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Evolution, Trends, and Potential Explanations of the Increase in the Incidence of Tuberculosis: the Case of Uruguay

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Abstract

Purpose of review A descriptive analysis of the trend of tuberculosis incidence in Uruguay between 1995 and 2018.
Recent findings In 2015, World Health Organization (WHO) proposed The END TB Strategy; the Latin American countries that implemented these strategies at the first level of care have had successful outcomes in terms of the reduction in the incidence, morbidity, and mortality of the disease.
Summary Uruguay is a striking case in the regional environment regarding tuberculosis epidemiology. The trend of tuberculosis had a turning point in 2006, which defines two clearly different periods. The first period covers the year 1995 to 2006 and shows a significant decrease in the incidence rate and the second period covers the year 2006 to 2018 and shows a significant increase in the incidence rate. The proportion of contacts of tuberculosis cases receiving prophylactic treatment, the percentage of cases lost to follow-up, and the magnitude of the bacillary burden at diagnosis moment are possible

factors linked to the changes in the trend of the incidence of tuberculosis. The initiation of a gradual transfer of the responsibilities of the National Program of Tuberculosis in diagnosis, treatment, and prevention to primary care health providers in the National Integrated Health System will hopefully contribute to reverse the epidemiological situation of tuberculosis in the country.

Introduction

Tuberculosis in the world and in Latin American countries

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and transmitted from one person to another through little drops generated in the respiratory system of people with active lung disease [1, 2].

The natural history of the disease results from a complex interaction between the host and its immune conditions, nutritional status, and health, socio-economic, cultural, and environmental characteristics [2, 3].

TB affected 10 million people in 2017, producing 1.6 million deaths, being among the first 10 causes of death in the world [4••].

Global rates of the TB burden (2005–2015) showed a decline in prevalence (– 0.7% [– 1.0 to – 0.5]) and incidence (– 1.6% [– 1.9 to – 1.2]), not as steep as the decline in mortality (– 4.1% [– 5.0 to – 3.4]) [5].

The WHO estimated 282,000 cases of TB for 2017 in the Region of the Americas (new cases and relapses), which represents 3% of the global burden of TB and an incidence rate of 28/100,000 inhabitants [4••].

In the Americas in 2017, the Caribbean region has the highest incidence (61.2/100,000), followed by South America (46.2/100,000), Central America and Mexico (25.9/100,000), and North America (3.3/100,000) [4••].

Latin America is among the regions with a higher-than-expected incidence, prevalence, and mortality rate according to the Global Burden of Disease study but in most countries, the burden of tuberculosis has decreased significantly [5].

Tuberculosis in Uruguay

National Tuberculosis Program (NTP) adopted the definitions proposed by the World Health Organization (WHO) for TB diagnosis (case clinically diagnosed or bacteriologically confirmed) as well as their classification according to anatomic location, HIV condition, drug resistance, and history of treatment [6]. TB treatment is done according to the Uruguayan National Guidelines for TB Management. The NTP follows WHO recommendations for the treatment of Isoniazid-resistant and multidrug-resistant TB [7, 8].

Since the 1980s, there has been a significant decrease in the incidence of TB as a result of the successful implementation of the directly observed therapy strategy (DOTS) implemented by the NTP. From 1994 to 2005, a steady average decrease in the incidence of the disease was observed, but from 2006 until the current date, there was a constant increase in the number of new cases and relapses (Fig. 1) [9•].

Evolution of the models of medical care of TB

The WHO has proposed several strategies to reduce burden from TB prioritizing accessibility to diagnosis, performance of directly supervised treatments, and control of contacts, particularly in the population under five years of age. These strategies should be framed within a national program of TB control supervised and conducted by the health authorities of each country. By contrast, during the last decades, we have seen several differences in strategies and involvement of health authorities in the control of TB, probably influenced by the burden of the disease in each country.

