Cuba's Strategy for Childhood Tuberculosis Control, 1995–2005

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ABSTRACT

INTRODUCTION Following a tripling of tuberculosis incidence in Cuba between 1991 and 1994 (from 4.7 to 14.7 per 100,000), the National TB Control Program was revamped in 1995 and the National Reference Center for Childhood TB and Provincial Childhood TB Commissions were created as a strategy for addressing this emerging health problem.

OBJECTIVE Assess the impact of Cuba's new strategy for TB control in children aged <15 years during the period 1995–2005.

METHODS A descriptive review of health services and systems was conducted in Cuba, examining 157 cases of TB diagnosed in children aged <15 years during the period 1995–2005 and comparing impact and process indicators for selected years (1995, 2000, and 2005). Impact indicators included reduction in: a) incidence; b) serious forms (peritoneal, meningeal, miliary, combined); c) mortality; and d) case outcomes (cure, death, treatment drop-out, treatment failure). Process indicators were proportion of cases with: a) microbiological tests; b) knowledge of infection source; c) diagnoses obtained through adult case contact tracing; d) time to diagnosis <60 days; and e) post-mortem diagnoses.

RESULTS During the period 1995–2005, TB rates in children aged <15 years fell by 50% (from 1.0 to 0.5 per 100,000), more evident in children <10 years. The Havana rate was three times the national rate. Diagnosis was post-mortem in three serious cases (1.9%); there were four deaths (2.5%), none after 2000. Only seven children (4.5%) had serious forms, none after 2002. Except for cases diagnosed post-mortem, all children received treatment directly supervised by health personnel. Cure rate was 99.4%; there were no treatment drop-outs or chronic cases; one relapse was reported (0.6%). Knowledge of infection source increased to 90% over the selected years. Microbiological tests were conducted in 90% of cases, with isolation in 30.9%. No isolate was drug-resistant, nor were there reports of infectious contacts with resistance. We found no HIV coinfection. At the end of the study, time to diagnosis of ≥60 days persisted in 40% of cases.

CONCLUSIONS Creation of a National Reference Center for Childhood TB and Provincial Childhood TB Commissions has contributed to improved TB diagnosis and control in children aged <15 years, achieving incidence similar to that during the period prior to TB re-emergence and to those of some developed countries. Improvements are needed in the work and systematic training of health personnel, especially at the primary health care level, in order to eliminate TB as a national health problem by 2015.

KEYWORDS Tuberculosis; tuberculosis/diagnosis; tuberculosis/epidemiology; tuberculosis/mortality; tuberculosis/prevention and control; tuberculosis/therapy; child health services; Cuba

INTRODUCTION

In Cuba, the first National Tuberculosis Control Program (PNCT, the Spanish acronym) was established in 1962–63 in response to the difficult epidemiological situation this disease posed by 1959, when the country underwent political and social changes.[1–3] The PNCT was incorporated into the developing Cuban public health system, the latter guided by principles of accessible, universal and free health care, with an intersectoral approach and active community participation.

