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REVIEW ARTICLE

Pediatric tuberculosis in Mexico and the COVID-19 phenomenon: Past and present

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ABSTRACT

In endemic regions, tuberculosis in children constitutes a bigger fraction of total cases as compared to those in low endemic regions, regardless of the implications, this phenomenon has been historically neglected. Pediatric tuberculosis has an insidious onset and quickly develops into disseminated disease and the young are at a special risk for dissemination. Some studies suggest that measures to contain adult tuberculosis are not enough to manage tuberculosis in children, meaning that pediatric tuberculosis needs dedicated attention. Children are harder to diagnose than adults, because collecting samples is difficult, and their bacterial yield is low. In endemic countries, such as Mexico, where contact with *Mycobacterium tuberculosis* is common, immunological tests are inconsistent, especially in immunocompromised children. With the disruption of Mexican healthcare services by the COVID-19 pandemic, there is an uncertainty of how the situation has evolved, current data about tuberculosis indicates a drop in the national report of cases: 15.4 per 100,000 persons in 2021, compared with pre-COVID 2019 17.7 per 100,000 persons, a small increase in mortality: 1.7 per 100,000 in 2021 compared with 2019 1.6 per 100,000, a drop in treatment success: 80.4% in 2021 compared with 85.4% in 2019, and a decrease in national vaccination rates: an estimate of 86.6% children between 1 and 2 years-old were vaccinated in 2021 compared with 97.3% reported national rate in 2018–2019. There is a need for new research on regions with high tuberculosis incidence, to clarify the current situation of pediatric tuberculosis and improve epidemiological surveillance.

KEYWORDS

tuberculosis, Mexico, pediatric tuberculosis, surveillance

INTRODUCTION

Pediatric tuberculosis

The presence of tuberculosis (TB) in pediatric populations is a largely ignored problem, the WHO started to include an estimate for childhood TB in their annual report, and focused World TB Day on children, in 2012 [1]. Pediatric TB has an insidious onset. The younger the patient, the more the risk of rapidly developing TB, in matter of weeks or months; young children (<2–3 years old) are at a special risk of developing meningitis and disseminated disease from *Mycobacterium tuberculosis* [2]. These disseminated diseases often leave life-long effects, making the task of an early as-possible diagnosis essential to an ideal recovery. The incidence of TB disease in this age group can be a sensitive indicator of the current rate of transmission within a community, an example of this is the resurgence of TB in adults followed the rise of pediatric TB in the United States (US) in the mid-1980s [3].

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Pediatric TB diagnostic challenges

An important fraction of the global TB caseload is still constituted by pediatric TB, which means that children do experience significant TB-related morbidity and mortality [4]. TB diagnostic in pediatric age is a challenge because of its insidious onset and lack of cardinal symptoms in up to 72% of cases [5]. Established diagnostic tools require the collection of sputum, which is difficult and when possible, bacterial yield is low. Sputum smears are positive in <10–15% of diagnosed [6], and culture is positive only in 30–40% [3]. The classic diagnostic triad: contact case, positive Tuberculin Skin Test (TST), and suggestive Chest Radiography (CXR) are affected in endemic areas where contact with *M. tuberculosis* is common, which leads physicians to rely on subjective interpretations of the CXR [7]. Childhood TB is characterized by nonspecific symptoms. Therefore, it is important to know the history of contacts of a child with TB, and TB contacts are usually close family members [8].

PCR is a useful tool for the early diagnosis of TB in children [1], but it is still controversial because in highly endemic countries, it tends to yield false positives [9]. In addition, the cost involved, need for sophisticated equipment, need to obtain multiple samples, and scrupulous technique to avoid cross-contamination preclude the use of PCR in many developing countries [10].

Interferon-Gamma Release Assay (IGRA) has been reported to be comparable with TST in its ability to detect latent TB [11], however this assay is prone to yield false-negative results in immunocompromised patients, such as those who are less than 5 years old and those who are Human Immunodeficiency Virus (HIV) positive [12]. IGRA has more utility for immunocompetent patients who are socioeconomically favored and older than five years due to factors such as costs, availability of healthcare resources, patient acceptability, distribution and storage means, which keep TST as the diagnostic standard for most of the country.

