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Diagnostic validity of an expert tuberculosis commission that assists the diagnosis of bacteriologically negative suspected TB cases in Havana, Cuba

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Summary The Provincial Tuberculosis Commission of Havana, Cuba, a multi-speciality committee, assists clinicians in diagnosing bacteriologically negative tuberculosis (TB). At its weekly meetings, clinicians present the files of suspected TB cases for discussion, diagnosis and recommendations. This prospective study assessed the validity of the diagnoses made by the Commission by comparing the diagnoses made with diagnoses ascertained after one year of follow-up. Between October 2002 and December 2003, 126 patients suspected to have TB but who were bacteriologically negative completed diagnostic work at the Commission. Fifty-three (42%) were diagnosed as TB cases. The definite diagnosis of 116 patients (92%) was ascertained after one year of follow-up. Six patients diagnosed by the Commission as TB cases were suffering from other diseases, while one patient diagnosed with pneumonia had a definite diagnosis of pulmonary TB. The diagnostic sensitivity and specificity of the Commission were 98% (95% CI 93—100) and 92% (95% CI 85—98), respectively. The Provincial Tuberculosis Commission of Havana can be considered a valuable tool for the diagnosis of TB in patients suspected of TB but who are bacteriologically negative. A comparable approach, adapted to the local conditions, could prove useful in other epidemiological and healthcare settings.

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1. Introduction

Diagnosing bacteriologically negative tuberculosis (TB) remains a challenge for clinicians. Sputum smear microscopy, the diagnostic tool recommended by the directly observed treatment, short-course (DOTS) strategy of WHO STOP TB, detects only 50—60% of pulmonary TB cases (PTB).[1—3] Culture, considered the gold standard, can improve sensitivity by an additional 20%, but has a delay of 6—8 weeks before results become available.[1,4] Although the specificity of sputum smear microscopy and culture is at least 97%, the methods clearly lack sensitivity and are thus far from ideal diagnostic tools for PTB.[5] In many low-income countries, diagnosis is further fraught due to the poor availability of quality laboratory services.[6,7]

The detection of bacteriologically negative TB cases has not been a priority for most TB programmes, as these cases are less infectious and thus less critical for the control of TB at the population level. The emergence of the HIV epidemic has led to a rise in the incidence of TB, and has also made the diagnosis of TB more difficult. This is because HIV-infected persons suffering from PTB excrete fewer bacilli and are often found to be sputum smear-negative, and because HIV/TB co-infection broadens the differential diagnosis of TB.[8,9] The increase in sputum smear-negative PTB cases boosts the pool of contagious patients, as paucibacillary PTB remains infectious if no treatment is given.[10]

Various clinical criteria, scoring systems and algorithms have been developed to assist the diagnosis of sputum smear-negative PTB, but reviews of these approaches conclude that there is little evidence for their effectiveness, as published data have serious limitations and do not permit the generalisation of results.[8,11] This emphasises the importance of clinical and operational research to improve the diagnosis of bacteriologically negative TB.

In Cuba, a middle-income country with a well-developed national healthcare system,[12] the National Tuberculosis Programme (NTP) has received high priority and achieved remarkable successes in the fight against TB. This is demonstrated by a steadily declining TB detection rate, which fell to 6.6 new TB cases per 100 000 inhabitants in 2004.[13—15] In 2004, Cuba reported 782 TB cases, of which 736 were new cases [62% sputum smear-positive, 23% sputum smear-negative and 15% extrapulmonary TB (EPTB)] and 46 were relapsed cases.[16] Surveillance of drug resistance in 2004 estimated 5% drug resistance and 0.3% multidrug resistance in new TB cases.[17]

From 1995 onwards, multidisciplinary expert commissions were created at provincial level to assist health staff in the diagnosis of bacteriologically negative TB.[18] This article assesses the diagnostic validity of the Tuberculosis Commission operating in Havana Province.

