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Tuberculosis notifications among children, Brazil

This online first version has been peer-reviewed, accepted and edited,
but not formatted and finalized with corrections from authors and proofreaders

Tuberculosis notifications among children and young adolescents, 2008–2019 compared to 2020–2023, Brazil

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(Submitted: 26 March 2025 – Revised version received: 15 September 2025 – Accepted: 15 September 2025 – Published online: 21 November 2025)

Abstract

Objective To evaluate the impact of the coronavirus disease 2019 (COVID-19) pandemic on tuberculosis-related notifications and mortality in Brazilian children and young adolescents aged 0–14 years.

Methods We conducted an ecological study using interrupted time series analysis with data from DATASUS, a nationwide open-access database of the Brazilian health ministry. We compared the notification rates of overall active tuberculosis, laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis and tuberculosis-related deaths between the pre-pandemic (January 2008 to February 2020) and post-pandemic (January 2022 to December 2023) periods.

Findings Between 2008 and 2023, 43 216 tuberculosis notifications were recorded among children and young adolescents. The average annual notification rate per 100 000 population rose from 5.75 pre-pandemic to 8.37 post-pandemic, a 45.6% increase. Children younger than 1 year consistently had the highest rates. Laboratory-confirmed tuberculosis notifications totalled 12 557, with rates increasing from 1.55 per 100 000 pre-pandemic to 3.01 per 100 000 post-pandemic (94.2% increase). The average annual notification rate for miliary and meningeal tuberculosis increased from 0.22 to 0.29 per 100 000 (31.8%), and for tuberculosis-related deaths from 0.09 to 0.14 per 100 000 (55.6%). In 2023, laboratory-confirmed tuberculosis and miliary and meningeal forms had the highest rates (3.37 and 0.33 per 100 000, respectively), while deaths were the second highest on record (0.15 per 100 000).

Conclusion COVID-19 disruptions to tuberculosis services led to increased tuberculosis notifications rates among Brazilian children and adolescents after the pandemic, due to higher transmission following a period of underdiagnosis. This setback hinders progress towards the End TB Strategy goals.

Introduction

Tuberculosis is one of the leading causes of death from a single infectious agent and among the top 10 causes of death worldwide.¹ In 2023, an estimated 1.25 million people died from tuberculosis, including 161 000 people living with human immunodeficiency virus (HIV).¹ According to the *Global tuberculosis report 2024*, the global number of tuberculosis case notifications decreased during the coronavirus disease 2019 (COVID-19) pandemic compared with the years before the pandemic, 7.1 million in 2019 compared with 5.8 million in 2020.¹ Data for children aged 0–14 years showed a similar drop: 521 001 notifications in 2019 compared with 398 923 in 2020.²

This reduction in notifications may have been partly due to mitigation measures implemented to contain the spread of severe acute respiratory syndrome coronavirus 2 (the etiological agent of COVID-19), such as social distancing, hand hygiene and mandatory mask use. These measures may have affected the transmission of *Mycobacterium tuberculosis* as well as other respiratory pathogens.^{3,4} However, evidence suggests that the reduction was primarily due to interruptions in the tuberculosis care cascade, reflecting underdiagnosis and/or undertreatment.^{5,6}

Mathematical modelling and analytical techniques have been used to predict the impact of COVID-19-related disruptions on tuberculosis services.^{7–10} For example, one model estimated that these disruptions could lead to a 20.0% increase in tuberculosis-related deaths up to 2024.⁹ Another study, which assessed the impact of COVID-19-related disruptions to health services on tuberculosis burden in India, reported that a 3-month suspension of tuberculosis services could lead to an estimated 9.2% increase in the number of cases and an estimated 3.6% increase in deaths up to 2025.¹⁰

Following the sharp decrease in global tuberculosis notifications in 2020 and 2021, the number of notifications has increased and now exceeds pre-COVID levels. In 2023, an estimated 10.8 million people developed tuberculosis worldwide compared with 7.1 million in 2019.¹ This trend is a setback in achieving the goals of World Health Organization's (WHO's) *The end TB strategy*, which aims to reduce incidence by 80%, reduce tuberculosis-related deaths by 90% and eliminate the catastrophic costs for tuberculosis-affected households by 2030.^{5,6,11} Understanding how these global setbacks affect vulnerable populations is critical. Children, in particular, may

serve as an early indicator of these impacts because of their higher risk of progression to severe forms of tuberculosis.¹²

However, data on tuberculosis incidence rates in children after the COVID-19 pandemic are sparse.¹³ We therefore aimed to evaluate the impact of the COVID-19 pandemic on tuberculosis-related notifications and mortality in Brazilian children and young adolescents aged 0–14 years by comparing the pre-pandemic and post-pandemic periods.