The WHO declared in 1993 that the situation of TB in the world represented a global emergency. As a response to this emergency, the WHO implemented from 1995 on the strategy TAES/DOTS (Directly Observed Treatment Shorthand) [10, 11].

This strategy consists of five basic elements: The first element is the political commitment to guarantee the necessary financing for the control of TB. The second element is the detection of cases through bacteriological tests, strengthening the laboratory network. The third element consists of standardizing the treatment, with

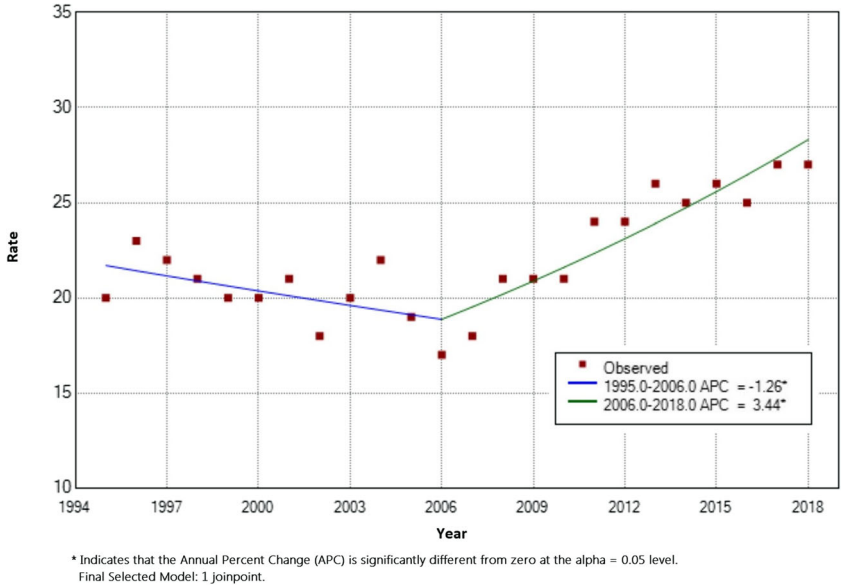

Fig. 1. Incidence of TBC 1995-2018, joinpoint model (Note: original figure).

supervision and support to the patient throughout it. The fourth element consists of an effective system of drug supply. The last element is the information system, which should be useful for recording cases and evaluating results at the individual level and for the entire program [10, 11].

In 2000, the Millennium Development Goals were launched, TB was included in Goal 6, and the goal consisted in stopping the progress and reducing the incidence for the year 2015. The strategy designed to achieve this objective was called Stop TB, which contained six components: the first was to expand and improve the quality of TAES/DOTS, the second approach addresses at-risk populations such as TB/HIV coinfection and multidrug-resistant TB, the third one strengthens the health systems, the fourth incorporates all health care providers, the fifth empowers patients and empower communities, and the sixth element is the promotion of research [12].

In 2015, the United Nations adopted the Sustainable Development Goals (SDG) for 2030, and one of its goals is to put an end to the global TB epidemic. In The END TB Strategy, WHO proposes reducing TB deaths by 95% and reducing new cases by 90% between 2015 and 2035 and ensure that no family suffers catastrophic expenses due to TB. This strategy is based on three pillars that seek to focus on treatment and prevention for all patients, achieve the greatest benefits of social and health policies, and obtain new scientific knowledge and technological innovations to drastically change prevention of tuberculosis and patient care [13].

Strategies for TB control in Uruguay

In Uruguay, control of TB is centralized by the National Tuberculosis Control Program of the Comisión Honoraria para la Lucha Antituberculosa y Enfermedades Prevalentes (CHLA-EP), which constitutes a nongovernmental public institution (public funding, management governed by private law) [14]. The institution is headquartered in Montevideo and is present throughout the territory of Uruguay through a network of peripheral effectors. In addition, it manages and finances two specialized laboratories: the Central Bacteriological Laboratory (National Reference Center for Mycobacteria) and the Albert Calmette Laboratory, and their main mandate is the storage and distribution of all vaccines (included or not in the National Immunization Program) and of the anti-tuberculosis medication [14].

