



## Trends in tuberculosis mortality among children and adolescents in Brazil, 1996-2020: a joinpoint analysis

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### TO THE EDITOR:

Tuberculosis remains one of the deadliest infectious diseases worldwide. In 2020, an estimated 1.5 million people worldwide died from tuberculosis; of those, 16% were children or adolescents (< 15 years of age).<sup>(1)</sup> Childhood tuberculosis has been neglected by researchers and policy makers for decades, despite the fact that children are at high risk of acquiring tuberculosis infection and dying from tuberculosis disease. This neglect can be explained by the difficulty in diagnosing tuberculosis in children; by the fact that the risk of childhood tuberculosis transmission is low; by misplaced faith in the BCG vaccine; and by the old dictum that the best way to prevent childhood tuberculosis is to treat tuberculosis in adults.<sup>(2)</sup> To achieve the WHO End TB Strategy target of a 95% reduction in tuberculosis mortality by 2035, more priority should be given to children and adolescents, especially those in the 30 countries with the highest tuberculosis burden (among which is Brazil). Although there are numerous reports of national and global tuberculosis mortality in the general population,<sup>(3-5)</sup> there are limited data on tuberculosis mortality in the pediatric population.<sup>(6)</sup> We therefore conducted a joinpoint analysis to identify time trends of tuberculosis mortality among children and adolescents in Brazil in the 1996-2020 period.

We used an open-access database (the Brazilian Unified Health Care System Information Technology Department database) to collect data on the number of deaths from tuberculosis, as well as data on population estimates of children and adolescents in the 0- to 19-year age bracket between January of 1996 and December of 2020. Tuberculosis was classified by the following ICD-10 codes: A15—respiratory tuberculosis, bacteriologically or histologically confirmed; A16—respiratory tuberculosis, not confirmed bacteriologically or histologically; A17—tuberculosis of nervous system; A18—tuberculosis of other organs; and A19—miliary tuberculosis. We calculated the tuberculosis mortality rate per 100,000 population. We used joinpoint regression analysis (Joinpoint Software, version 4.9.0.0; National Cancer Institute, Information Management Services, Inc., Calverton, MD, USA) to estimate the annual percent change (APC) in mortality rates between trend-change points, the average APC (AAPC) during the entire study period, and 95% CIs. When there are no joinpoints (i.e., no changes in trend),

the APC is constant and equals to the AAPC; otherwise, the entire period is segmented by the points with trend changes (an increasing trend, a decreasing trend, or no changes in trend). In this case, the AAPC is estimated as a weighted average of the estimated APC in each segment by using the segment lengths as weights.<sup>(7)</sup>

During the study period, 3,072 children and adolescents died from tuberculosis. Of those, 2,047 (66.6%) had respiratory tuberculosis (A15, n = 228; A16, n = 1,819), 517 (16.8%) had tuberculosis of nervous system, 129 (4.2%) had tuberculosis of other organs, and 379 (12.4%) had miliary tuberculosis. Approximately 47% of the 3,072 children and adolescents who died during the study period were female, and 76% were non-White. In addition, 892 (29%) were in the 0- to 4-year age bracket, 276 (9%) were in the 5- to 9-year age bracket, and 1,904 (62%) were in the 10- to 19-year age bracket. The overall tuberculosis mortality rate (per 100,000 population) decreased from 0.32 in 1996 to 0.17 in 2020, and the absolute number of deaths decreased from 212 to 101 in the same period. The tuberculosis mortality rates (per 100,000 population) in 1996/2020 were 0.48/0.16, 0.15/0.05, and 0.33/0.22 for children/adolescents in the 0- to 4-year age bracket, in the 5- to 9-year age bracket, and in the 10- to 19-year age bracket, respectively.

The AAPC (95% CI) in the tuberculosis mortality rate throughout the study period was -2.8% (-4.6 to -1.0), -4.2% (-7.3 to -0.9), -3.3% (-5.3 to -1.3), and -1.4% (-3.3 to 0.5) for the sample as a whole, for those in the 0- to 4-year age bracket, for those in the 5- to 9-year age bracket, and for those in the 10- to 19-year age bracket, respectively (Table 1). The joinpoint analysis identified three trends in tuberculosis mortality in the sample as a whole: the 1996-2005 period, with a larger decreasing trend (APC, -7.9%; 95% CI, -10.0 to -5.7), the 2005-2017 period, with a smaller decreasing trend (APC, -2.3%; 95% CI, -4.0 to -0.6), and the 2017-2020 period, with a nonsignificant increasing trend (APC, 11.8%; 95% CI, -1.5 to 26.9). In the 0- to 4-year age group, the joinpoint analysis identified a decreasing trend in the 1996-2015 period (APC, -8.5%; 95% CI, -10.3 to -6.7) and a nonsignificant increasing trend in the 2015-2020 period (APC, 14.4%; 95% CI, -1.7 to 33.1). In the 10- to 19-year age group, the joinpoint analysis identified a slight decreasing trend in the 1996-2016

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**Table 1.** Trends in tuberculosis mortality (per 100,000 population) among children and adolescents in Brazil, 1996-2020.