Methods

We conducted an ecological study using data from January 2008 to December 2023, extracted from DATASUS, a nationwide open-access database maintained by the Brazilian health ministry.¹⁴ The database contains anonymized, individual-level data on all notifications of active tuberculosis and tuberculosis-related deaths. We extracted data for all children and young adolescents diagnosed with tuberculosis (notified cases), including information on overall active tuberculosis, laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis, and tuberculosis-related deaths. We stratified the study population into four age groups: < 1 year, 1–4 years, 5–9 years and 10–14 years.

For this study, we defined the pandemic period as March 2020 to December 2021, corresponding to the implementation and gradual relaxation of mitigation measures.¹⁵

Data sources

In Brazil, health workers officially notify all people diagnosed with tuberculosis in public and private health-care facilities to the Brazilian Notifiable Diseases Information System.¹⁶ Notification must be done within 7 days after diagnosis. After notification, patients receive tuberculosis treatment free of charge, provided exclusively through the public health system. The information system primarily records notifications and data on notifiable diseases listed in the National Compulsory Notification List of Diseases and Hazards, established by the Consolidation Law No. 4 of 28 September 2017.¹⁷ The tuberculosis module in the system includes specific data on the date of diagnosis, form of tuberculosis, microbiological confirmation and other sociodemographic information.

Deaths caused by tuberculosis are officially recorded as tuberculosis-related deaths in the Brazilian Mortality Information System. This system is primarily populated with death certificates issued by physicians and processed by municipal health authorities, who are trained

in International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) coding standards. Reported data are transferred to a state-level database. After local review and coding, data are consolidated at the state level and subsequently unified nationally by the health ministry, ensuring comprehensive coverage. This system is recognized for its high quality and completeness,^{18,19} and it provides microdata on deaths by age, sex, cause and residence of the deceased. Causes of death are reviewed and coded by trained municipal health workers, according to ICD-10, including tuberculosis-related ICD codes A15, A16, A17, A18, and A19. In cases of HIV–tuberculosis co-infection, deaths are recorded as HIV-related, in accordance with ICD-10 guidelines.

We obtained the total population by age from the Brazilian Institute of Geography and Statistics census data.²⁰

Outcomes

The primary outcome of interest was the diagnosis of active tuberculosis. Secondary outcomes included laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis and tuberculosis-related deaths.

Among children younger than 10 years, the diagnosis of pulmonary tuberculosis is usually presumptive based on the clinical judgement of the attending physician. To improve diagnostic accuracy, the health ministry recommends the use of a scoring system developed in Brazil, which contains multiple criteria, such as clinical manifestations, radiological findings, history of close contact with a person with tuberculosis in the previous two years, nutritional status and results of tuberculin tests.²¹ This score has an estimated sensitivity of 89% and a specificity of 86%.²² Although the diagnosis of extrapulmonary tuberculosis may also be presumptive, it is more often laboratory-confirmed using methods that can also be used to confirm pulmonary tuberculosis. These methods include: (i) microbiological confirmation, defined as at least one smear positive for acid-fast bacilli; (ii) rapid molecular testing (Xpert® MTB/RIF, Cepheid, Sunnyvale, United States of America, from 2014 to 2019 or Xpert® MTB/RIF Ultra from 2019 to 2023); and (iii) solid culture using Löwenstein-Jensen or Ogawa-Kudoh media, or liquid culture using the mycobacteria growth indicator tube (Becton Dickinson, Sparks, USA).²³ We considered miliary and meningeal tuberculosis diagnoses according to the reported notification data.

Data extraction

We extracted data on 28 October 2024, using TabWin, the DATASUS tabulation software. We imported, processed and analysed all data in R (R Foundation, Vienna, Austria) and stored them in a database container (DBC) file format. To ensure data quality, two researchers independently reviewed the data, and a third researcher was consulted in case of discrepancies.