A symptom-based approach for diagnosing pediatric TB in endemic zones was proposed by Marais BJ, et al. [4]. It consisted of three defined symptoms: persistent, non-remitting cough for >2 weeks, weight loss during the preceding 3 months, and reported fatigue. They reported an 81% sensitivity in HIV uninfected children aged ≥3 years. In HIV uninfected <3 years-old children the evaluation of fatigue was difficult, but persistent cough and weight loss were still useful as diagnostic tools. The TST improved the diagnostic performance for <3 years-old non-HIV group, since they are less likely to have been exposed to *M. tuberculosis*. In general, HIV-positive and immune-compromised children are harder to diagnose, they fail to provide consistent results in immunoassays, and often show TB-like symptoms due to other etiologies which complicate diagnostics.

It looks like that for endemic low-resources countries like Mexico, the best current option of diagnosing pediatric TB may be to use the wide arrange of available tools the physician and patient has access to, but the interpretation of discordant results for pediatric TB remains as a challenging issue due to both the lack of a gold standard, and lack of accessibility to diagnostic tools for socioeconomically susceptible patients.

TB reports and the COVID-19 phenomenon

Global TB reports. The COVID-19 pandemic on health, social, and economic issues had clear effects on the availability of TB diagnostics and treatment on a global scale. This was evident by observing the 18% global drop in notification of people getting a TB diagnosis between 2019 and 2020, probably as an effect of supply and demand disruptions, such as the reduction in the capacity of health systems to continue providing services, restriction in movement via lockdowns, and concerns about the risks of visiting health facilities during a pandemic. There are an estimate 1.3 million TB-related deaths among HIV-negative people, a one million increase from 2019, with 214,000 added deaths from HIV-positive people, a 5,000 increase of deaths from 2019. This represents the first time TB mortality has increased since 2005 [13]. The COVID-19 pandemic has imposed a burden on the global health care system and has reverted years of effort into the End TB Strategy. This might prevent the reach of the Global TB targets and milestones for 2030, recovery from the COVID-19 pandemic will require worldwide coordination and awareness.

TB reports in Mexico. From 2006 to 2019, the incidence report on TB showed a slight steady increase until the COVID pandemic started, which interfered with TB surveillance and created a drop in cases reported by health facilities. Preliminary data showed that mortality associated with TB remained approximately the same as in previous years until the start of the pandemic in 2020 (1.7 per 100,000 persons) but had a slight increase compared with 2018 (1.6 per 100,000 persons). However, treatment success has clearly dropped by 5.4% from the start of the pandemic, which may indicate an unreported increase in total cases. Therefore, after the COVID pandemic, people are not only more unlikely to be diagnosed with TB, but also more unlikely to be successfully treated, this may lead to a delayed increase in mortality in the future. Currently, Baja California, Sinaloa, Sonora, Tamaulipas, Tabasco, Nayarit, Nuevo Leon, Guerrero, Quintana Roo and South Baja California are the top 10 states in TB incidence, as it can be observed in Fig. 1 which contrasts with shade the incidence reported in each individual state. Baja California is the state with the highest incidence: 58.8 per 100,000 persons, which is significantly higher than the other states with already high incidence; for comparison, Sinaloa is the state with the second highest incidence of 38.7 per 100,000 persons. Notably, all Mexican states bordering the US have a tendency to report higher incidence compared with non-bordering states; this may be due to the immigrant population that concentrates and navigates on these borders. According to this same source, in 2021 approximately 67% of total TB cases presented with a

