An Alternative for Improving the Diagnosis of Smear-Negative Tuberculosis and Other Bronchopulmonary Disorders in Cuba

José Sevy Court,[a] Delfina Machado Molina,[a] Luisa Armas Pérez,[b] Mariana Peralta Pérez,[b] Libertad Carreras Corzo,[a] Reinaldo Sánchez de la Osa,[a] Carmen Rosas Valladares,[a] and Edilberto González Ochoa[b]

[a]Hospital Universitario Neumológico Benéfico Jurídico, La Habana, Cuba
[b]Grupo de Investigaciones y Vigilancia de Tuberculosis, Lepra e IRA, Instituto Pedro Kourí, La Habana, Cuba

OBJECTIVE: The diagnosis of tuberculosis in patients with negative acid-fast bacillus smears poses a challenge to both clinicians and public health authorities. In an attempt to aid diagnosis in such cases, an expert committee was established in the province of Ciudad de La Habana, Cuba in 1995. The aim of this study was to describe the progress of the committee's work and the corresponding results for the period 1996 through 2003.

PATIENTS AND METHODS: For each patient studied by the committee, we analyzed the following data: patient's residence and referring center, tentative diagnosis proposed by the attending physician, history of antibiotic treatment, and final diagnosis made by the committee.

RESULTS: Of the 1703 patients studied, 84.8% were from the province of Ciudad de La Habana, 48.4% were 55 years or older, and 63.8% were men. Between 2001 and 2003, 11.3% of patients were already on antituberculosis treatment when their case was studied by the committee. The corresponding percentage for 1996 through 2000 was 16.9% (*P*=.001). Active tuberculosis was confirmed in 43.1% of a total of 918 patients with full test results during the period 1996 through 2000 and in 52.2% of a total of 619 patients (52.2%) during the period 2001 through 2003 (*P*<.001). Of 344 patients with suspected pulmonary tuberculosis and negative acid-fast bacillus smears between 2001 and 2003, 128 (37.2%) were diagnosed with active tuberculosis.

CONCLUSIONS: These findings indicate that the work of the committee is viable, sustainable, and useful for preventing overdiagnosis and inappropriate treatment, and that it also serves an educational purpose.

Key words: *Tuberculosis. Diagnosis. Negative acid-fast bacillus smear. Monitoring.*

Una alternativa para mejorar el diagnóstico de la tuberculosis con baciloscopia negativa y otros problemas broncopulmonares en Cuba

OBJETIVO: El diagnóstico de los pacientes con tuberculosis pulmonar y muestras negativas para bacilos ácido-alcohol resistentes (BAAR) representa un desafío clínico y de salud pública, por lo que en Ciudad de La Habana se creó en 1995 una comisión para esclarecer su diagnóstico. El objetivo de este estudio ha sido describir los progresos y resultados del trabajo de esta comisión entre 1996 y 2003.

PACIENTES Y MÉTODOS: Se han analizado los datos recogidos de cada paciente presentado en las sesiones de la comisión: procedencia, diagnóstico de sospecha planteado por el médico que presentó el caso, antecedentes de tratamiento anterior con antibióticos y diagnóstico realizado por la comisión.

RESULTADOS: Del total de 1.703 pacientes presentados a esta comisión para esclarecer el diagnóstico, un 84,8% procedía de la Ciudad de La Habana, el 48,4% pertenecía al grupo de edad igual o mayor de 55 años y el 63,8% eran varones. El porcentaje de casos consultados con tratamiento específico contra la tuberculosis ya comenzado fue en 2001-2003 del 11,3%, y en el período 1996-2000, del 16,9% (p = 0,001). En 1986-2000, de 918 pacientes que completaron sus exámenes, tuvo diagnóstico final de tuberculosis activa un 43,1%, y en 2001-2003, el 52,2% de 619 (p = 0,000). De un total de 344 casos estudiados con sospecha de tuberculosis pulmonar con BAAR y cultivo negativos en 2001-2003, el diagnóstico se corroboró en 128 (37,2%).

CONCLUSIONES: Los resultados indican que el trabajo de la comisión es viable, sostenible y de utilidad porque evita el sobrediagnóstico y el tratamiento inapropiado, además de cumplir una función docente.

Palabras clave: *Tuberculosis. Diagnóstico. Baciloscopia negativa. Vigilancia.*

Introduction

Tuberculosis continues to have a major impact on human health in many countries.[1,2] and its association with human immunodeficiency virus (HIV) infection has brought about even more worrying consequences, such as a rise in the incidence of tuberculosis and the introduction of more deadly varieties.[2] Diagnosis is particularly complicated in patients who have signs or symptoms suggestive of the

Study conducted within the framework of a collaboration agreement with the Institute of Tropical Medicine in Antwerp, Belgium.