Currently, the CHLA-EP is developing a pilot decentralization strategy, which involves a process of progressive transfer of the basic actions of the tuberculosis program (prevention, diagnosis, and treatment) to the different health care providers, under the supervision of the CHLA-EP and Ministry of Health. This model is

Table 1. Estimates of the joinpoint model

Segment	Lower endpoint	Upper endpoint	APC	Lower CI	Upper CI	Test statistic (t)	*p* value
1	1995	2006	− 1.3*	− 2.4	− 0.1	− 2.2	< 0.05
2	2006	2018	3.4*	2.4	4.5	6.7	< 0.05

*annual percent change (APC) is significantly different from zero at the alpha = 0.05 level
Original table

consistent with the guidelines of the End of Tuberculosis Strategy [15].

Trends of TB in Uruguay

A descriptive analysis of the trend of TB incidence in Uruguay between 1995 and 2018 was carried out in order to discuss how TB control model has been implemented in the last 20 years.

The source of data was the National Registry of Tuberculosis of the CHLA-EP of Uruguay.

For the analysis of trends, the joinpoint regression model was used through the computer program provided by the Surveillance Research Program of the National Cancer Institute of USA [16].

The joinpoint regression model is one of the most used methods to estimate changes in the trend of rates [17]. This model allows to identify the moment in which significant changes occur in the trend of a series and estimates the magnitude of the increase or decrease observed in each interval or period of time. In this way, the years that make up each period are identified, as well as the annual change percentage (APC) and its confidence intervals.

For the estimation of the model, the natural logarithm of the incidence rates was used, the minimum number of data in the linear trend was fixed in 4, and a maximum of 3 inflection points were searched. The final selection of the model was made following the Bayesian information criterion (BIC).

To analyze possible explanatory factors of the variability in the TB incidence rate, a multiple linear regression model was used. The assumptions of normality and homoscedasticity were evaluated by means of the calculation and graphical analysis of standardized residues. The variables considered for the model were the percentage of contacts who did not receive prophylactic treatment for TB, the percentage of cases with low bacillary load at the time of diagnosis (less than ++) and the proportion of losses to follow-up or drop-out of treatment.

During the analyzed period, the incidence rate of TB ranged from a minimum of 17.0 cases per 100,000 inhabitants in 2006, to a maximum of 27.2 in 2018.

Figure 1 shows the trend of TB by year, with a turning point in 2006, which separates two clearly differentiated periods. The first period covers the years 1995 to 2006 and shows a significant decrease in the incidence rate, the percentage of annual change in this period was − 1.3% with a confidence interval of − 2.4 to − 0.1% (Table 1). The second

Table 2. Multiple linear regression model

	Coef.	Std. err.	*t*	*p* > [*t*]	95% conf. interval	
Percentage of contacts that did not receive prophylactic treatment	**0.193715**	**0.052145**	**3.71**	**0.001**	**0.084940**	**0.302489**
Percentage of cases with low bacillary load	− 0.168224	0.069155	− 2.43	0.025	− 0.312480	− 0.023967
Percentage of cases lost during the follow-up	0.000509	0.000159	3.20	0.004	0.000177	0.000841
Constant	0.193624	0.036512	5.30	0.000	0.117460	0.269788

Original table

period covers the years 2006 to 2018 and shows a significant increase in the incidence rate, the percentage of annual change in this period was 3.4% with a confidence interval of 2.4 to 4.5% (Table 1).

When evaluating the possible factors linked to the changes in the trend of the incidence of TB, it is observed that both the percentage of contacts that did not receive prophylactic treatment for TB and the percentage of cases lost during the follow-up are directly associated with the incidence of TB (positive coefficient), while the percentage of cases with low bacillary load at the time of diagnosis (early diagnosis) is inversely associated with the incidence of TB. The results of the regression model show that the three factors are significant ($p < 0.05$) and together, they explain approximately 70% of the variability in the incidence rate of TB, R-squared = 0.7015 (Table 2).