Statistical analysis

We calculated notification rates by dividing the total number of notified cases according to the date of diagnosis by the age-specific population and multiplying by 100 000. We interpolated monthly population estimates between the census years of 2010 and 2023 to adjust the denominator. To assess significant differences, we calculated notification rate ratios with 95% confidence intervals (CIs), between epidemiological periods with COVID-19 mitigation measures and those without.

We compared the pre-pandemic period (January 2008 to February 2020) with the post-pandemic period (January 2022 to December 2023), and considered the pandemic period (March 2020 to December 2021) as an intervention phase. We also compared the three periods for the following outcomes: all active tuberculosis diagnoses; laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis diagnoses; and tuberculosis-related deaths. We included all children and young adolescents in the main analyses and conducted subgroup analyses by age group.

We used an interrupted time series analysis to assess the impact of COVID-19 on tuberculosis control. Notifications and mortality were compared across three periods: pre-pandemic, pandemic and post-pandemic, assuming that the average and trend of the time series remain constant throughout the study period.

The linear model was specified as follows:

$$Y_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon_t \quad (1)$$

where Y_t is the outcome at time t , X_1 is a continuous variable representing the time in months during the pre-pandemic period, X_2 is a categorical variable indicating changes in the pandemic phase (0 is pre-pandemic, 1 is during the pandemic and 2 is post-pandemic), and X_3 is an interaction term between time and pandemic phase, representing the change in slope after the pandemic. ε_t is the error term. The coefficients have the following interpretations: β_0 is the baseline level of the outcome at the start of the pre-pandemic period, β_1 is the monthly change in

the outcome during the pre-pandemic period, β_2 is the change in the average level of the outcome during and after the pandemic compared to the pre-pandemic period, and β_3 is the change in the slope of the trend after the pandemic. Time was measured in months for all periods.

We performed all descriptive analyses and statistical tests in R, using the R packages `readxl`, `dplyr`, `forecast`, `rstatix` and `read.dbc`.

Ethical considerations

The institutional review board exempted this study from approval because the DATASUS database is publicly available and contains no personal information.

Results

Between 2008 and 2023, 43 216 tuberculosis cases were notified among children and young adolescents. The average annual notification rate per 100 000 population increased from 5.75 in the pre-pandemic period to 8.37 in the post-pandemic period, representing a 45.6% increase. Across all years, children younger than 1 year had the highest notification rates of active tuberculosis. Up to 2021, children aged 10–14 years had the second highest rates; however, following the COVID-19 pandemic, rates among children aged 1–4 years surpassed those in the older age groups (Table 1). Tuberculosis notifications increased significantly between the pre-pandemic period and post-pandemic period (0.192 per 100 000 population; 95% CI: 0.142–0.235; Fig. 1). Annual notification rates for laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis, and tuberculosis-related deaths also increased after the pandemic. In 2023, notifications of laboratory-confirmed tuberculosis and miliary and meningeal tuberculosis reached their highest recorded rates: 3.37 and 0.33 cases per 100 000 population, respectively. Tuberculosis-related deaths in 2023 were the second highest on record, at 0.15 deaths per 100 000 population; only in 2014 were more deaths reported (0.18 deaths per 100 000 population; Table 2). Detailed subgroup analyses by age and sex are available in the online repository.²⁴

During the study period, 12 557 laboratory-confirmed tuberculosis cases were notified among children and young adolescents. The average annual notification rate per 100 000 population increased from 1.55 in the pre-pandemic period to 3.01 in the post-pandemic period, representing a 94.2% increase. This upward trend was significant and consistent across age groups (0.078 per 100 000 population; 95% CI: 0.060–0.094; Fig. 2).

A total of 1659 children and young adolescents were notified with miliary and meningeal tuberculosis. The average annual notifications per 100 000 population increased from 0.22 in the pre-pandemic period to 0.29 in the post-pandemic period, representing a 31.8% increase. We observed no decline in reported cases during the pandemic (annual average of 0.23 cases per 100 000 population). The upward trend in notification rate was significant (0.003 per 100 000 population; 95% CI: 0.002–0.004; Fig. 3).

During the study period, 716 children and young adolescents died from tuberculosis. The average annual notification rate of tuberculosis-related deaths per 100 000 population increased from 0.09 in the pre-pandemic period to 0.14 in the post-pandemic period, representing a 55.6% increase. As with the other outcomes, the upward trend in notification rate was also significant (0.003 per 100 000 population; 95% CI: 0.001–0.007; Fig. 4).