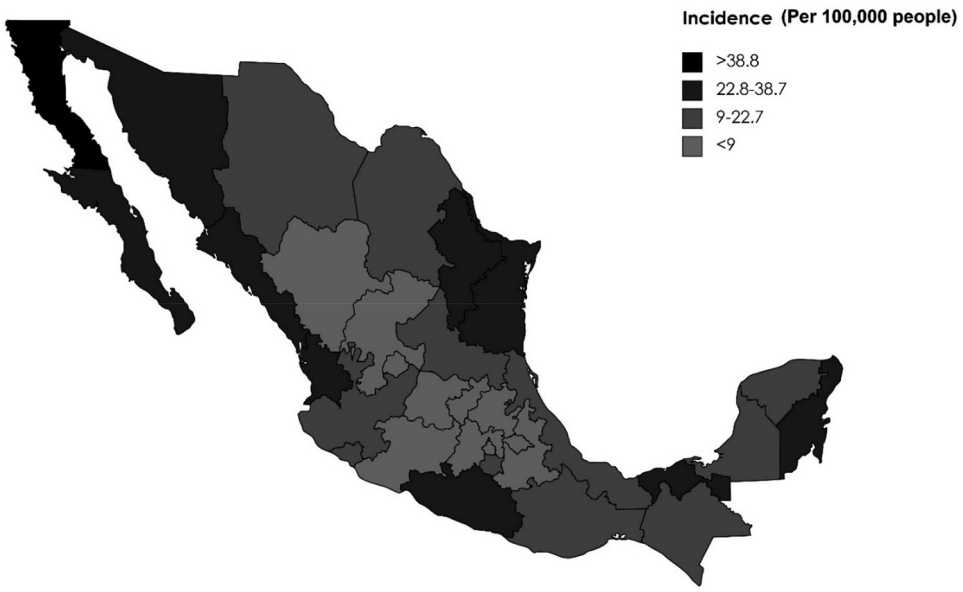

Fig. 1. Mexican states shaded by incidence of TB
Source: CENAPRECE, 2021.

related comorbidity disease: 30% diabetes, 16% malnutrition, 16% smoking, 14% alcoholism, 15% other risk factors, 12% drug users, 9% HIV, 6% other immunosuppression and 1% presented with neoplasm. 9% of all cases (1,813) were 0–19 years old and 1% (236) were younger than 5 years-old [14]. In 2019 it was reported that 1% (235) of all reported cases were <5 year old and that 8.4% (1,871) were 0–19 years-old; there is no clear changes in the report of TB in this area [15], but TB reports have been clearly been affected by the COVID-19 pandemic, which makes it hard to determine if the epidemiological situation of pediatric TB has truly remained the same.

Bacillus Calmette Guerin (BCG) vaccine in Mexico

In Mexico, the National Survey of Health and Nutrition (ENSANUT) 2022 estimated that in 2021, 86.6% of children between 1 and 2 years-old, were immunized with the BCG vaccine nationwide. Mexico City and the border were the zones with most children vaccinated, 92.2% and 91.2% respectively, and the Pacific-center was the region with significantly less BCG vaccination (76.6%) [16]. In contrast, The ENSANUT 2018–19 reported that North and South Baja California, Colima, Jalisco, Mexico State, Sonora, Tamaulipas, and Yucatan states achieved 100% BCG vaccination; Campeche was the state with the lowest vaccination rate (89.1%). The reported national rate was 97.3% [17]. As observed, there has been a clear drop in vaccination rates nationwide, which may indicate that after the COVID-19 pandemic, there will be a drop in children's immunity against meningeal and disseminated TB disease, which may result in an increased burden of severe forms of TB induce on the pediatric population. It is also possible that it might had already been present but was unnoticed, as a consequence of decreased of TB reports. The COVID-19 pandemic not only made it necessary to make a recovery into the accessibility of diagnosis and treatment of TB for all ages, but also set a new effort to ensure vaccination rates recovery.

Pediatric TB in Mexico

Comparison of study characteristics: location, sample characteristics, clinical form, diagnostics, BCG vaccine, comorbidities, contact history, treatment outcome, anti-TB drug use, and resistance can be observed in Table 1, which includes the four studies conducted on non-specific pediatric TB.