Correspondence: Prof E. González Ochoa
Instituto Pedro Kourí, Autopista Novia del Mediodía, km 6,5
La Lisa, La Habana, Cuba
E-mail: ochoa@ipk.sld.cu

Manuscript received June 1, 2007. Accepted for publication May 28, 2008.

disease but several negative acid-fast bacillus (AFB) smears.[3-6] In Cuba, as many as 40% of patients with tuberculosis-HIV coinfection have negative AFB smears.[7,8] Even in immunocompetent persons, the diagnosis of smear-negative pulmonary tuberculosis can be confused with lung diseases such as bronchopulmonary cancer and bronchiectasis.[4-8]

When the downward trend in tuberculosis incidence reversed in Cuba in 1993,[9-11] efforts to improve tuberculosis monitoring and control were intensified with the updating of the National Tuberculosis Control Program (PNCT) by an expert advisory group under the auspices of the Cuban Department of Epidemiology in May 1994. One of the measures taken was to expand the criteria used to define smear-negative tuberculosis to cover all patients with negative AFB smears, whether with positive or negative cultures.[12-16] Prior to this, such cases had been treated but not reported but from the second half of 1994 onwards, notification was compulsory.[12-15] This was a crucial decision in view of the risk of tuberculosis-HIV coinfection.[6-11] It was also decided that cases of smear-negative pulmonary tuberculosis should be reported to and treated under the supervision of expert medical specialists, hence the creation of an expert committee for the diagnosis of smear-negative tuberculosis (CODIBAARNE) in the province of Ciudad de la Habana in September 1995.[11,12] The committee was formed by a multidisciplinary group of experts and headquartered in the university hospital specializing in respiratory medicine, Hospital Benéfico Jurídico, in La Habana.[12] Although the results of the work performed by the CODIBAARNE between 1996 and 2000 have been published,[11,12] they cannot be compared to results from earlier years because the records of such cases in primary health care centers (family medicine practices) are incomplete. The CODIBAARNE is still functioning and the aim of this paper is to describe the progress and results of their work for the period between 1996—when data collection procedures were standardized—and 2003.[13,14]

Patients and Methods

We studied all patients whose cases were examined by the CODIBAARNE between 1996 and 2003; the majority were from the provinces of Ciudad de La Habana (2.2 million inhabitants) and La Habana (0.7 million). The following patients were examined by the committee[11,12] :

1. Patients with suspected active pulmonary tuberculosis and *a)* 2 or more negative direct AFB smears and cultures combined with a clinical picture and radiologic findings suggestive of tuberculosis and *b)* a positive but scanty or equivocal direct AFB smear or culture combined with a highly equivocal clinical picture and radiologic findings.
2. Patients with suspected extrapulmonary tuberculosis.
3. Difficult-to-treat patients.

The Cuban tuberculosis control program, the PNCT, stipulates that any patient who reports a productive cough for at least 14 days and has 2 negative direct AFB smear results and a chest radiograph indicating tuberculosis must be followed by the attending physician. If the culture proves to be negative and the symptoms persist, the patient should then be treated with broad-spectrum antibiotics (other than quinolones). Finally, the case should be presented to the CODIBAARNE if no radiographic changes are observed on completion of treatment.

The CODIBAARNE responsible for the province of Ciudad de La Habana[12,13] is made up of 5 specialists (3 pulmonologists, 1 epidemiologist, and 1 radiologist) who meet at Hospital Benéfico Jurídico to discuss cases every Wednesday at 10 AM. Doctors wishing to present cases do not need to make a prior appointment. The group discusses possible diagnoses and treatment issues for the different cases, which are generally presented by family physicians and clinical specialists from polyclinics and hospitals. Examined are medical records and results from microbiologic tests (AFB smears and cultures), radiologic studies (simple anteroposterior chest radiographs and other exams such as tomography scans and bronchograms), tuberculin tests (performed using purified protein derivative and the standard Mantoux method), and epidemiologic evidence (possible contact with cases in the home or other environments). All these issues are discussed in the absence of the patient, who is only called in for an interview on very rare occasions. This above information is recorded in a journal and on a standardized purpose-designed form.[13,14] The CODIBAARNE experts involve the attending physician and other physicians who might attend the discussions. When certain information is lacking, the person presenting the case is asked to complete the study or to repeat certain tests. A new appointment is then proposed in order to re-examine the case once all the necessary results from laboratory tests (a new smear and re-culturing for *Mycobacterium tuberculosis* smears and culture, cytology of sputum and bronchial lavage fluid) and exploratory procedures (bronchoscopies) have been obtained. The committee reaches its conclusions only after taking account of all relevant factors. These conclusions are recorded in the patients' medical records and the physician presenting the case is given a report detailing the recommendations.

The PNCT stipulates the procedures to be followed by each CODIBAARNE so that municipal coordinators can guide the presentation of cases by family practitioners and other health care support staff and so that cases can be registered and followed. The CODIBAARNE meetings are generally attended by the provincial coordinator of the PNCT and the head microbiologist of the provincial referral laboratory for tuberculosis. Most of the cases presented are from the province of Ciudad de La Habana but as Hospital Benéfico Jurídico is the PNCT's national referral hospital, the committee also deals with cases from other provinces.