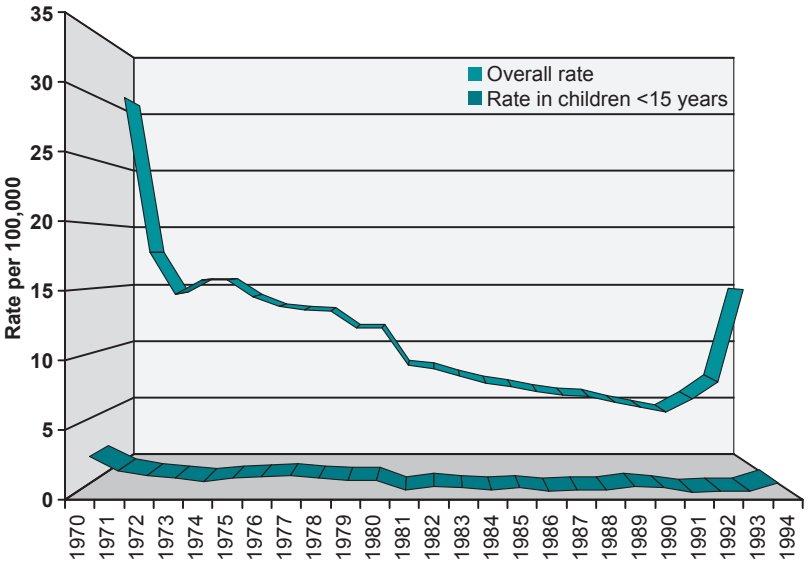
For TB diagnosis, since 1970 the country has had a decentralized network of laboratories for sputum smear microscopy and initial specimen cultures, permitting identification of individuals with respiratory symptoms, as well as surveillance of resistance and periodic quality control. All patients are studied epidemiologically, with intensive contact tracing to identify other ill persons and those with latent infections who meet criteria for isoniazid prophylaxis.[4,5] Under the National Immunization Program, all newborns are vaccinated with BCG before discharge from hospital.[5,6] There are also geographic risk stratification and intervention activities among institutionalized populations and in the community.[3,5] The primary health care (PHC) physician is responsible for the bulk of these activities: case-finding; contact tracing and follow-up; teaching patients to give a sputum sample; supervised administration of treatment and isoniazid prophylaxis; and importantly, individual and group educational activities in the community. The Cuban government has committed the resources necessary for program implementation.[3,5,7]

Beginning in 1970, the PNCT conducted nationwide activities that helped reduce TB incidence and serious forms of the disease in all age groups over the next two decades, with an 85% decline in incidence among children aged <15 years (from 2.7 to 0.4 per 100,000 from 1970 to 1990).[4,5,8] (Figure 1)

A re-emergence of TB occurred worldwide at the end of the last century, with a reported 9 million new cases and almost 3 million deaths in all age groups; 1.3 million of these new cases and some 450,000 deaths were children.[9] The United States reported a 20% rise in cases, with a higher increase in children (40%).[10] The situation turned more critical in developing countries, where 95% of new TB cases are reported, the majority in Sub-Saharan Africa and Southeast Asia.[10,11] PAHO reported a slight increase in the Americas starting in 1991.[12] This re-emergence has been associated with worsening social problems, increased resistance to tuberculosis drugs, HIV coinfection, and abandonment of control programs.[5,7,12]

In 1992, Cuba also began to see a steady rise in reported cases, related to PNCT implementation problems and deteriorating social and economic conditions stemming from the breakup of the European socialist camp and the tightening of the US economic embargo on Cuba, which together caused a 37% drop in per capita Gross Domestic Product (GDP). All of this undermined population nutritional status and standard of living,[13,14] reversing the previous downward trend in TB.[7] In response, the PNCT was revamped, adopting new guidelines aimed at lowering incidence rates.[1–5]

Figure 1: Tuberculosis incidence in Cuba, 1970–1994



Source: National Statistics Division, Ministry of Public Health, Havana

Strategy to fight childhood TB, 1995 To diagnosis and manage TB in children aged <15 years, the National Reference Center for Childhood TB (CRTB, the Spanish acronym) was created, as well as Provincial Commissions for Childhood TB Control (CPTB, the Spanish acronym) staffed by pediatricians specializing in respiratory illnesses.[4] These Commissions are responsible for monitoring children aged <15 years identified during contact tracing of adults with TB in each province. They also assess children with suspected TB referred for medical attention from PHC facilities.

Once a diagnosis is made, the responsible CPTB physician uses clinical records to create a patient profile, sending a copy to the CRTB, headquartered at the Central Havana Children's Hospital. A number of specialists see and discuss each pediatric patient, and TB diagnosis is confirmed by the CRTB. Pediatric cases follow the standard PNCT treatment protocol at the primary care level, based on the Directly Observed Treatment-Short Course strategy (DOTS).[5,7] Discharge is ratified by the CPTB and the CRTB as progress warrants.

A national course is held annually to update CPTB members, who replicate the course for pediatricians in primary and secondary care settings in their provinces.