2. Materials and methods

2.1. Study setting

The strategy of the NTP in Cuba is based on passive case finding through sputum smear microscopy and culture in persons who present with a productive cough of 14 days or more duration; free standard treatment with isoniazid, rifampicin, pyrazinamide and streptomycin or ethambutol under direct supervision for all TB cases; chemoprophylaxis for contacts of TB cases and BCG vaccination for newborns. Bacteriologically negative TB cases have been included in the official notification system since 1995.[19,20] In 1999, the NTP introduced a requirement for patients with a persistent respiratory syndrome but negative bacteriology to undergo, within 30 days, a diagnostic process including thorax X-ray, a course of broad-spectrum antibiotics and repeat microscopy and culture. Cases that remain without a diagnosis after this process must then be referred to the multidisciplinary Provincial Tuberculosis Commissions.[21]

The Commission of Havana Province is composed of two lung specialists, one radiologist and one epidemiologist.[18] It meets every Wednesday at the national reference hospital for TB, the Hospital Benéfico Jurídico in Havana City, and discusses patients suspected of TB whose diagnosis is not yet established and also patients who present clinical or therapeutic problems. The Commission is easily accessible and can be consulted by care providers from all provincial health structures, without appointment or joining a waiting list.

During the sessions, family doctors and specialists from polyclinics and hospitals present their cases based on anamnesis, clinical signs, available laboratory results, X-ray films, tuberculin skin test results and other relevant information, including epidemiological criteria. The diagnosis is made after thorough discussion, taking into account important criteria such as persistence of respiratory symptoms after a full course of antibiotic treatment, radiological findings compatible with TB, positive tuberculin reaction if repeated cultures remain negative or contact with a bacteriologically positive PTB case. Some cases requiring supplementary or repeat investigations are presented a second time for diagnosis once those complementary investigations are complete. All information collected and decisions made by the Commission are routinely registered in a log book. Patients themselves are not present during these sessions; they remain under the full responsibility and care of the presenting doctor who may, if necessary, rectify the diagnosis made by the Commission and adjust treatment during the follow-up of the patient.

2.2. Study design

All smear- and culture-negative suspected TB cases that were presented to the Provincial TB Commission of Havana between October 2002 and December 2003 for assistance in making a diagnosis were included in a prospective study. Cases living outside Havana City and prisoners were excluded as it would have been difficult to follow them up after their presentation to the Commission. All patients presented to the Commission were HIV-negative, as HIV-positive patients suspected of TB are discussed at another commission at the ''Pedro Kourí'' Institute of Tropical Medicine in Havana (IPK). During the study period, one of the investigators attended all sessions at the Commission. Information on age, gender, occupation, residence, health structure referring the case, proposed diagnosis of the medical doctor presenting the case, clinical and epidemiological data, available laboratory results, thorax X-ray findings, possible new investigations required and their eventual results, recommendations, conclusions

Table 1 Diagnosis of bacteriologically negative suspected tuberculosis (TB) cases presented to the TB commission

Diagnosis initially proposed by the consulting doctor	Final diagnosis of the TB commission				
	PTB bacteriologically positive[a]	PTB bacteriologically negative[b]	EPTB	Other diagnosis	Total
PTB bacteriologically negative	2	31	2	61	96
EPTB	0	0	16	7	23
Other	0	2	0	5	7
Total	2	33	18	73	126

PTB: pulmonary tuberculosis; EPTB: extrapulmonary tuberculosis.
[a] Smear- or culture-positive.
[b] Smear- and culture-negative.

and final diagnostic conclusion of the Commission were recorded on a specially designed form completed by the investigator attending the sessions.

Each case enrolled in the study was visited at home, one year after their presentation to the Commission, by two independent lung physicians who had never been members of the Commission. Both lung physicians interviewed the patient, performed a full anamnesis, verified new clinical information in the records of the patient's general practitioner and ascertained the evolution and outcome of the disease. They made a definite diagnosis of TB based on the following criteria: culture results became positive during the follow-up period, disappearance of the symptoms at the end of TB treatment, clearance or improvement of the lesions on thorax X-ray, no changes made in the diagnosis of TB during the year of follow-up. Patients for whom the diagnosis was changed during the year of follow-up received the revised diagnosis as a definite diagnosis. All study participants were informed of the objectives and procedures of the study and gave verbal consent.

2.3. Data management and statistical analysis

All data were entered in a database and analysed using Epi-Info 6 (CDC, Atlanta, GA, USA). Cases were classified in the following categories: bacteriologically positive PTB (sputum smear-positive or culture-positive), bacteriologically negative PTB (sputum smear-negative and culture-negative), EPTB and other diagnosis. The definite diagnosis obtained during the home visits was compared with the final diagnosis made by the Commission. The sensitivity, specificity, positive and negative predictive values of the Commission's diagnosis was calculated using the definite diagnosis after one year of follow-up as the reference. The characteristics and symptoms of the patients at the time of their presentation to the Commission were compared between definite TB and non-TB cases. The Kruskal-Wallis and two-tailed Fisher's exact tests were used to compare, respectively, the mean and proportions between groups. A P-value <0.05 was considered to be statistically significant.