There has been little research regarding the epidemiologic and demographic characteristics of pediatric TB in Mexico, but from looking at the four studies that evaluated pediatric TB in all clinical forms, the most common symptoms were fever, cough, weight loss and adenopathy. Most diagnostic tools were inconsistent; positivity of a diagnostic tool was defined as the percentage of positive results from all the patients with TB diagnosis it was applied to. In most cases, bacterial confirmation was achieved, but it was only done after using different bacterial confirmation methods instead of a single reliable confirmatory tool, it looks like for the diagnostic of pediatric TB in Mexico physician criteria and awareness of epidemiological factors are important. There is controversy about the lack of systematic diagnosis in the pediatric population, which makes it unclear if physicians should choose among complete pharmacological treatment, prophylaxis, or just close observation of children with probable latent TB. In the studies conducted by Carreto-Binaghi, et al. and Gonzalez-Saldaña et al., most contacts were confirmed, while in the other two they were not searched or it was a low percentage, which exposes a lack of epidemiological control even before the COVID-19 pandemic, derived from lateness in the search and identification of adults infected as a source: and this effect allows

Table 1. Pediatric TB studies done in Mexico without specific clinical form selected

Authors	Study period, Age range (mean), Location, Sample size	Most common clinical forms (%)	Most common symptoms (%)	Diagnostic tool positivity % Microbiological confirmation %, BCG vaccine %, Confirmed contact %	Presence of comorbidities %	Treatment outcome % Treatment drug use %	Drug resistance %
Gonzalez-Saldaña N, et al. (2021)*	2011-2018, <18 years (6.5 years), Mexico City 127 patients	Ganglionic (39) Muscle-skeletal (15.7) Pulmonary (12.5)	Fever (48.8) Adenopathy (45.6) Cough (24.4)	PCR 53, Culture 37.7, AFB 29, TST 47.6, Radiological findings 64.5 Micro. Confirmation 74 BCG vaccine 75.5 Confirmed contact 65.4	39 Primary immunodeficiency (mostly associated with skin and miliary TB)	97.4 Successful 2.3 Died (3 cases) 7.8 Lost to follow-up 73.5 First-line 19.3 Other drugs used, concomitantly or to replace primary medication	There was no detection of rifampicin resistant genes in PCR testing. <1 MDR TB (1 case)
Carreto-Binaghi LE, et al. (2018)*	2015-2017, 17 months – 15 years (6 years), Mexico city and metropolitan area of Mexico State, 22 patients	Pulmonary (63.6) Ganglionary (18.2) Pleural (9.1)	Cough (63.6) Fever (40.9) Weight loss (27.2)	AFB 27.7, PCR 31.5, TST 75, Culture 59.1, Biopsy 40. Micro. Confirmation 59.1% BCG vaccine 63.6 Confirmed contact 59.1	9.1 of cases (2 cases: Pulmonary alveolar proteinosis and absence crisis)	72.7 receive full treatment 9.1 second line treatment 13.6 did not receive treatment 4.5 (1 patient) received isoniazid prophylaxis	There was no detection of rifampicin resistant genes in PCR testing
Vazquez-Rosales JG, et al. (2017)	2010-2013, 9 months – 16 years and 3 months (6 years 11 months), Mexico City (54%), Chiapas (10%), Guerrero (6%), Veracruz (2%), Oaxaca (1%), Other (27%), 93 patients	Pulmonary (30.1) Ganglionary (24.7) Miliary/ Disseminated (16.1)	Fever (48.4) Weight loss (37.6) Adenomegaly (25.8, mostly presented in ganglionary TB)	TST 50, AFB 29, Culture 10, PCR 82, Biopsy 90, ADA 60, Micro. Confirmation – BCG vaccine 96.8 Confirmed contact 6.4	25.8 of cases	Successful treatment 93.6 Treatment failed 3.2 Relapse 3.2 78 used HRZE 3 used HRZ 1 HRE Steroids were used in 22.5 of the population	Not reported
Macias-Parra M. (2011)	2002-2003, <18 years (13 years), 18 federal states, 90 patients	Pulmonary (71.4) Meningeal (8.8) Disseminated (5.5)	–	All patients were confirmed by culture	21.1 (19 patients) unknown 14 (10/71 cases) with information had a comorbidity: 8.4 severely malnourished 2.8 HIV co-infection 1.4 (1 patient) Diabetes mellitus 1.4 Alcoholism	–	26.7 resistance to at least one drug 8.8 resistant to a single drug 4.4 resistance to 5 first line drugs 23.3 Isoniazid 11.1 Rifampicin 8.8 Pyrazinamide 10.0 Ethambutol 12.2 Streptomycin