Given the challenge to eliminate TB as a national health problem by 2015,[5,7] it is important to evaluate results of the PNCT's new strategy from its inception. This study assesses the strategy's impact on TB control in children aged <15 years from 1995 to 2005.

METHODS

A retrospective health system and services review was conducted, covering an 11-year period from 1995 through 2005. The years 1995, 2000, and 2005 were selected to study behavior of TB incidence in children aged <15 years by age group, province of residence, and PNCT process indicators. For impact indicators, the universe included all children aged <15 years diagnosed with TB: 157 patients; the number for operational or process indicators (Table 1) was 144, due to missing data on 13 as explained below.

Diagnostic inclusion criteria were based on PNCT 1999:[4] case of pulmonary TB (PTB) with positive sputum smear (SS+); case of PTB with negative sputum smear (SS-) but positive culture, or clinical and x-ray findings compatible with active PTB; and case of extrapulmonary TB (EPTB). Since the majority of children are SS-, a new case of childhood PTB is defined as a patient with epidemiologic criteria of close contact with a TB patient, clinical symptoms and x-ray suggestive of TB, and positive tuberculin skin test (TST).

Pediatric cases described earlier as "without demonstrable lesions," were excluded,[4] as were patients with incomplete clinical records; there were 13 of these cases, all from 1995.

Clinical and epidemiologic variables included: age (in years completed): <1, 1–4, 5–9, and 10–14; known source of infection; isolation of *Mycobacterium tuberculosis* and resistance to tuberculosis drugs; HIV coinfection; and serious TB: rapidly progressing, life-threatening, or with serious sequelae.

Data were stored in an SPSS database, analyzed with descriptive and inferential statistics using EPIDAT 3.1,[15] and displayed in tables.

Incidence per 100,000 for each year selected (total, by age group, and by province) was estimated using demographic data for the population aged <15 years.[5]

The study protocol was approved by the ethics committee of the Central Havana Pediatric Hospital, and its methods were based on chart review of cases seen by PCTB and CRTB, ensuring patient anonymity. The beneficence principle was operative and all patients received standard treatment.

RESULTS

During the period 1995–2005, PNCT impact indicators exhibited the following behavior:

Childhood TB incidence fell nationally by 50%, with a sharper decline in children aged <10 years (Table 2). Rates in all provinces fell during the period studied. Havana City province reported the highest rates, three times national incidence in 2005 (1.5 per 100,000 vs. 0.5 per 100,000).

There was a decline in frequency of serious forms: seven of the eight cases reported presented between 1995 and 2000, with no cases reported after 2002. There were three cases of peritoneal TB (1.9% of cases), two of meningeal (1.3%), two of miliary (1.3%) and one combined miliary and meningeal (0.6%).

There were four deaths during the period studied, or 2.5% of the 157 children diagnosed with TB. There were no deaths after 2000.

Except for three cases diagnosed post-mortem, all children received treatment directly supervised by health personnel; cure rate was 99.4% (153/154). There were no drop-outs or chronic cases. One relapse was reported in the fourth child who died, who

Table 1: National TB Control Program: process and impact indicators studied

Impact Indicator	Description
Reduction in incidence	Declining incidence over the period
Reduction in serious forms (miliary, meningeal, peritoneal, combined)	Declining frequency over the period
Reduction in mortality	Declining mortality rate over the period
Impact Indicator: Case Outcome	**Target (% of cases)**
Cure • SS+ patient finishing treatment with ≥3 negative smears (including one at end of treatment) • SS- patient with good clinical and radiographic outcome	≥95
Treatment failure • SS+ patient since diagnosis and/or four months after start of treatment • **Relapse** Patient cured after treatment returning with positive smear or culture; or cured patient who later dies and autopsy exhibits active TB, whether or not cause of death • **Chronic case** SS+ patient after completing supervised retreatment regimen	<2
Drop-out Patient who interrupts treatment for ≥2 months	<1
Death Patient who dies from any cause during treatment	<4
Process Indicator	**Target (% of cases)**
Cases with microbiological tests	100
Cases with known source of infection	≥90
Diagnosis obtained through contact tracing of an adult case	≥80
Time to diagnosis <60 days	≥80
Post-mortem diagnosis	<2.5

Source: National TB Control Program

had suffered from a serious immunodeficiency and been cured of TB peritonitis as an infant (1998), relapsing at age 2 years.