3. Results

Between 1 October 2002 and 31 December 2003, 170 patients were presented to the Provincial TB Commission of Havana for assistance in making a diagnosis. Of these, 36 patients came from outside Havana City, six were prisoners, one HIV-positive patient was referred by the IPK commission and one patient did not complete the diagnostic process at the Commission. The remaining 126 smear- and culture-negative suspected TB cases, of which 58 (46%) were women and 68 (54%) men, met the inclusion criteria and were enrolled in the study. Fifty-nine cases (47%) were referred from the primary healthcare level, 65 (52%) from the secondary level and two (2%) from the tertiary healthcare level. Thirty-two cases were re-evaluated after the completion of complementary investigations requested by the Commission during the first visit. The principal diagnoses proposed by the doctors who presented the cases are summarised in Table 1.

Of the 126 patients suspected of TB, the Commission diagnosed 53 (42%) with TB, 35 with PTB and 18 with EPTB. Two initially smear-negative cases became smear-positive on repeated sputum smear analysis between the first and second visits to the Commission. Two patients with bacteriologically negative PTB had multiple diagnoses; one patient also had lung cancer, the other also had bronchiectasis. The 33 sputum smear- and culture-negative PTB cases diagnosed by the Commission represented 65% (33/51) of all sputum smear- and culture-negative PTB cases officially notified in Havana City during the study period. Six of the 18 cases not presented to the provincial Commission were, however, seen at the IPK commission for HIV/TB co-infected patients. The

Table 2 Definite diagnosis of the bacteriologically negative suspected tuberculosis (TB) cases after one year of follow-up

Diagnosis	n (%)
TB	44 (38)
Bronchiectasis	15 (13)
Pneumonia	13 (11)
Cancer	13 (11)
Fibrosis	10 (9)
Pleuritis (no TB)	5 (4)
Chronic bronchitis and emphysema	5 (4)
Atypical mycobacteria	3 (3)
Other	7 (6)
Not available	1 (1)
Total	116 (100)

Table 3 Cross classification of bacteriologically negative suspected tuberculosis (TB) cases' final diagnosis by the TB Commission and definite diagnosis after one year of follow-up

Diagnosis by the TB Commission	Definite diagnosis after one year of follow-up				
	PTB bacteriologically positive	PTB bacteriologically negative	EPTB	Other diagnosis	Total
PTB bacteriologically positive[a]	2	0	0	0	2
PTB bacteriologically negative[b]	5	21	0	4	30
EPTB	0	0	15	2	17
Other	1	0	0	66	67
Total	8	21	15	72	116

PTB: pulmonary tuberculosis; EPTB: extrapulmonary tuberculosis.
[a] Smear- or culture-positive.
[b] Smear- and culture-negative.

18 EPTB cases diagnosed at the Commission represented 75% (18/24) of all EPTB cases officially notified in Havana city during the study period. Three other EPTB patients were diagnosed at the IPK commission for HIV/TB co-infected patients. As such, 76% of all bacteriologically negative PTB cases and 88% of all EPTB cases were presented to a commission for assistance in diagnosis.

Of the 126 cases that were presented to the Commission, 116 (92%) were visited at home after one year. Of the ten cases that could not be traced, four had been diagnosed by the Commission as TB and six as non-TB cases. Amongst the 116 patients who could be traced and were evaluated by the two lung physicians, 44 had a definite diagnosis of TB (38%) (Table 2). One hundred and four of the 116 cases (90%) remained in the same category of diagnosis at the time of the home visit as that determined at the Commission one year earlier (Table 3). Five bacteriologically negative PTB cases remained PTB cases, but changed category as they became bacteriologically positive during follow-up. One case diagnosed at the Commission with pneumonia was diagnosed with PTB as culture results became positive during the follow-up period. This patient was successfully treated for TB and must be considered as a false negative diagnosis by the Commission. Six cases diagnosed with TB by the Commission were ascertained during the home visit to be non-TB cases. Of these, four cases diagnosed as bacteriologically negative PTB changed diagnosis as they were found to be suffering from bronchiectasis (two patients), lung cancer (one patient) and pneumonia (one patient), while two other cases diagnosed with EPTB at the Commission were diagnosed with lung cancer during the follow-up period. These six cases must be considered as false positive diagnoses of TB.