TST: Tuberculin Skin Test, BCG: Bacillus Calmette-Guérin AFB: Acid-Fast Bacilli, PCR: Polymerase Chain Reaction, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol. *At least 1 confirmed non-TB Mycobacterium infection.

the spread of exposure of *M. tuberculosis* to uninfected people. Approximately one-fourth of patients in three of the four studies presented some type of comorbidity. Clinicians must have high clinical suspicion when epidemiological and socioeconomic factors favor its presence and for patients with pediatric TB to be screened for immunodeficiency and vice versa [5, 18–20].

A study conducted over a 2-year period that took advantage of the characteristic of pediatric TB as a sentinel event, evaluating *M. tuberculosis* bacilli in children is an indication of the properties of ongoing transmission of TB within a community. This study found a 23% drug resistance, which is higher than the 18% prevalence that was reported in population-based studies in Mexico at the time of publication, which could indicate a spike in drug resistance for people infected with *M. tuberculosis* during the study that would not be reflected until they developed active TB [19]. More studies like this should be conducted in Mexico to have a constant surveillance of drug resistance genes and the characteristics of current ongoing transmission.

Studies focused on clinical forms

As shown in Table 2, studies of specific clinical forms of pediatric TB are juxtaposed with each other to appreciate differences in location, sample characteristics, diagnostics, BCG vaccine, comorbidities, contact history, treatment outcome, anti-TB drug use, and resistance.

The studies done by Laniado-Laborín, et al. and Plascencia-Hernandez, et al. focused on latent pediatric TB in Mexico, it was observed in one of them that there was no difference between transmission of drug resistant *M. tuberculosis* and drug susceptible *M. tuberculosis*, they both compared TST and QFT-GIT for the detection of latent pediatric TB and their results were inconsistent: Laniado-Laborín found nearly double positivity for TST compared with QFT-GIT when applied to the same group of patients, while Plascencia-Hernandez found the opposite: QFT-GIT resulted in more positive results when compared to TST against the same patients, this may due to the fact that Baja California, where the study by Laniado-Laborín was conducted, is the Mexican state with the highest TB incidence, meaning that the higher likelihood of being exposed to *M. tuberculosis* may have resulted in higher rate of TST positive results compared with IGRA, which suggests IGRA could be useful for the diagnostic of latent pediatric TB in endemic zones. There is a need for research on latent TB infection in the pediatric population in Mexico [21, 22].

Three studies were found about the specific clinical form of TB in children, evaluating pulmonary, osteoarticular, and intestinal/peritoneal TB, respectively: the first one evaluated clinical file from hospitalized children with pulmonary TB. The high microbiological confirmation, age of the patients, and low pulmonary TB frequency could be explained by the fact that pulmonary TB patients are only hospitalized when they present severe forms of the disease. The authors stated that radiological studies played an important role in the diagnosis, although interpretations varied. Consolidation image was a frequent finding in all age groups, and significantly more frequent in patients older than 5 years, and they suggest that any children with 2 of the 3 following criteria: presence of fever or cough of at least 2 weeks and positive TST of $\geq$10 mm should be evaluated with CXR and smear microscopy [23].

Osteoarticular TB was retrospectively studied in a study published in 2021. 35 (79.5%) cases consisted of osteoarticular TB in children younger than 6 years, four (9.1%) of those aged between 7 and 12 years, and five (11.4%) between 13 and 16 years old. The most common findings in imaging studies were osteolytic lesions in all cases and abscesses in 70% of cases. Tomography studies reported that most common findings were osteolytic lesions, kyphosis, and spinal cord compression in all cases. The authors discussed the reason for the prevalence of reported extrapulmonary modalities by mentioning that lung TB is usually treated in second-level hospitals, and reports are relatively high regarding the prevalence of bone and joint TB. Based on the symptoms shown, the authors recommended that in cases of lytic bone lesions, fever, and local pain; pediatric osteoarticular TB should be considered. Noteworthy, in countries with BCG immunization programs, such as Mexico, *Mycobacterium bovis* should not be disregarded as an etiological agent [24].