Discussion

Here, we report decreased tuberculosis notifications among children and young adolescents in Brazil during the COVID-19 pandemic, followed by increased notification in the two years after the lifting of stringent mitigation measures. These findings are consistent with the 2024 epidemiological report on children and adolescents from the Brazilian health ministry.²⁵ In the general population, data from other countries in the Region of the Americas also showed that the notifications in 2022–2023 were similar to or higher than the pre-pandemic levels.¹ In contrast, notifications in the WHO European Region showed a downward trend during the same period.

After the onset of the COVID-19 pandemic, estimated global tuberculosis-related deaths in the general population increased. The global number of estimated deaths did not fall below pre-pandemic levels until 2022 and 2023 (1.34 million deaths in 2019 versus 1.32 million in 2022 and 1.25 million in 2023).¹ In the Region of the Americas, deaths in the general population only began to decline in 2023, although they remained above pre-pandemic levels.¹ In contrast, our data show that deaths among children and young adolescents continued to rise through 2023, highlighting the need for more data on this population to ensure that policy responses consider all age groups.

The reported impact of nonpharmacological measures implemented to mitigate COVID-19 on the transmission of other infectious agents has been heterogeneous.^{26,27} For example, the detection of respiratory syncytial virus decreased, while the incidence of rhinovirus

increased.^{26,27} Evidence shows that the global incidence of tuberculosis declined during periods of stringent movement restrictions. This decrease was mainly attributed to disruptions across all stages of the tuberculosis care cascade, most likely reflecting underreporting rather than a true reduction in incidence.^{1,11,28,29} This hypothesis is reinforced by findings of low to no reduction in miliary and meningeal tuberculosis during the pandemic,³⁰ which align with our data showing increased notifications of these forms after the easing of mitigation measures. These forms are typically severe and almost always require hospitalization, making them easier to detect and notify even during service disruptions. The stable incidence of these severe forms suggests that the observed decline in overall notifications was driven by underreporting of less severe cases rather than a true decrease in disease burden. These findings, along with increased tuberculosis-related deaths among children and young adolescents in 2022 and 2023, may be early markers of care disruptions during the COVID-19 pandemic.³¹ Such disruption would be expected to result in an early rise in all forms of tuberculosis among children,³² given their distinct progression and clinical presentation. One contributing factor may have been the decrease in the overall vaccination coverage in Brazil during the pandemic, including coverage of Bacille Calmette–Guérin vaccine, which protects children from severe forms of tuberculosis.³³

Our study adds to the existing literature on the impact of the COVID-19 pandemic on the epidemiology of tuberculosis in children. A global study using WHO-collated notification data compared observed childhood tuberculosis notifications in 2020 with predicted notifications based on trends from 2014–2019. All age groups experienced a reduction in notifications, with children aged 0–4 years showing the largest decrease (35.4%; 142 525 observed notifications versus 220 794 predicted notifications), followed by those aged 5–14 years (27.7%; 256 398 observed notifications versus 354 578 predicted notifications).² Comparing the period 2010–2019 with 2020–2021, an Italian cohort study showed a decrease in tuberculosis notifications and diagnoses, and an increase in the incidence of severe forms according to Wiseman’s classification.¹³ In our study, the increase in notifications may be explained by Brazil’s being a high-tuberculosis-burden country, unlike Italy.

Resumption of tuberculosis services depends on several factors, such as the level of disruption of services due to the COVID-19 response, political commitment and availability of resources.³⁴ The increase in notifications after the lifting of the mitigation measures in Brazil, as shown here and in the 2024 epidemiological report,²⁵ indicates that implementation of

tuberculosis control policies must be reinforced, considering the Brazilian heterogeneous territorial specificities. A possible explanation for the increase in overall tuberculosis notification rates could be the interruptions in the diagnostic and treatment cascade among adults,^{35–37} leading to increased transmission in households and the communities. Findings from a systematic review show that children exposed to a household member with tuberculosis were 3.79 (95% CI: 3.01–4.78) more likely to be infected than unexposed children.³⁵ These findings point to household transmission as a likely setting for the increase in notifications among children, suggesting the need to strengthen household-level interventions to decrease childhood tuberculosis and minimize the disruption in the care cascade for tuberculosis contacts.³⁸

