed a sensitivity of 100% when symptoms and CXR assessments were combined, an awareness of symptoms increased sensitivity. Surprisingly in our study we found the opposite to be true: Fewer patients from the SSC group were categorized as normal (17.9%) compared to Jensen et al. non-blinded study (22.2%). In their daily work, the four readers do not assess CXRs with such a high TB incidence, which could have led to an over-reporting of normal CXRs. However our results suggest that spot sputum culture examination identifies TB patients that would not have been found by CXR screening alone.

Almost 36% of CXRs in the SSC group were categorized as normal by at least one reader. In this study, respiratory physicians and radiologists had unlimited time to assess each CXR. In daily work evaluation of CXRs may not be as thorough because of time limitations. It is therefore likely that the number of normal CXRs might be around 36% or perhaps even higher. This is an important finding, because of CXRs central role in TB diagnostics and screening [4–6, 12–22] and may indicate the complementary roles of CXR and sputum analysis in screening for tuberculosis in high risk groups.

Table 1 illustrates that 1 individual in the SSC group and 9 in the PCF group were culture negative. The patient in the SSC group had microscopy verified tuberculosis, and was therefore was included. The 9 patients in the PCF group were defined as TB patients based on a combination of chest x-ray findings, symptoms, such as weight loss, fatigue, and haemoptysis, and a good response to anti- tuberculosis treatment. According to ECDC guidelines diagnoses of culture-negative pulmonary tuberculosis should be based on above mentioned criteria

Table 2
Chest x-ray results from patients found by spot sputum culture screening (SSC group), and patients identified by passive case finding (PCF controls); Assessed by two respiratory physicians and two radiologists.

	Respiratory physicians Physician 1			Physician 2		
	SSC group *n*(%)	PCF controls *n* (%)	*P value*	SSC group *n* (%)	PCF controls *n* (%)	*P value*
Normal	6 (15.4)	3 (7.7)	0.2877	13 (33.3)	6 (15.4)	0.0648
Abnormal						
Acute changes	23 (59.0)	28 (71.8)	0.2340	20 (51.3)	21 (53.9)	0.8206
Acute changes, suggestive of TB	15 (38.5)	21 (53.9)	0.1730	12 (30.8)	17 (43.6)	0.2414
Chronic changes	13 (33.3)	12 (30.8)	0.8083	7 (18.0)	13 (33.3)	0.1197
Total*	33 (84.6)	36 (92.3)	0.2877	26 (66.7)	33 (84.6)	0.0648
	Radiologists Radiologist 1			Radiologist 2		
	SSC group *n* (%)	PCF controls *n* (%)	*P value*	SSC group *n* (%)	PCF controls *n* (%)	*P value*
Normal	4 (10.3)	3 (7.7)	0.6920	8 (20.5)	1 (2.6)	0.0131
Abnormal						
Acute changes	32 (82.1)	33 (84.6)	0.7613	26 (66.7)	29 (74.4)	0.4563
Acute changes, suggestive of TB	20 (51.3)	24 (61.5)	0.3611	19 (48.7)	22 (56.4)	0.4963
Chronic changes	8 (20.5)	13 (33.3)	0.2018	10 (25.6)	14 (35.9)	0.3264
Total*	35 (89.7)	36 (92.3)	0.6920	31 (79.5)	38 (97.4)	0.0131

* Total represents the number of patients with some kind of abnormality. Each abnormality is only counted for once.

Table 3
Chest x-ray results from patients found by spot sputum culture screening (SSC group, $n = 38$), and patients identified by passive case finding (PCF controls, $n = 30$); assessed by two respiratory physicians and two radiologists. Only culture positive patients were included.