Although the original purpose of the CODIBAARNE was to study cases of smear-negative tuberculosis, over time, the committee has also come to study extrapulmonary forms of the disease as well as bronchopulmonary conditions in the differential diagnosis. In the present study, we analyzed the following variables for each patient: place of residence (province), age bracket, sex, referring center, existence of tuberculosis treatment at the time the case was presented, tentative diagnosis proposed by the attending physician (pulmonary tuberculosis with positive or negative AFB smears), and diagnostic conclusions made by the committee. Because smear-negative tuberculosis cases were not reported prior to the second half of 1994, we were unable to compare findings from before and after the creation of the CODIBAARNE (September 1995), essentially because this information had not been recorded. We were, however, able to determine the number of smear-negative cases reported between 1995 and 1997 and hence gain an idea of what proportion of pulmonary tuberculosis cases reported in the province corresponded to smear-negative tuberculosis and ascertain whether the CODIBAARNE might have had an effect on the PNCT. It should be borne in mind that Hospital Benéfico Jurídico is the only respiratory medicine hospital in the city and smear-negative tuberculosis cases are only included in the official statistics once they have been confirmed by the CODIBAARNE. The only exceptions are extremely serious cases or cases involving tuberculosis-HIV coinfection, which are discussed by a committee based at the infectious disease center, Instituto Pedro Kourí.

TABLE 1
Cases Presented to the Expert Committee for the Diagnosis of Smear-Negative Tuberculosis (CODIBAARNE) by Province, Age Group, and Sex. Hospital Docente Benéfico Jurídico, 1996-2003[a]

	1996-2000	2001-2003	1996-2003	*P*[b]
Cases presented	1037 (100)	666 (100)	1703 (100)	
Provinces				
Ciudad de La Habana	863 (83.2)	581 (87.2)	1444 (84.8)	.029
La Habana	139 (13.4)	31 (4.7)	170 (10.0)	.0001
Other provinces	35 (3.4)	54 (8.1)	89 (5.2)	.0001
Age group, y				
0-14	6 (0.6)	18 (2.7)	24 (1.4)	.0001
15-34	229 (22.1)	133 (20)	362 (21.2)	.32
35-54	297 (28.6)	195 (29.3)	492 (28.9)	.81
≥55	505 (48.7)	320 (48.0)	825 (48.4)	.83
Sex				
Male	664 (64)	422 (63.4)	1086 (63.8)	.81
Female	373 (36)	244 (36.6)	617 (36.2)	.81

[a]All values except *P* values are shown as number of patients (percentage).
[b]Comparison of proportions between periods (Z test).

Statistical analysis was not required to test hypotheses related to comparisons of random samples, as the numbers presented here cover the entire population of cases. We did, however, apply tests to compare portions to the entire sample (statistical significance, *P*=.05), in the same manner as would be done to draw inferences regarding a subsample of the entire population.[17] It should also be noted that the national health care system in Cuba offers free, comprehensive health care to all citizens; as such, there is a single health care provider that guarantees full coverage, standardized procedures, and reliable health statistics.

Results

The CODIBAARNE studied 1703 cases between 1996 and 2003. Specifically, 1037 cases were discussed between 1996 and 2000 (annual mean, 207) and 666 cases between 2001 and 2003 (annual mean, 222) (Table 1). As can be seen, the annual mean for the later period was slightly higher than for the first.

Of the total number of cases presented over the 8 years, 84.8% were from the province of Ciudad de La Habana, a proportion that had increased from 83.7% to 87.2% between 1996-2000 and 2001-2003 (*P*=.029), and the remaining 15% or so were from other provinces. The proportion from other provinces had also increased significantly from one period to the next (*P*=.0001). The creation of the CODIBAARNE led to a significant reduction (of 65%) in the number of cases referred from the province of La Habana between 2001 and 2003 (*P*=.0001), contrasting with an increase of 138% in the number of cases from other provinces by the end of the same period (Table 1).

Almost half (48.4%) of the cases presented corresponded to patients aged 55 years or older. Statistically significant differences were found between the 2 periods for patients aged 14 years or younger (*P*=.001) but not for patients aged 15 years or older. Men accounted for 63.8% of all patients (male-female ratio, 1.76; Table 1) and this distribution was similar in both periods. Of the 18 patients aged 14 years or younger discussed between 2001 and 2003 (2.7% of patients studied in this period), 12 (66.7%) were diagnosed with active tuberculosis; the disease was pulmonary in 5 cases and extrapulmonary in 7. In the preceding period, 1996 to 2000, only 6 children in this age group had been studied (0.6%) and 4 (66.7%) of them had been diagnosed with active tuberculosis (2 pulmonary and 2 extrapulmonary cases). As can be seen, there was a clear increase in the number of pediatric patients, whose cases are usually more difficult to diagnose.

Of the 1703 cases presented between 1996 and 2003, 924 (54.2%) were from polyclinics. Only 8.6% (n=80) of these patients were receiving specific tuberculosis treatment at the time their cases were discussed, contrasting with 21.9% (171/779) of those from hospitals. On analyzing the group as a whole, 251 patients (14.7%) with suspected tuberculosis were receiving specific treatment at the time their cases were studied by the CODIBAARNE; the breakdown by period was 176 (16.9%) for 1996 to 2000 and 75 (11.3%) for 2001 to 2003 (overall decrease of 33%; *P*=.004). On analyzing the situation by type of health care center, it was seen that, in polyclinics, the number of patients receiving treatment for tuberculosis at the time their cases were examined had increased by 29% (*P*=.24) between 1996 to 2000 and 2001 to 2003; the caseload for hospitals had decreased by 59% in the same period (*P*=.0001) (Table 2).