This study has some limitations. First, we used public secondary notification data, which may be subject to missing data or underreporting. Due to uncertainty regarding data fluctuations throughout the study period, we used the notification rate as the primary outcome of the study, which does not reflect the true incidence. However, most estimates on underreporting suggest that the underreporting in Brazil is usually low.³⁹ Second, data on deaths extracted from the mortality database could also have issues, such as inadequate coverage and misclassifications. However, several quality assessments have found this database to be of high quality and usability.^{18,19} Third, the diagnosis of pulmonary tuberculosis in children is primarily presumptive. Nonetheless, notifications of laboratory-confirmed and miliary and meningeal tuberculosis showed similar trends. Fourth, the introduction of rapid molecular tests for tuberculosis during the study period might bias our findings. However, the increase in the incidence of all other forms reinforce the upward trend. Lastly, the DATASUS database has not been updated since 2023. Even if updated, it is usually based on a small number of remaining cases, which would not substantially change our data or alter the observed trends, but would make the differences more pronounced.

The rise in tuberculosis notifications among children and adolescents in Brazil after the easing of COVID-19 restrictions is a considerable setback to disease control and to achieving the goals of WHO's *The end TB strategy*.⁴⁰ Improvements in integrated, patient-centred care policies are needed to restore the downward trend in childhood tuberculosis in Brazil and to reach the strategy's milestones. As children are at increased risk of progression from latent to active tuberculosis, including miliary and meningeal forms, paediatric patients should be prioritized at

all stages of the tuberculosis care cascade, especially regarding tuberculosis preventive treatment.

Acknowledgements

AdS was supported by a master's scholarship from the Conselho Nacional de Desenvolvimento Científico e Tecnológico. RTS and MCS are also affiliated with the Hospital Moinhos de Vento, Porto Alegre, Brazil.

Competing interests:

None declared.

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Table 1. Notifications of active tuberculosis in children and young adolescents, by age group, Brazil, 2008–2023