Age group	AAPC (95% CI)	p	Joinpoint section	APC (95% CI)	p
Sample as a whole	-2.8% (-4.6 to -1.0)	0.003	1996-2005	-7.9% (-10.0 to -5.7)	< 0.001
			2005-2017	-2.3% (-4.0 to -0.6)	0.01
			2017-2020	11.8% (-1.5 to 26.9)	0.08
0- to 4-year age bracket	-4.2% (-7.3 to -0.9)	0.01	1996-2015	-8.5% (-10.3 to -6.7)	< 0.001
			2015-2020	14.4% (-1.7 to 33.1)	0.07
5- to 9-year age bracket	-3.3% (-5.3 to -1.3)	0.002	N/A	-	
10- to 19-year age bracket	-1.4% (-3.3 to 0.5)	0.14	1996-2016	-3.4% (-4.4 to -2.5)	< 0.001
			2016-2020	9.3% (-2.2 to 22.0)	0.11

AAPC: average annual percent change; and APC: annual percent change.

period (APC, -3.4%; 95% CI, -4.4 to -2.5) and a nonsignificant increasing trend in the 2016-2020 period (APC, 9.3%; 95% CI, -2.2 to 22.0).

Overall, the tuberculosis mortality rate in Brazilian children and adolescents in Brazil has decreased in the last two decades, with an AAPC of -2.8%. The overall tuberculosis mortality rate and the absolute number of deaths in these age groups are relatively low. However, at least three findings of this study merit attention. First, a nonsignificant increasing trend in tuberculosis mortality with an APC of 11.8% in the 2017-2022 period highlights the need to confirm this trend by continuous nationwide surveillance of tuberculosis deaths among children and adolescents in Brazil. Second, 76% of all tuberculosis deaths occurred among non-White individuals, a rate that is much higher than 56%, which is the proportion of non-White individuals in the population of children and adolescents in the 0- to 19-year age bracket. A disproportionately high tuberculosis mortality rate among non-White children and adolescents might reflect the socioeconomic inequalities in Brazil that give rise to differences in exposure and vulnerability to infection and disease, as well as in access to prompt diagnosis and treatment. Third, children/adolescents in the 10- to 19-year age bracket accounted for 62% of all tuberculosis deaths, a rate that is higher than the proportion of children/adolescents in this age group in the pediatric population (i.e., 52%). Moreover, the tuberculosis mortality rate in this age group did not decrease significantly throughout the study period, showing a nonsignificant increasing trend with an APC of 9.3% in the 2015-2020 period. The period between adolescence and early adulthood is increasingly recognized as a key period for tuberculosis disease and adverse outcomes.<sup>(8)</sup> The higher tuberculosis mortality rate among adolescents

might be related to poor treatment adherence, high loss to follow-up rates, and increased comorbidities such as tuberculosis/HIV coinfection, diabetes, and risky substance use.<sup>(9)</sup> Tuberculosis has been reported as the underlying cause in less than 1% of deaths from tuberculosis/HIV coinfection,<sup>(10)</sup> and this can lead to an underestimation of tuberculosis deaths.

Despite remarkable progress in reducing tuberculosis cases and deaths in the last few decades, Brazil remains among the 30 countries in the world with the highest tuberculosis burden. This study highlights the need for establishing a specific and effective national strategy to control childhood tuberculosis in Brazil, prioritizing racial equity in health care and paying special attention to adolescent patients.

## AUTHOR CONTRIBUTIONS

TGP: study conception and design; data collection, analysis, and interpretation; and drafting of the manuscript. YMC: study conception and design; data collection and interpretation; and critical revision of the manuscript for important intellectual content. MLC: data interpretation; and critical revision of the manuscript for important intellectual content. LRE: data analysis and interpretation; and critical revision of the manuscript for important intellectual content. LZ: research project coordination; study conception and design; data interpretation; and critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## CONFLICTS OF INTEREST

None declared.

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