The diagnostic study was completed for 1537 (90.2%) of the 1703 patients whose cases were presented between 1996 and 2003; 719 (46.7%) of these were diagnosed with tuberculosis, which was pulmonary in 480 cases (66.7%) (Table 3). Of the 619 patients studied by the CODIBAARNE between 2001 and 2003, 323 (52.2%) were diagnosed with active tuberculosis, reflecting a 21% increase in the percentage of correct tentative diagnoses as between 1996 and 2000, 396 of the 918 patients examined were diagnosed with active tuberculosis (43.1%, *P*=.0001) (Table 3).

The CODIBAARNE discussed 666 patients between 2001 and 2003 and of these, 535 had lung involvement. The difference between the number of cases originating from polyclinics and hospitals was statistically significant (Table 4). Diagnosis was confirmed in 496 (92.7%) of the 535 patients presented to the CODIBAARNE with some

TABLE 2
Cases Presented to the Expert Committee for the Diagnosis of Smear-Negative Tuberculosis (CODIBAARNE) by Health Care Centers and Patients Already Receiving Tuberculosis Treatment at the Time of Examination, 1996 to 2003[a]

	1996-2000	2001-2003	1996-2003	*P*[b]
Polyclinics				
Cases presented	598 (57.7)	326 (48.9)	924 (54.2)	.001
Already on specific treatment	47 (7.8)[c]	33 (10.1)[c]	80 (8.6)[d]	.29
Hospitals				
Cases presented	439 (42.3)	340 (51.1)	779 (45.7)	.0001
Already on specific treatment	129 (29.4)[d]	42 (12.3)[c]	171 (21.9)[d]	.0001
Total already on specific treatment	176 (16.9)	75 (11.3)	251 (14.7)	.004
Total cases presented	1037 (100.0)	666 (100.0)	1703 (100)	

[a]Values are shown as number of patients (percentage) unless otherwise indicated.
[b]Comparison of proportions between periods (Z test).
[c]*P*=.43.
[d]*P*=.0001.

TABLE 3
Cases Presented to the Expert Committee for the Diagnosis of Smear-Negative Tuberculosis (CODIBAARNE) and Basic Diagnoses for Those With a Full Study, 1996-2003

	1996-2000		2001-2003		1996-2003		*P*[a]
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Cases presented	1037	100	666	100	1703	100	
Full study	918	88.5	619	93	1537	90.2	.003
Tuberculosis	396	43.1	323	52.2	719	47	.0001
Pulmonary	257	64.9	223	69	480	66.7	.274
Extrapulmonary	139	35.1	100	31	239	33.7	.274
Other diagnosis	522	56.9	296	47.8	818	53	.0001
Pending studies[b]	119	11.5	47	7	166	9.7	.003

[a]Comparison of proportions between periods (z test).
[b]Patients who had not completed all required tests at the time of the reports.

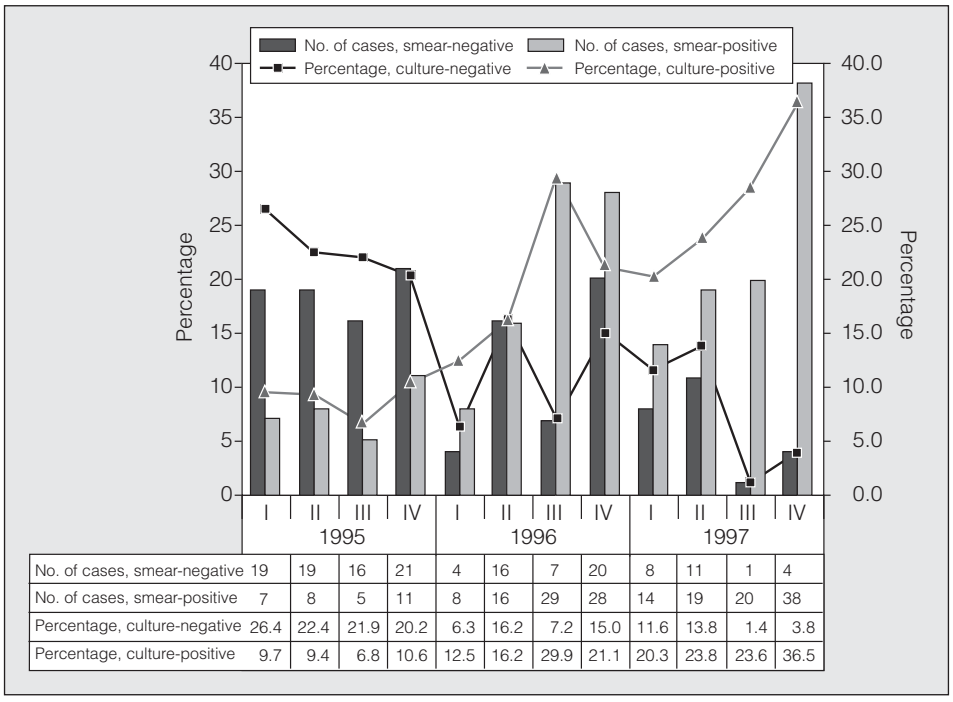
TABLE 4
Cases Presented to the Expert Committee for the Diagnosis of Smear-Negative Tuberculosis (CODIBAARNE) and Diagnosed With Active Tuberculosis By Health Center, 2001 to 2003