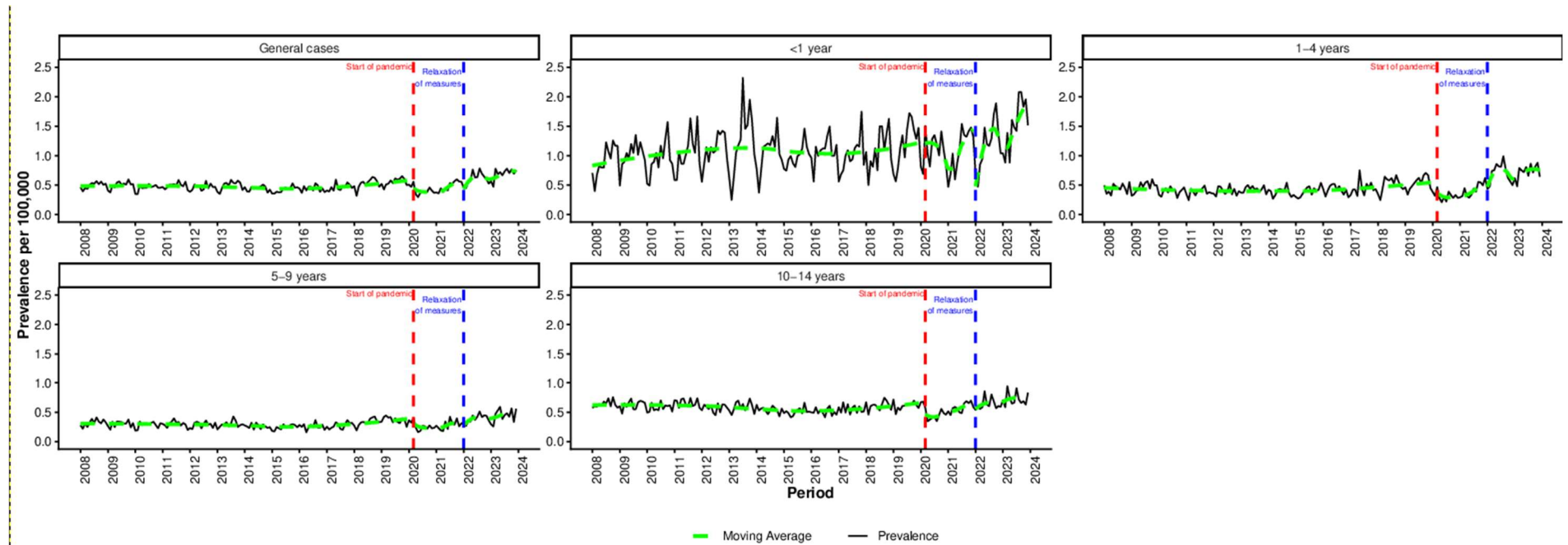
Year	No. of notified cases (cases per 100 000 population)				
	< 1 year	1–4 years	5–9 years	10–14 years	Total
2008	369 (11.03)	701 (5.28)	657 (3.83)	1287 (7.57)	3014 (5.94)
2009	402 (12.06)	728 (5.6)	608 (3.58)	1250 (7.46)	2988 (5.97)
2010	379 (11.38)	599 (4.68)	559 (3.34)	1129 (6.82)	2666 (5.39)
2011	417 (12.57)	568 (4.52)	590 (3.57)	1284 (7.87)	2859 (5.87)
2012	439 (13.27)	583 (4.74)	559 (3.43)	1095 (6.8)	2676 (5.57)
2013	488 (14.81)	614 (5.1)	567 (3.52)	1110 (6.99)	2779 (5.88)
2014	418 (12.67)	542 (4.59)	495 (3.11)	1014 (6.47)	2469 (5.29)
2015	392 (11.89)	539 (4.66)	457 (2.91)	936 (6.05)	2324 (5.05)
2016	427 (13.00)	562 (4.97)	476 (3.08)	916 (6.01)	2381 (5.26)
2017	393 (11.96)	587 (5.32)	497 (3.26)	986 (6.57)	2463 (5.53)
2018	431 (13.17)	652 (6.05)	585 (3.91)	1074 (7.27)	2742 (6.26)
2019	514 (15.79)	708 (6.73)	673 (4.58)	1094 (7.52)	2989 (6.95)
2020	428 (14.26)	390 (4.02)	459 (3.28)	820 (5.93)	2097 (5.2)
2021	430 (14.66)	501 (5.46)	485 (3.52)	970 (7.17)	2386 (6.09)
2022	460 (16.07)	803 (8.84)	651 (4.95)	1047 (7.87)	2961 (7.75)
2023	590 (21.52)	819 (9.23)	736 (5.88)	1187 (9.01)	3332 (8.99)

Table 2. Laboratory-confirmed tuberculosis, miliary and meningeal tuberculosis and tuberculosis-related deaths among children and young adolescents aged 0–14 years, Brazil, 2008–2023

Year	No. of notified cases (cases per 100 000 population)		
	Laboratory confirmed	Miliary and meningeal	Deaths
2008	629 (1.23)	125 (0.24)	50 (0.10)
2009	738 (1.47)	116 (0.23)	44 (0.08)
2010	661 (1.34)	100 (0.20)	49 (0.10)
2011	753 (1.54)	109 (0.22)	38 (0.07)
2012	638 (1.33)	97 (0.20)	44 (0.09)
2013	701 (1.48)	82 (0.17)	39 (0.08)
2014	687 (1.47)	97 (0.21)	86 (0.18)
2015	699 (1.52)	89 (0.19)	30 (0.06)
2016	714 (1.57)	98 (0.22)	31 (0.07)
2017	706 (1.58)	98 (0.22)	36 (0.08)
2018	863 (1.97)	134 (0.31)	35 (0.08)
2019	911 (2.11)	77 (0.18)	41 (0.09)
2020	718 (1.75)	87 (0.20)	41 (0.09)
2021	814 (2.04)	112 (0.24)	38 (0.09)
2022	1049 (2.67)	107 (0.26)	52 (0.12)
2023	1276 (3.37)	131 (0.33)	62 (0.15)