PNCT process indicators exhibited the following behavior in the selected years (Table 3):

The proportion of cases with microbiological testing remained low, at no time reaching the target indicator of 100%. Studies of gastric aspirates predominated, followed by sputum, with a 30.9% *Mycobacterium tuberculosis* isolation rate. There were no reports of resistance to tuberculosis drugs in the strains isolated from patients and their infectious contacts, or of HIV coinfection.

It was only in 2005 that the target of identifying the source of infection in ≥90% of cases was met. Predominant sources were close family members, followed by neighbors.

The indicator "diagnosis in contact tracing for an adult case" exhibited values well below the target level of 80%. The highest percentage—50%—was reached in 2005.

Time to diagnosis continued to be lengthy during the period studied. In fact, the proportion of cases diagnosed within the 60-day target was lower in 2005 than in 2000 and 1995 (60% vs. 66.6% and 75%, respectively). Post-mortem diagnosis was made in three children (1.9% of cases). They were: a 1-year-old boy with miliary TB, an 11-month-old boy with miliary and meningeal TB, and a 4-year-old boy with meningitis.

DISCUSSION

In the period prior to TB's re-emergence, 1981–1993, incidence rates in children aged <15 years remained under 1 per 100,000,[5] averaging 0.3 (0.1–0.5).[8] In our research, a 50% incidence decline was observed during the period studied, from an initial 1 per 100,000 in 1995. The decline was steeper than the average decline reported from 1964 until re-emergence,[7] and the rate of decline was slower after 2000.

Table 2: Childhood TB incidence in Cuba by age group for selected years, 1995–2005

Year	Age Group								Total	
	< 1 year		1–4 years		5–9 years		10–14 years			
	No./pop.	Rate	No./pop.	Rate	No./pop.	Rate	No./pop.	Rate	No./pop.	Rate
1995	0 (154,501)	0.0	10 (655,315)	1.5	7 (853,632)	0.8	8 (771,844)	1.0	25 (2,435,292)	1.0
2000	0 (142,674)	0.0	9 (593,070)	1.5	5 (766,709)	0.6	2 (877,706)	0.2	16 (2,380,159)	0.6
2005	0 (130,017)	0.0	3 (556,252)	0.5	1 (697 300)	0.1	6 (1,591,064)	0.8	10 (2,974,633)	0.5

Rate per 100,000 population
Source: National Statistics Division, Ministry of Public Health, Havana

Table 3: Cuba's National TB Control Program: selected process indicator results, 1995–2005

Indicator	Target %	Selected years		
		1995*	2000	2005
		No. (%)	No. (%)	No. (%)
Microbiology tests performed	100	11 (91.6)	12 (75.0)	9 (90.0)
Time to diagnosis <60 days	≥80	8 (66.6)	12 (75.0)	6 (60.0)
Known source of infection	≥90	10 (83.3)	13 (81.2)	9 (90.0)
Diagnosis in contact tracing for an adult case	≥80	2 (16.7)	6 (37.5)	5 (50.0)
Total cases studied		12	16	10

* In 1995, process indicators were studied for only 12 of 25 reported cases.

Source: National TB Control Program

Globally, infants and adolescents are the age groups at highest risk of developing the disease and dying after primary infection.[16,17] In this Cuban study, the group with the least decline in incidence rate was children aged 10–14 years.

In the United States, Nelson et al. reported falling TB incidence rates in children aged <15 years, from 2.9 per 100,000 in 1993 to 1.5 per 100,000 in 2001, representing a 48.3% decline.[18] Higher rates persisted in children aged >5 years, children in urban areas, children from ethnic or racial minorities, and children from families who had immigrated from high-prevalence countries. Since 2003, the United

States has reported an annual decline of just 3.8% for all ages and new TB elimination strategies are being pursued.[19]

The European surveillance network reports rising incidence in all ages since 1997. The countries of Eastern Europe, with only one-third of Europe's population, reported two-thirds of cases in children aged <15 years. The rest of Europe reports rates of 1.5–3 per 100,000 over the past 15 years, although the situation is worse in capitals and major cities.[20]

From 1992 to 2001 in New Zealand, Howie et al.[21] described an average annual incidence rate of 4.8 per 100,000 in those aged <16 years; TB was also more common in children aged <5 years and certain ethnic groups, with a clear association with social disadvantage.