Categories	Presented by			Diagnosed by CODIBAARNE		
	Polyclinic[a]	Hospital[a]	Total[a]	Polyclinic[b]	Hospital[b]	Total[b]
Lung disorders	302 (92.6)[c]	233 (68.5)[c]	535 (80.3)	269 (89.0)	227 (97.4)	496 (92.7)
Extrapulmonary disorders	24 (7.4)[c]	107 (31.5)[c]	131 (19.7)	24 (100)	99 (92.5)	123 (93.9)
Total	326 (100)	340 (100)	666 (100)	293 (89.9)	326 (95.9)	619 (93.0)
Lung disorders						
Clinical radiologic findings	189 (62.6)[c]	185 (79.4)[c]	374 (69.9)	164 (86.8)[c]	180 (97.3)[c]	344 (92.0)
Final diagnosis of tuberculosis				33 (20.1)	95 (52.8)	128 (37.2)
Positive AFB smear	91 (30.1)[c]	39 (16.7)[c]	130 (24.3)	84 (92.3)	39 (100)	123 (94.6)
Final diagnosis of tuberculosis				52 (61.9)	27 (69.2)	79 (64.2)
Negative AFB smear and positive culture	22 (7.3)[d]	9 (3.9)[d]	31 (5.7)	21 (95.4)	8 (88.9)	29 (93.5)
Final diagnosis of tuberculosis				10 (47.6)	6 (75.0)	16 (55.2)
Total cases of pulmonary tuberculosis diagnosed				95 (35.3)	128 (56.4)	223 (44.9)
Extrapulmonary disorders				22 (91.7)	78 (78.8)	100 (81.3)
Total cases of tuberculosis				117 (39.9)	206 (63.2)	323 (52.2)

[a]Values are shown as number of patients (percentage of total number of patients whose cases were presented).
[b]Patients with symptoms and chest radiograph suggestive of tuberculosis but negative acid-fast smear and culture results.
[c]*P*=.0001.
[d]*P*=.135.

form of lung involvement (Table 4). Of the 535 patients with suspected lung involvement, 374 were reported as having clinical and radiologic signs of tuberculosis only (negative AFB smears and cultures); the CODIBAARNE confirmed this tentative diagnosis in 344 (69.9%) patients and following further tests such as smears and radiographs, tuberculosis was confirmed in 128 (37.2%) of these.

The expert committee completed discussion and confirmed the diagnosis for 16 cases (55.2%) of the 29 presented with a tentative diagnosis of smear-negative pulmonary tuberculosis and a positive culture result. It is noteworthy that although the committee completed discussion of 123 cases of suspected tuberculosis with positive AFB smear results (out of a total of 130 cases



	1995				1996				1997			
No. of cases, smear-negative	19	19	16	21	4	16	7	20	8	11	1	4
No. of cases, smear-positive	7	8	5	11	8	16	29	28	14	19	20	38
Percentage, culture-negative	26.4	22.4	21.9	20.2	6.3	16.2	7.2	15.0	11.6	13.8	1.4	3.8
Percentage, culture-positive	9.7	9.4	6.8	10.6	12.5	16.2	29.9	21.1	20.3	23.8	23.6	36.5

Figure 1. Number of cases and percentage (of total cases) of smear-negative tuberculosis reported in the province of Ciudad de La Habana in the period 1995 to 1997, by quarters.

presented), the diagnosis was confirmed in just 79 cases (64.2%). A total of 323 patients were diagnosed with tuberculosis, which was diagnosed as extrapulmonary in 100 cases (Table 4). Most cases of extrapulmonary tuberculosis in the period from 2001 to 2003 involved the pleural space (63/100, 63%); 12% of cases involved the lymph nodes, 9% the bones, and 4% the peritoneum. Others sites were less often affected (Table 5).

Diseases other than tuberculosis were diagnosed in 296 patients (47.8%); the most common of these in 2001 to 2003 were bronchiectasis, pneumonia, chronic bronchitis, lung cancer, and pulmonary fibrosis (Table 5). This information was not available for 1996 to 2000.