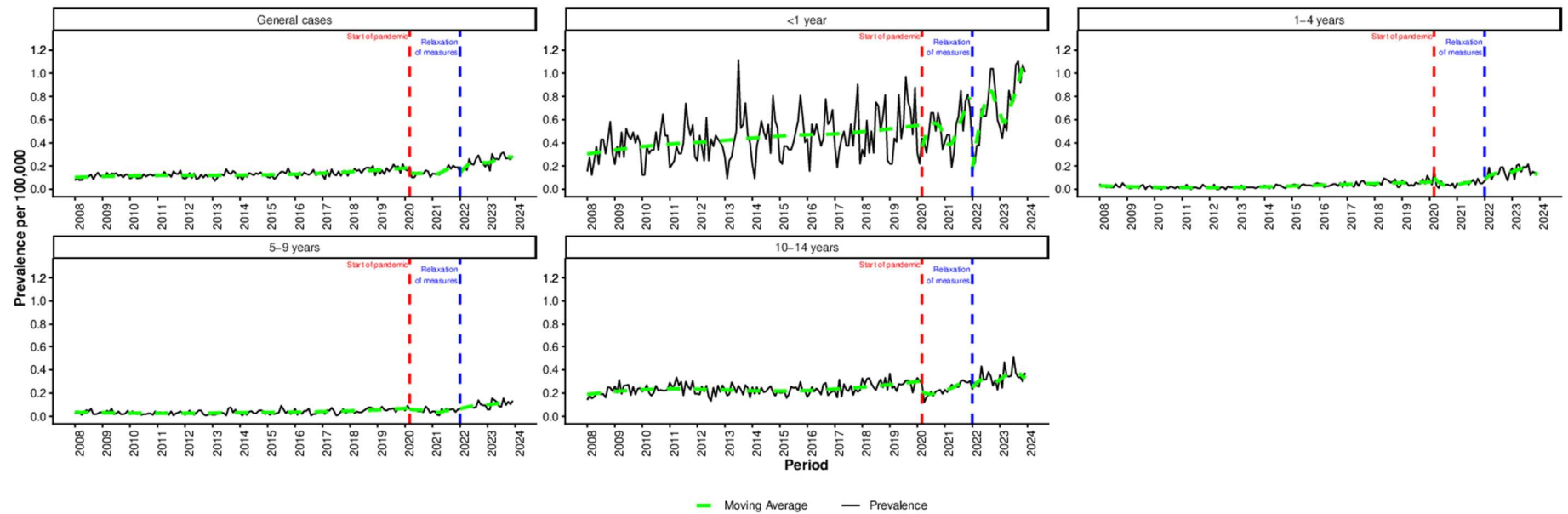
Note: notification data for active tuberculosis are presented in Table 1.

Fig. 1. Overall rates of tuberculosis notifications among children 0–14 years, Brazil, 2008–2023



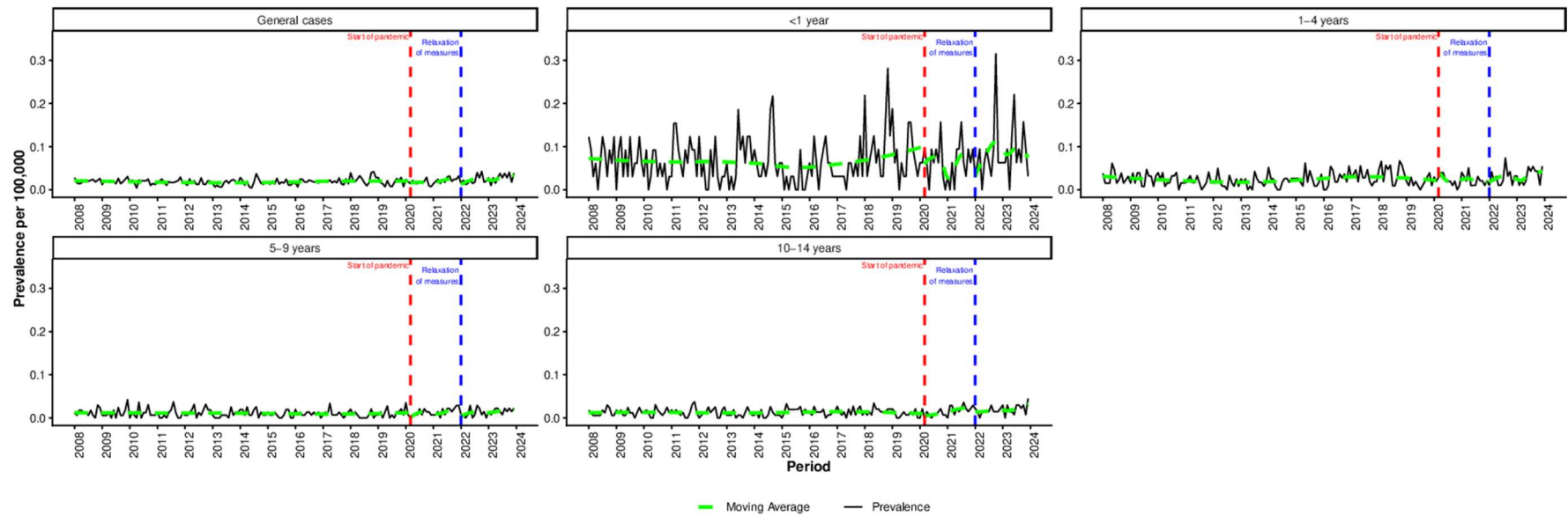
Note: we estimated the smoothed trends using locally weighted regression.