Percentage of contacts receiving prophylactic treatment, percentage of cases lost to follow-up, and the magnitude of the bacillary burden are factors linked to aspects of the natural history of the disease and its ways of transmission. It is estimated that within that 10 to 15 narrow contacts of a bacilliferous patient could be infected within one to 2 years and get sick with the disease within two to 3 years. These infections could be reduced by 60 to 70% if prophylactic treatment was done.

Therefore, as untreated contacts increase, the number of people who become ill in the community increases and the infection continues to spread. In the same sense, the cases with loss and follow-up constitute a reservoir of the disease while they remain bacilliferous.

Finally, the presence of patients with a high bacillary load in smear microscopy at the time of diagnosis implies an extensive or evolved disease with a long evolution with a high probability of transmission over time.

The TB control programs with the aim of reducing the morbidity and mortality of the disease, propose three basic strategies: to make an early diagnosis of TB, achieve success in anti-tuberculosis treatment, and achieve control of contacts, which implies the detection, study and preventive treatment of them.

The Latin American countries that have developed TB control programs that implemented these strategies at the first level of care have had successful outcomes in terms of the reduction of the incidence, morbidity and mortality of the disease [18]

What are the potential explanations for this evolution of the disease?

Uruguay was classically placed among the countries with the lowest incidence of TB, and the possibility of eradicating the disease as a public health problem was raised in the late 1990s. However, the burden of this disease has not changed as expected as the country progressed through the epidemiological transition and socio-economic improvement [5]. Uruguayan socio-economic development is not accompanied by the reduction of the incidence of TB.

After a severe socio-economic crisis in 2002, Uruguay has had a continuous economic growth and a reduction in poverty levels during the last 16 years. Since 2015, Uruguay has been classified by the World Bank as a high-income country; however, as one would expect, the incidence of TB has not declined [19]. Although we are facing a disease strongly influenced by the social determinants of health, these cannot explain the evolution of TB in Uruguay by themselves [20]. Socio-economic improvement reduced health determining social factors in a high percentage of the population, but still persists a number of people still living in critical context of social and cultural exclusion extremely vulnerable to this disease (homelessness, population living in slums, people living with HIV, prisoners and illicit drugs users) [20]. These groups have difficulties in the access to early diagnosis and treatment, what maintains the widespread of infection in the community [21].

There are also other factors that could explain the evolution of the disease during the last decade.

One of them is the underestimation of the magnitude of TB potential consequences in the population by the health personnel and the community, explained by the relatively long period of successful control of the disease before 2006.

Another factor to take into account is the characteristics of the structure and functioning of the National Tuberculosis Control Program, a vertical program that concentrated the activities related to the control of TB in the country (diagnosis, treatment and prevention) since its creation in the 1940s [14].

The health reform that occurred in the country in 2007 resulted in the creation of the National Integrated Health System (NIHS), a milestone in the public health of the country [22]. At that moment, the National Program of Tuberculosis was not integrated to the system.

These problems in the organization of health care negatively influenced the accessibility to diagnosis, cases finding, early initiation of treatment, and preventive measures on the transmission of the disease.

The recognition of this situation determined in 2015 (within the framework of the strategy of Tuberculosis in Large Cities, PAHO/WHO), the initiation of a gradual transfer of the basic responsibilities of the Program in diagnosis, treatment, and prevention to primary care health providers in the NIHS.

This process, which is still in consolidation, hopefully will strongly contribute to achieve the reverse of the epidemiological situation of TB in the country.

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Compliance with Ethical Standards

Conflicts of Interest

Dr. Alegretti reports non-financial support from Comisión Honoraria de Lucha Antituberculosa, outside the submitted work. Dr. Contrera reports personal fees from Comisión Honoraria de Lucha Antituberculosa, outside the submitted work. Dr. Aleman has nothing to disclose.

Human and Animal rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

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- • Of importance
- •• Of major importance

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