The total number of pulmonary tuberculosis cases reported in the province of Ciudad de La Habana was 331 in 1995, 482 in 1996, and 323 in 1997. During this period, the proportion of smear-negative pulmonary tuberculosis cases increased from 32% in 1995 to 36.5% in 1997; this increase was mainly due to the increase in the number of cases with negative AFB smears and positive cultures reported from the first quarter of 1996 onwards. Finally, the percentage of patients with negative AFB smears and cultures decreased steadily from 22.6% in 1995 to 7.7% in 1997. Thanks to the intervention of the CODIBAARNE, in the same period, the percentage of patients with positive cultures increased while that of those with negative cultures

TABLE 5
Diagnoses of Extrapulmonary Tuberculosis and Other Nontuberculous Diseases in 619 Cases Studied by the Expert Committee for the Diagnosis of Smear-Negative Tuberculosis (CODIBAARNE), 2001 to 2003

Diagnosis	No. of Patients	%	Diagnosis	No. of Patients	%
Extrapulmonary tuberculosis	100	16.1	Nontuberculous disease	296	47.8
Pleural space	63	63.0	Bronchiectasis	40	13.5
Lymph nodes	12	12.0	Pneumonia	38	12.8
Bone	9	9.0	Chronic bronchitis	32	10.8
Peritoneum	4	4.0	Lung cancer	27	9.1
Pericardium	3	3.0	Pulmonary fibrosis	24	8.1
Liver	2	2.0	Mycobacterial infection	20	6.7
Meninges	2	2.0	Pulmonary suppuration	19	6.4
Pancreas	1	1.0	Blisters	14	4.7
Eyes	1	1.0	Pulmonary abscess	10	3.4
Cerebellum	1	1.0	Pulmonary fibrosis and emphysema	7	2.4
Skin	1	1.0	Pleural effusion	6	2.0
Disseminated[a]	1	1.0	Bronchopneumonia	2	0.7
			Pulmonary eosinophilia	2	0.7
			Pleural thickening	1	0.3
			Mycetoma	1	0.3
			Other	53	18.0

[a]Pleural space, liver, and peritoneum

(tuberculosis diagnosed only on the basis of clinical and radiologic signs) decreased (Figure 1).

Discussion

Our findings show that the findings of the CODIBAARNE for the period 2001 to 2003 are in part similar to and in some aspects possibly even better than those for 1996 to 2000. Of particular note is the improvement in the validity and reliability of the data from the later period due to the standardization of data registry.[13,14]

Recent studies suggest that there is no approach that in isolation can effectively diagnosis smear-negative, culture-negative cases, whether the approach is based on clinical scoring systems or statistical modeling, algorithms, results of specific or nonspecific treatment, or specific tests.[6] It would appear that a combination of the above is required even though the complexity and cost increase. In an attempt to overcome this problem in Cuba, it was decided to combine the use of an algorithm[18] (involving treatment with broad-spectrum antibiotics) and the expert opinion of a specially created committee. As indicated by the results up to 2003, this strategy has proven viable, acceptable, and sustainable. We are unaware of the existence of similar processes in other countries.

The Cuban PNCT falls within the context of a reintervention effort designed to contribute to eliminating tuberculosis.[16,19] If this goal is to be achieved, however, diagnosis must be accurate, and this is particularly true when there is a possibility of HIV coinfection.[7,8] The CODIBAARNE seems to have achieved the goal for which it was created in terms of improving diagnostic accuracy for tuberculosis. The expert committee confirmed 37% of tentative diagnoses of pulmonary tuberculosis in patients with negative smears and cultures made by a large group of general physicians in primary health care centers and hospitals; all these cases then had to be reported to the departments responsible for national statistics and epidemiology.[16] It would be important to establish a systematic checking system to ensure that all cases are reported as it is important to check that the physicians presenting the cases actually report these to the PNCT.

On analyzing the total number of patients with pulmonary tuberculosis and negative AFB smears and cultures (ie, patients with only clinical and radiologic signs of the disease), it was seen that 20.1% of those with confirmed diagnoses were from polyclinics and 52.8% from hospitals. We believe that this difference is due to the fact that pulmonologists working in secondary health care centers have a greater level of knowledge and experience than their primary care counterparts and also that hospitalized patients tend to have clearer respiratory signs and symptoms. If the CODIBAARNE had not been created, many patients would very probably have received unnecessary tuberculosis treatment following an incomplete or erroneous diagnosis, leading to additional risk and suffering as well as unnecessary expenditure. At present, only smear-negative pulmonary tuberculosis cases confirmed by provincial expert committees[15] are treated and registered, with a few exceptions such as very serious acute clinical forms of tuberculosis (eg, miliary tuberculosis or tuberculous meningoencephalitis).

While it could be speculated that there is a certain level of underdiagnosis, this seems highly unlikely. In 77 341 autopsies performed in Cuba over a period of 10 years, 445 cases of pulmonary tuberculosis (0.6%) and 39 cases of extrapulmonary tuberculosis (0.05%) were detected, and the autopsy diagnosis coincided with the antemortem clinical diagnosis in 63% of cases.[20] Between 2% and 4% of new tuberculosis cases have been reported to be detected at autopsy.[21] It should be noted that diagnostic errors still occur in general hospitals as well as at the tertiary health care level, causing physicians to consider other diagnoses and considerably delaying the diagnosis of tuberculosis.[22-25]

It is also noteworthy that only 64.2% of cases of suspected pulmonary tuberculosis and positive AFB smears discussed by the expert committee were actually diagnosed with active tuberculosis; in patients with positive cultures, this diagnosis was confirmed in just 55.2% of cases, sometimes because of the presence of nontuberculous mycobacteria. These results nevertheless indicate the need to improve diagnosis and quality control procedures in certain polyclinic laboratories.[26]