Fig. 2. Notification rates of laboratory-confirmed tuberculosis among children 0–14 years, Brazil, 2008–2023



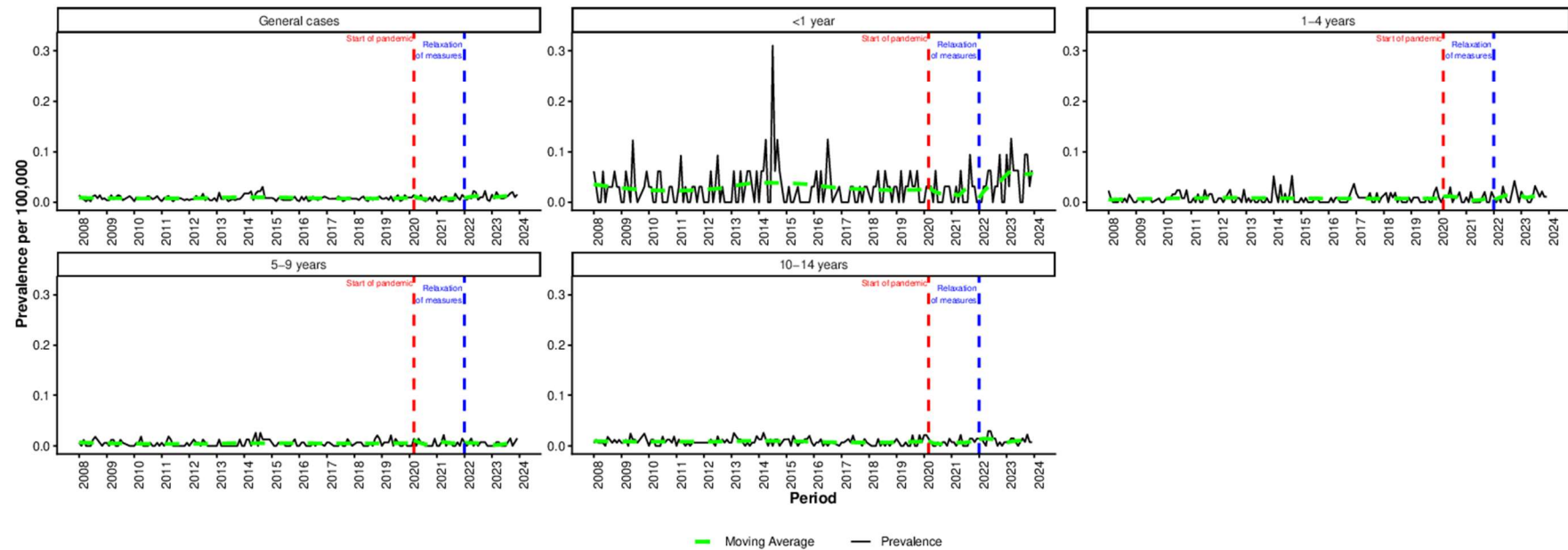
Note: we estimated the smoothed trends using locally weighted regression.

Fig. 3. Notification rates of miliary/meningeal tuberculosis among children 0–14 years, Brazil, 2008–2023



Note: we estimated the smoothed trends using locally weighted regression.

Fig. 4. Notification rates of tuberculosis-related deaths among children 0–14 years, Brazil, 2008–2023



Note: we estimated the smoothed trends using locally weighted regression.