The WHO Stop TB Initiative notes that the global decline in TB has generally been very slow, compromising WHO's goal of eliminating TB by 2050.[22] The WHO Stop TB Working Group published trends in TB incidence rates for the general population of 134 countries for the period 1997–2006 and found an annual variation of ±10% in that period, with reduced averages in only 93 countries. Rates fell more rapidly in countries with a higher ranking in the human development index, lower child mortality, and access to better sanitation systems.[23]

This suggests that although national tuberculosis control programs play a vital role in curing TB, preventing mortality, and reducing transmission and incidence,[23] in the long run, eliminating TB requires conceptualizing health in its broadest sense as wellbeing, addressing underlying causes by garnering support from all sectors of society, without trivializing the importance of the health sector's coordinating role.[24]

One of this study's limitations is that it was not designed specifically to explore the social factors contributing to TB incidence in Cuba, although the country's place on the Human Development Index rose during the period under study;[25] infant mortality continued to decline (from 9.4 per 1,000 live births in 1995 to 6.2 in 2005 and 4.8 in 2009); survival in children aged <5 years rose from 98.8% in 1995 to 99.2% in 2005 and 99.4% in 2009;[26] and access to improved sanitation rose from 87.7% of the population in 1995 to 95.8% in 2008.[27] Nor does Cuba have significant immigration from high-prevalence countries.[3,7] Nevertheless, the higher incidence of TB in Havana City may indicate the presence of vulnerable populations requiring special attention to risk factor control, as recommended by the WHO Stop TB Initiative.[28]

Havana has an incidence of childhood TB three times that of the country as a whole and usually accounts for some 25% of all cases reported.[1] Since 1981 it has undergone major demographic changes (a positive migration balance with the rest of the country and high population density, with 100% of its area urbanized),[29,30], phenomena that increase the probability of TB transmission and make PNCT investigation activities difficult.[1] Geographic risk stratification is an important part of PNCT strategies; in 2009, the country's 169 municipalities were classified by their average incidence in the period 2001–2005 as high (≥7 per 100,000), medium (6.9–4 per 100,000), and low risk (<4 per 100,000),[31] to develop specific targeted activities in each municipality and assess local Program compliance.[3]

Serious forms of TB are very rare in Cuba, and had not been reported until re-emergence of the disease;[1,7] during the study period, they accounted for a small proportion of cases (less than 4%)[5] and were more common in children aged <5 years, especially infants, whose immature immune systems put them at high risk of progression and poor organism containment.[2,16]

All deaths observed in our series occurred prior to 2002 and in three cases were related to serious forms diagnosed only post-mortem. The fourth child who died had a very guarded prognosis due to severe primary immunodeficiency and developed a serious form of TB very early on.

In 83,183 autopsies performed on adults during the period 1994–2003,[32] TB was not reported as a common cause of death in Cuba, but it was among the more common causes of discrepancies between clinical diagnosis and underlying cause of death. TB poses even greater diagnostic challenges in the pediatric age group, especially since serious forms had not been seen before TB's re-emergence.[7] In Havana from 1998 through 2002, there were 23 cases of TB diagnosed by autopsy, or 1.7% of all new cases.[33]

HIV coinfection is a very important factor in progression from latent to active disease and is also associated with poverty and social deprivation in general, but in Cuba is not a health problem.[2,3,7] Although all cases are screened for HIV, no coinfected children were reported during the period studied.

As reported above, except for those diagnosed post-mortem, 100% of the children studied received supervised treatment from health personnel under DOTS.[5] In 2000, PAHO reported DOTS coverage of 73% in the Americas; the cure rate with DOTS was 81% vs. 69% with unsupervised treatment;[34] while our study showed a higher DOTS cure rate of 99.4%.