Another important observation to emerge from this study is that there was a decrease in the number of patients with smear-negative tuberculosis receiving specific treatment when their case was presented to the CODIBAARNE. Health care practitioners in Cuba are advised not to administer tuberculosis drugs for diagnostic purposes.[15] Rather, they are advised to administer other types of broad-spectrum antibiotics. One of the main arguments against using tuberculosis drugs for diagnostic purposes is their potential to cause harmful side effects.[27-32] The Cuban PNCT proposes using an algorithm that includes the administration of broad-spectrum antibiotics in patients who have negative AFB smears and cultures but persistent symptoms and radiographic lesions suggestive of active tuberculosis.[15,18] While the number of patients with a tentative diagnosis of tuberculosis receiving specific treatment prior to examination by the expert committee has decreased since the creation of the CODIBAARNE, it is still high. Administration of tuberculosis drugs to patients with only a tentative diagnosis is less common in patients from other hospitals in the city, possibly due to the greater experience of the secondary health care specialists at those facilities. It is also possible that hospital staff adhere better to the guidelines set out in the PNCT. More detailed studies are required to analyze this issue.

The fact that almost 60% of patients thought to have smear-negative pulmonary tuberculosis examined by the CODIBAARNE did not actually have tuberculosis highlights the need to follow these patients in order to explore other possible diagnoses. While this can be done in the respiratory-medicine–specific Hospital Benéfico Jurídico through follow-up visits, home visits, or other common activities, in the vast majority of cases, patient follow-up occurs in other university hospitals with other clinical or surgical specialties. It would be necessary to implement data feedback mechanisms, which could be set up through a relevant outpatient department. A study of the follow-up of cases examined by the CODIBAARNE is currently being performed.

The quarterly trend in smear-negative tuberculosis notification rates between 1995 and 1997 offers interesting insights although it does not provide conclusive evidence of the effectiveness of the CODIBAARNE. In 1995, approximately 1 in every 5 cases of pulmonary tuberculosis with negative AFB smear and culture results was reported to the PNCT in the province of Ciudad de la Habana but this rate was less than 1 in 10 in 1997, very possibly due to the work the CODIBAARNE has been doing. Improvements were also seen in the percentage of patients with pulmonary tuberculosis and negative AFB smear and positive culture results, possibly because the committee insisted on repeating tests and also because the general diagnostic criteria were more rigorous.

The fact that the average number of cases presented to the CODIBAARNE has increased and stabilized is encouraging; the work of this committee, which is sustainable, didactic, and closely linked to the objectives of the PNCT, has also increased the initial range of cases presented. Moreover, in a move that complements the practical approach to lung health strategy organized by the World Health Organization,[33,34] general practitioners and internal medicine specialists now readily conduct consultations with each other in attempt to confirm or rule out suspected diagnoses of cancer and lung disorders and to resolve treatment difficulties in certain patients.

In conclusion, our findings indicate that the work of the CODIBAARNE is viable, sustainable, and useful for improving diagnosis in cases of suspected smear-negative pulmonary tuberculosis, and that it also serves an educational purpose

Acknowledgments

We thank Dr Alexander González Díaz for his assistance with data analysis in this version of the article.