The diagnostic sensitivity and specificity of the Commission were estimated by comparing the final diagnosis made by the Commission with the definite diagnosis assessed after one year of follow-up. The sensitivity (43/44) was 98% (95% CI 93—100) and specificity (66/72) was 92% (95% CI 85—98). The positive and negative predictive values reached 88% (95% CI 79—97) and 98% (95% CI 96—100), respectively.

The characteristics and clinical symptoms of definite TB and non-TB cases (diagnosis as ascertained one year after presentation to the Commission), recorded at the time of their presentation to the Commission, are summarised in Table 4. The patients presented to the Commission were between 18 and 93 years old. Definite non-TB cases had a mean age of 60.8 years and were significantly older than the TB cases, with a mean age of 52.5 years ($P = 0.02$). Also, non-TB cases had suffered from TB more frequently in the past than TB cases, 17% vs. 2% ($P = 0.02$). None of the clinical symptoms that patients presented at the time of diagnosis by the Commission were statistically different between TB cases and non-TB cases or between bacteriologically negative PTB cases and non-TB cases. However, amongst those patients tested during the diagnostic work-up, significantly more non-TB cases (46%) than TB cases (21%) had a tuberculin skin test <5 mm ($P = 0.03$).

4. Discussion

Culture is considered to be the gold standard for the diagnosis of TB, but up to 15—20% of adults with PTB have negative sputum culture, and are diagnosed based on clinical, radiological and histopathological findings and their response to anti-TB treatment.[4] Molecular techniques, not readily available in Cuba, may improve the diagnosis of TB but are not 100% sensitive and specific and some cases may still be missed.[22] Follow-up of patients by family doctors is strict and well organised in Cuba; if health problems are not solved, do not evolve as expected or a new episode of disease occurs, patients are referred to correct the diagnosis. Although the definite diagnosis ascertained by the two independent lung specialists remains, strictly speaking, presumed, the strict follow-up of patients over one year improves the accuracy of diagnosis.

Cultures from six patients became positive during follow-up, while the remaining 36 patients classified as definite TB cases responded positively to the TB treatment. Six patients initially diagnosed with TB were found to be suffering from another disease during the year of follow-up. There is a small possibility that some patients diagnosed by the Commission with another disease were also suffering from bacteriologically negative TB, but cured spontaneously. No diagnostic test is, however, available to verify this hypothesis. We used the classification after one year of follow-up as the reference to estimate the diagnostic sensitivity and specificity of the Commission. The diagnosis making of the Commission

Table 4 Characteristics and clinical signs of the definite tuberculosis (TB) and non-TB cases at the time of presentation to the TB Commission

	All TB cases ($n = 44$) n (%)	Bacteriologically negative PTB ($n = 22$) n (%)	Non-TB cases ($n = 72$) n (%)	All ($n = 116$) n (%)	P-value[a]	P-value[b]
Characteristic						
Median age (years) (interquartile range)	56.5 (40—64)	61 (52—70)	61.5 (49—78)	58 (42—72)		
Mean age (years)	52.5	58.3	60.8	57.7	0.02	
Gender						
Male	23 (52)	10 (45)	40 (56)	63 (54)	0.73	
Female	21 (48)	12 (55)	32 (44)	53 (46)		
Contact of TB case	11 (25)	5 (23)	16 (22)	27 (23)	0.73	
Previous TB case	1 (2)	1 (5)	12 (17)	13 (11)	0.02	
Chronic mental illness	4 (9)	2 (9)	4 (6)	8 (7)	0.47	
Alcohol abuse	7 (16)	3 (14)	9 (13)	16 (14)	0.61	
Diabetes	1 (2)	0	6 (8)	7 (6)	0.25	
Ex-prisoner	3 (7)	2 (9)	4 (6)	7 (6)	1.00	
Clinical signs						
Cough	23 (52)	15 (68)	43 (60)	66 (57)	0.51	0.47
Expectoration	12 (27)	8 (36)	25 (35)	37 (32)	0.40	0.88
Asthenia	17 (39)	10 (45)	27 (38)	44 (38)	0.90	0.50
Fever	14 (32)	7 (32)	16 (22)	30 (26)	0.25	0.36
Dyspnoea	14 (32)	7 (32)	17 (24)	31 (27)	0.33	0.44
Weight loss	14 (32)	10 (45)	25 (35)	39 (34)	0.74	0.36
Chest pain	12 (27)	5 (23)	14 (19)	26 (22)	0.32	0.76
Night sweating	3 (7)	2 (9)	5 (7)	8 (7)	1.00	0.66
Haemoptysis	5 (11)	4 (18)	4 (6)	9 (8)	0.29	0.08