A study published in 2012, concerning intestinal/peritoneal TB, studied the differences of the intestinal and peritoneal infection of *M. tuberculosis* and *M. bovis* in children by evaluating autopsy cases, 24 pediatric cases with TB were selected. From the total sample, 17 (71%) cases showed intestinal disease, 14 (58%) presented peritoneal involvement, and 7 (29%) had peritoneal TB without the presence of intestinal disease. It was reported that most of the isolated peritoneal TB cases occurred because of dissemination from a primary infection elsewhere. Eight Intestinal TB cases were reported as primary infection and nine as secondary infection. The presence of *M. bovis* as the etiological agent of primary intestinal TB was statistically significant, such finding can be explained by the main pathogenic mechanism of *M. bovis*, which would be the ingestion of milk from diseased cows, and the secondary form as the result from *M. tuberculosis* hematogenous spread or ingestion of contaminated material. The study also discussed that children with primary intestinal TB died younger than those with secondary form, which suggests that primary infection of *M. bovis* occurs at an early age. 95.2% of children with peritoneal TB reported disease origin from other different sites, which suggests that primary peritoneal TB is a rare form of the disease and should only be suspected when peritoneal contamination could have occurred [25].

Pediatric TB-HIV co-infection in Mexico

Nowadays, the TB-HIV co-infection is an important factor to consider for early diagnostic. The risk of death for patients co-infected with TB and HIV is much higher than that observed in TB patients [26]. It may lead to increased disease

Table 2. Pediatric TB studies conducted in Mexico with a specific clinical form selected

Authors	Study period, Age range (mean), Location, sample size	Clinical form	Most common symptoms (%)	Diagnostic tool positivity % Microbiological confirmation % BCG vaccine % Confirmed contact %	Presence of comorbidities/Risk factors %	Treatment outcome % Treatment drug use %	Drug resistance %
González-Saldaña N, et al., (2021)*	1999 – 2018, 8 months – 18 years (4.9 years), Mexico City, 43 patients	Osteoarticular TB	Pain (All cases) Fever (37) Asthenia-Adynamia (27)	Culture 15, AFB 29, PCR 55, Histology 97, TST 46 Micro. Confirmation – BCG 86 Confirmed contact 23	Comorbidities present in 13	90 completed 7 maintenance phase 2 abandoned treatment First line drugs used in all cases	No reports of multidrug resistance found
Plascencia-Hernandez A, et al., (2016)	March 2013 – November 2015, <19 years (–), Guadalajara, Jalisco, 225 patients	Latent TB	–	TST 12 QFT-GIT 21.7 Micro. Confirmation – BCG – Confirmed contact 27.5	HIV: 3 TST+ Pt, 8 QTF-GIT+ Pt RHU disease 7 TST+ Pt, 10 QTF-GIT+ Pt Nephropathy TST+ 1 Pt, QTF-GIT 1 Pt Orphanage 2 TST+ Pt, 7 QTF-GIT Pt	–	–
González-Saldaña N, et al., (2014)	1994 – 2013, 3 months to 17 years (–), Mexico City (54% Mexico City/State of Mexico, the rest from other parts of the republic), 87 patients	Pulmonary TB	Fever, cough and weight loss	Culture 30.4, PCR 74.1, TST 59.2, AFB 51.7 Micro. Confirmation 95.4 BCG 79.3 Confirmed contact 98.9	Mild acute malnutrition 9.2 Severe malnutrition 17.2 Underlying disease 16.1	3.5 died (1 HIV-MDR TB case, 2 of unrelated causes) 96.5 successful 44.8 used HRZ 6.9 used HRZS 48.3 used HRZSE	Only one case mentioned to have multidrug resistance
Laniado-Laborín R, et al., (2014)	August 2011 – June 2013, 1–16 years (DS 7.79, DR 7.36), Tijuana, Baja California, 77 DS contacts, 96 DR contacts	Latent TB	–	DS TST 83.1, DR TST 76 DS QFT-GIT 42.3, DR QFT-GIT 57.7 Micro. Confirmation – DS BCG 94.8 DR BCG 95.8 Confirmed contact: All cases	–	DS contacts were treated with isoniazid or rifampicin DR contacts did not receive treatment	DR contacts: Monoresistant 41 Polyresistant 14.6 Multidrug resistant 42.7
Ridaura-Sanz C, et al., (2012)*	1971 – 2010, 9 months – 14 years (7.6 years), Mexico City, 17 patients	Intestinal/ Peritoneal TB	Abdominal pain (all cases) Diarrhea (76.5) Ascites (58.8)	Culture 76.9 Histological/ bacteriological demonstration of AFB was obtained in most cases	None of the cases was associated with HIV infection	All patient were already deceased at the time of the study	–