REFERENCES

1. World Health Organization. The Global Plan To Stop Tuberculosis. WHO/CDS/STB 2001.16. Geneva: WHO; 2002.
2. Organización Panamericana de la Salud. Guía sobre atención integral de personas que viven con la coinfección TB/VIH en América Latina y el Caribe. Washington, DC: OPS; 2003.
3. Long R. Smear-negative pulmonary tuberculosis in industrialized countries. Chest. 2001;120:330-3.
4. Caminero JA, Casal M, Austina V, Pina JM, Sauret J. Diagnóstico de la tuberculosis. Arch Bronconeumol. 1996;32:85-99.
5. Colebunders R, Bastian J. A review of the diagnosis and treatment of smear negative pulmonary tuberculosis. Int J Tuberc Lung Dis. 2000;4:97-107.
6. Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low income countries: the current evidence. Lancet Infect Dis. 2003;3:288-96.
7. Reyes A, Díaz M, Pérez A. Tuberculosis y sida: algunos aspectos clínicos y epidemiológicos en 72 enfermos cubanos. Rev Cubana Med Trop. 2004;56:335-41.
8. Díaz M, González I, Saladrigas C, Pérez J, Millán J, Valdivia J. La coinfección de la tuberculosis y el VIH en Cuba. Rev Cubana Med Trop. 1996;48:214-7.
9. González E, Armas L, Machín A. Tendencias por provincias de la tuberculosis en Cuba: 1979-1993. Bol Oficina Sanit Panam. 1995; 119:396-404.
10. Torres E, Joanes J, Carreras L, Pérez J, Hernández O, Marrero A, et al. La infección por el virus de la inmunodeficiencia humana y la tuberculosis en Cuba. Bol Oficina Sanit Panam. 1995;119:66-73.
11. Sevy JI, Machado D, Carreras L, Sánchez R, Fernández N, Rosas C, et al. Tuberculosis BAAR negativa de la Ciudad de La Habana. Quinquenio 1996-2000. Boletín Epidemiológico Semanal IPK. 2001;11:266-70.
12. Sevy J, Machado D, Carreras L, González E. Antecedentes de la Comisión Provincial de Diagnóstico de Tuberculosis de Ciudad de La Habana. Rev Cubana Med Trop. 2004;56:23-6.
13. Armas L, Peralta M, D'Fana J, Sevy JI, González E. Instrumento para el registro de datos de casos de tuberculosis con baciloscopia negativa. Boletín Epidemiológico semanal IPK. 2005;15:377.
14. Sevy J, Machado D, Carreras L, Sánchez R, Armas L, Llanes MJ, et al. Propuesta de instrucciones para el funcionamiento de las comisiones provinciales para el diagnóstico de los enfermos de tuberculosis y otras enfermedades broncopulmonares. Boletín Epidemiológico Semanal IPK. 2004;14:17-9.
15. Grupo Nacional Técnico Asesor de Tuberculosis. Ministerio de Salud Pública. Dirección Nacional de Epidemiología. Programa Nacional de Control de la Tuberculosis. Manual de Normas y Procedimientos. La Habana, 1999. Available from http://www.aps.sld.cu/bvs/materiales/programa/protuberculosis.htm. Consulted on February 15, 2007.
16. Llanes MJ, Armas L, González E, Lazo MA, Carreras L, Mathys F, et al. Tuberculosis pulmonar con baciloscopia negativa, peculiaridades de su frecuencia en Cuba 1992-2002. Rev Cubana Med Trop. 2006;58.
17. Silva LC. Cultura estadística e investigación científica en el campo de la salud. Una mirada crítica. Madrid: Díaz de Santos SA; 1967. p. 145.
18. Armas L. Necesidad de prestar atención a la tuberculosis con baciloscopia negativa. Boletín Epidemiológico Semanal IPK. 2008;18:50-2.
19. González-Ochoa E, Armas L, Llanes MJ. Progress towards tuberculosis elimination in Cuba. Int J Tuberc Lung Dis. 2007;11:405-11.
20. Martínez AI, Hurtado de Mendoza L, González E. Valor del diagnóstico de la tuberculosis por autopsia en Cuba. Actas del VIII Congreso Virtual Iberoamericano de Anatomía Patológica; 2005, octubre 1-3. Available from http://www.conganat.org/7congreso/pdf/301.pdf . Consulted on February 15, 2007.
21. Martínez AI, Armas L, Hurtado J, González E. El diagnóstico de la tuberculosis por autopsia en Ciudad de la Habana como indicador valioso en el control y eliminación de la tuberculosis. (1998-2002) Rev Esp Salud Pub. 2007;81:221-5.
22. Pilaya J, Clarke A. An evaluation of completeness of tuberculosis notification in the United Kingdom. BMC Public Health. 2003;3:31.
23. Aisenberg GM, Jacobson K, Chemaly RF, Rolston KV, Rand U, Safdar A. Extrapulmonary tuberculosis active infection misdiagnosed as cancer: Mycobacterium tuberculosis disease inpatients at a comprehensive cancer center (2001-2005). Cancer. 2005;104:2882-7.
24. Lee JH, Han DH, Song JW, Chung HS. Diagnostic and therapeutic problems of pulmonary tuberculosis in elderly patients. J Korean Med Sci. 2005;20:784-9.
25. Swaminathan S, Paramasivan CN, Kumas SR, Mohan V, Venkatesan P. Unrecognised tuberculosis in HIV infected. Int J Tuberc Lung Dis. 2004;8:986-8.
26. Martínez MR, Montoro E. Evaluación del control de calidad de las baciloscopias en el diagnóstico de la tuberculosis en Cuba. Rev Cubana Med Trop. 2006;58:58.
27. Sterling TR. The WHO/IUATLD diagnostic algorithm for tuberculosis and empiric fluoroquinolone use: potential pitfalls. Int J Tuberc Lung Dis. 2004;8:1346-400.
28. Harvies AD, Hargreaves NJ, Kumwenda J, Kwaniana J, Salaniponi FM. Trials of anti-tuberculosis treatment in areas of high human immunodeficiency virus prevalence in Sub Saharan Africa. Int J Tuberc Lung Dis. 2000;4:988-1001.
29. Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. Trans R Soc Trop Med Hyg. 1997;91:422-4.
30. Fourier B. Trials of anti-tuberculosis treatment as a diagnostic tool in smear-negative tuberculosis are of questionable benefits. Int J Tuberc Lung Dis. 2000;4:997.
31. Yoon JS, Lee HJ, Yoon HI, Yoo CG, Kim YW, Han SK, et al. Impact of fluoroquinolones on the diagnosis of pulmonary tuberculosis initially treated as bacterial pneumonia. Int J Tuberc Lung Dis. 2005;9:1215-9.
32. Wang JY, Lee LN, Hsneh PR. Factors changing the manifestations of pulmonary tuberculosis. Int J Tuberc Lung Dis. 2005;9: 777-83.
33. Murray JF, Pio A, Otman S. PAL: a new and practical approach to lung health. Int J Tuberc Lung Dis. 2006;10:1188-91.
34. Organización Panamericana de la Salud. Plan Regional de Tuberculosis 2006-2015. Washington, DC: OPS; 2006. p. 43.