Nelson et al. report 90% of pediatric cases completed treatment in the period 1993–2001 in the United States, with 2.5% case fatalities. Treatment using DOTS rose from 37.2% in 1993 to 82.9% in 1999.[18] In New Zealand, 1992–2001, only 40% of patients received treatment under DOTS and there were two deaths among 274 patients <16 years old, for a case-fatality rate of 0.7%. Moreover, there were reports of sequelae in 4%, especially in children with TB meningitis, and relapses in 2%.[21]

Microbiologic testing confirms diagnosis and enables resistance studies.[35–37] In this study, small children predominated, a group that characteristically presents with primary pulmonary TB. These lesions are generally paucibacillary and closed, resulting in low isolation rates for *Mycobacterium tuberculosis*.[16,21,37] In developed countries, with early diagnoses based largely on contact investigations, isolation rates are low.[18,21,38] Positivity increases when more than one specimen is taken from children aged <5 years.[21] In our study, the goal of 100% microbiologic sputum examination was not reached at any time, although we consider microbiologic testing to be critical, with meticulous attention to quality in collection and processing.

Identifying the source of infection, an infectious adult, makes monitoring, prophylaxis, and early diagnosis possible[5,28] and

prevents progression to severe forms of the disease, especially in children aged <3 years.[38–41] Some 60–80% of children who have prolonged contact with infectious people in the home, whether family or other caregivers, may contract the disease.[2,16] Ideally, childhood TB should be diagnosed during the investigation of a smear-positive adult.

While in this study, the target of identifying the source of infection in 90% of cases was met, many times the source was identified by studying the contacts of the sick child, the opposite of what should occur. Thus, the related indicator, diagnosis during contact tracing of an infectious adult case, remained far below the goal of ≥85% throughout, although slight improvement was observed at the end of the study period. Results below this figure have also been observed in New Zealand (83.9%), South Africa (80%), Spain (68.6%), and Peru (74.2%).[16,21,40,41]

PNCT includes in its process indicators tracing of 100% of contacts;[5] if the process is effective, at least 90% of exposed children who develop active disease will be diagnosed during contact tracing for an adult case. However, unless contact tracing improves, it will be impossible to eliminate TB as a health problem.[7,40,42,43]

Late diagnosis, particularly attributable to health system factors, is infrequently studied in countries with low TB prevalence.[7] Late diagnosis contributes to progression to advanced or serious forms of the disease occurring chiefly in the first 12 months after infection, especially in children aged <3 years; it also contributes to continued transmission.[7,9,43] Although childhood TB poses a diagnostic challenge,[1,2,9,37] this does not justify the late diagnosis observed in this study, especially in patients with known exposure to the disease, with pulmonary symptoms similar to those in adults or prolonged adenitis.[41,44] This suggests that pediatricians have low risk perception concerning TB in children aged <15 years and overconfidence in BCG vaccination, among other factors identified by the National Reference Center for Childhood TB. More education and training are needed for the general population and health personnel, particularly pediatricians in CPTB and family physicians in PHC, to reduce the interval between symptom onset and diagnosis.

In a country like Cuba with very low incidence and universal health coverage, it is even more important to emphasize good contact tracing, proper administration of prophylaxis for latent infection, and an exhaustive study of contacts or symptomatic children with probable TB, discussing the cases collegially with teams of experts in CPTB and the CRTB to obtain an earlier and more accurate diagnosis.

CONCLUSIONS

The strategy of creating the CRTB and PCTB to revamp and reinforce the Cuban health system's National Tuberculosis Control Program contributed to TB diagnosis in children aged <15 years during the 11-year period studied and also to reducing incidence in that age group to levels similar to those prior to re-emergence and to those in some developed countries. Improvements are needed in the work and systematic training of health personnel and PHC staff involved in implementing PNCT, especially in Havana, to increase laboratory confirmation, early diagnosis, and diagnosis in contact tracing if we are to eliminate TB as a health problem in Cuba by 2015.

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