PTB: pulmonary tuberculosis.
[a] TB cases versus non-TB cases.
[b] Bacteriologically negative PTB cases versus non-TB cases.

reached high sensitivity, specificity and predictive values and contributed positively to diagnosing bacteriologically negative TB. However, some misdiagnoses were made and an external quality assessment is justified. As this Commission is already the highest reference body in the country, only systematic feedback to the Commission from the doctors who follow the patients will permit the monitoring of the quality of diagnoses on a continuous basis.

The Commission was well appreciated by the medical doctors who used it and it was consulted for diagnostic assistance in the vast majority of bacteriologically negative PTB cases and EPTB cases in HIV-negative patients notified during the study period in Havana city. Most patients presented came from the secondary (52%) and primary (47%) healthcare levels, with very few (<1%) from the tertiary level, most probably because more diagnostic possibilities and lung specialists are available at this level. Although most patients had already followed a diagnostic pathway that included sputum smear, culture, thorax X-ray, tuberculin skin test, blood analysis and a trial treatment with antibiotics, for one in four patients presented to the Commission additional or repeated investigations were requested, e.g. pleural puncture, lymph puncture, tomography, bronchoscopy, bronchoalveolar lavage, biopsy, ultrasound, etc. This illustrates the difficulty of diagnosing bacteriologically negative PTB and EPTB, even for a team of experts, and despite the fact that the patients were HIV-negative.

The Commission confirmed TB in 42% of the suspected cases presented. If the Commission had not been consulted, the 72 definite non-TB cases would have received presumptive TB treatment, potentially causing harm to those patients, and delay in their correct diagnosis and corresponding therapeutic measures.

The patients presented to the Commission had gone through all the available diagnostic options, and no further algorithms or standardised approaches were available to reach a diagnosis. Risk factors such as alcohol abuse and diabetes were equally present in both TB and non-TB cases, probably because these are also risk factors for other non-TB diseases common in this patient group. The frequency of the more specific risk factor, known contact with a TB case, was not statistically different between TB cases and non-TB cases. This suggests that TB in this older patient group might be due to reactivation of old infections with *Mycobacterium tuberculosis*. A history of previous TB disease was more common amongst those patients in whom the commission did not diagnose smear-negative or EPTB at presentation. This may indicate that the risk factor of having suffered from TB in the past is used by clinicians as a criterion to suspect TB in patients with an unclear respiratory syndrome. All clinical symptoms were equally present in bacteriologically negative PTB patients and non-TB patients. These symptoms are, however, also associated with other respiratory diseases and cancers and, thus, are of low predictive value for TB in this older patient group. This underlines the difficulty of developing clinical algorithms and scoring systems that have sufficient validity to assist in the diagnosis of bacteriologically negative TB.

The clinical judgement of a reference body composed of experienced specialists with complementary competencies, is discerning in the diagnostic process. While consultation and referral between clinicians is not new, the implementation of a systematic, regular and easily accessible system for improving the diagnosis of bacteriologically negative TB may be considered innovative. The diagnosis is reached collectively, taking into consideration individual, clinical and epidemiological factors, while the responsibility for patient care and follow-up remains with the clinician presenting the case. At the same time the system provides continuous training for medical doctors, especially family doctors. From an organisational point of view the specific set-up in Havana may not be directly transferable outside Cuba, especially in developing countries, where not only is the burden of TB high, but also the diagnosis is hampered by a lack of diagnostic tools and clinical expertise. However, in many resource-poor urban settings it should be possible to install committees of healthcare workers who can systematically assist their colleagues in the diagnosis of suspected TB patients who are bacteriologically negative.

Authors' contributions: FM, EGO and PVdS participated in the conception and design of the study protocol; SVD, EGS, TCD and LAP participated in the clinical assessment; MPP, SVD, EGS, TCD and LAP participated in the data collection; FM, MPP, SVD, EGS, TCD and LAP participated in the analysis of data; FM, MPP, SVD, EGS, TCD, LAP, EGO and PVdS participated in the interpretation of data and the drafting of the paper; FM, EGO and PVdS participated in the revision of the paper. All authors read and approved the final manuscript. EGO and PVdS are guarantors of the paper.

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