	Respiratory physicians Physician 1 SSC group *n* (%)	PCF controls *n* (%)	*P value*	Physician 2 SSC group *n* (%)	PCF controls *n* (%)	*P- value*
Normal	5 (13.2)	1 (3.3)	0.1561	12 (31.6)	3 (10.0)	0.0331
Abnormal						
Acute changes	23 (60.5)	24 (80.0)	0.0844	20 (52.6)	18 (60.0)	0.5434
Acute changes, suggestive of TB	15 (39.5)	18 (60.0)	0.0926	12 (31.6)	15 (50.0)	0.1232
Chronic changes	13 (34.2)	8 (26.7)	0.5038	7 (18.4)	10 (33.3)	0.1585
Total*	33 (86.8)	29 (96.7)	0.1561	26 (68.4)	27 (90.0)	0.0331
	Radiologists Radiologist 1 SSC group *n* (%)	PCF controls *n* (%)	*P value*	Radiologist 2 SSC group *n* (%)	PCF controls n (%)	*P value*
Normal	4 (10.5)	1 (3.3)	0.2592	7 (18.4)	0 (0)	0.0131
Abnormal						
Acute changes	31 (81.6)	26 (86.7)	0.5716	26 (68.4)	26 (86.7)	0.0782
Acute changes, suggestive of TB	20 (52.6)	20 (66.7)	0.2429	19 (50.0)	20 (66.7)	0.1676
Chronic changes	8 (21.1)	9 (30.0)	0.3975	10 (26.3)	8 (26.7)	0.9740
Total*	34 (89.5)	29 (96.7)	0.2592	31 (81.6)	30 (100)	0.0131

* Total represents the number of patients with some kind of abnormality. Each abnormality is only counted for once.

Table 4
Overall levels of agreement between respiratory physicians and radiologists when evaluating chest x-rays for culture positive and negative patients. Categorizations: Normal, with acute changes and with changes specifically suggestive of active TB.

Kappa - value	Respiratory physicians	Radiologists
Normal	0.69	0.65
Acute changes	0.61	0.54
Changes suggestive of TB	0.56	0.67

[23].

Two readers reported significantly more frequent CXR changes among culture positive PCF controls compared to culture positive SSC patients (Table 3). A similar but non-significant difference in rate of abnormal CXRs between PCF controls and SSC patients were seen in the results from the two other readers. The patients in the SSC group may be in an early stage of their disease and therefore have less pulmonary infiltrations. Whereas, the PCF controls seek help from health care authorities, which implies that they have more pronounced symptoms and perhaps their TB stage is more advanced, leading to progressive pulmonary infiltrations. As shown in Table 1, patients in the SSC group are significantly more likely to be homeless and have an abuse (cannabis) compared to the PCF controls. Thus, access to health care providers and awareness of TB symptoms may be limited in this group; therefore we would expect them to have a more progressive stage of TB when diagnosed. This is not found in our study where the SSC group had a higher median of normal CXRs (17.9%) compared to the PCF group (7.7%), highlighting that the SSC patients in this study were found at an early stage. To establish the stage of TB we would need to know about the onset of symptoms, but there has been no data available for that.

Table 4 shows an equally, good agreement among the respiratory physicians and among the radiologists categorizing CXRs as normal. However, difference in agreement between respiratory physicians and radiologists was seen in the subgroups. This observation suggests that radiologists are more likely to find the specific changes of TB, whereas respiratory physicians have a higher agreement when it comes to the general acute changes. This is also the main discovery by Abubakar et al., who reported a higher agreement between radiologists when it came to finding specific changes as for instance cavities, whereas the respiratory physicians were more likely to agree on general acute changes [24]. These variations underscore indeed the limited sensitivity of CXR in differentiating between subtle pathological changes and normal anatomical structures. In this regard it is interesting in future studies to investigate the potential role of low-dose CT in screening for the earliest pathological changes of tuberculosis in high-risk groups.

This study would have benefitted from a higher number of readers, which could demonstrate whether doctors from different specialities have a different approach to interpreting CXR images. Another limitation is the study's very homogeneous patient group, with 66.7% diagnosed with TB. The rate of TB in this particular population is much higher than the four readers are used to in their daily clinical practice, which might have lead to over-reporting of normal CXRs.

New innovative tools such as digital radiography with computer – automated reading and nucleic acid amplification tests are being applied and evaluated with the aim of improving early detection and diagnosis of TB in vulnerable populations [25] However, mobile x-ray screening continues to have a central role in active case finding in TB.

In conclusion our findings suggest that a substantial minority of patients diagnosed with TB by spot sputum culture screening had normal CXRs, and therefore might not have been identified by chest x-ray alone. As indicated by the result of the SSC- as well as the PCF-control group, a normal CXR does not exclude pulmonary TB. Patients suspected of TB seeking medical help are more likely to have CXR abnormalities suggestive of TB compared to patients found by active screening, indicating a more advanced disease stage.

Conflict of interest

We have no conflict of interest.

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