DR: Drug Resistant, DS: Drug Susceptible, TST: Tuberculin Skin Test, BCG: Bacillus Calmette-Guérin, AFB: Acid-Fast Bacilli, PCR: Polymerase Chain Reaction, RHU: Rheumatology, QFT-GIT: QuantiFERON TB Gold In-Tube, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin. *At least 1 confirmed or suspected non-TB Mycobacterium infection.

transmission and amplification of drug-resistant TB [27]; symptomatology can be scarce because HIV-positive patients may present lessen inflammatory response. It has been reported that in children, extrapulmonary TB-HIV co-infection is accompanied by pulmonary manifestations in 32–51% of cases, while HIV-negative children report 24–28%, and there are also reports of nervous system involvement in 14–15% of cases [28]. The two reviewed articles about HIV-TB co-infection are summarized in Table 3, and the differences between the clinical forms, diagnostics, population, and treatment outcomes are reported.

The study was carried out by reviewing data from the International Site Development Initiative (NISDI) pediatric protocol. The authors commented that since in Latin American countries, TB immunization is carried out with the BCG vaccine, and most of the children in the study were not known to be HIV-infected at the time they received the BCG vaccines; *M. bovis* infection from the administration of the BCG vaccine cannot be disregarded. Patients were enrolled at 15 sites in four countries over a 9-year period, so there was probably not only variation in diagnosis and treatment for TB and HIV per site, but also across time. Only 10.1% of cases were from Mexico, which may reduce the relevance of this study for pediatric Mexican population, which is the main focus of the present article [28]. Specifically, in Mexico, one study reviewed the medical records of children with perinatal HIV infection hospitalized with TB diagnosis. Seventy-three children with perinatal HIV infection were followed-up. During the study period, 13 of the selected HIV-infected children (18%) were diagnosed with TB. HIV diagnosis was performed at a mean age of 3.6 years, and TB diagnosis was achieved at a mean age of 5.3 years. In the study, authors highlighted the importance of searching for co-infection whenever one of those two diseases are diagnosed and the importance of counting on with early diagnosis for optimal treatment. It should be noted that the study was composed of a small sample size and only a few mycobacterial cultures were performed; therefore, infection from other mycobacteri*a* cannot be disregarded [29]. The main takeaway from this study is that it could be vital for every patient with immunodeficiency, in this case HIV, a constant high suspicion of TB, in the same way as for patients with TB, tests in search of an immunodeficiency must be performed so that every patient receives a complete treatment; the importance of this can be observed by the number of patients in whom disseminated TB was present; physicians with HIV-infected children in their care should also be aware of any contact with an adult TB case.

Malnutrition, HIV in Mexico in pediatric TB

One misconception around the treatment of pediatric TB is the idea that dealing with adult TB is the best way of dealing with pediatric TB; however, it has been studied that measures against adult TB will only marginally affect the pediatric population. For example: the WHO Millennium Development Goals were ineffective in making changes in Pakistani children of less privileged strata exposed to TB [30], while programs directed to pediatric TB will cause rapid declines in both the amount and severity of childhood TB, as calculated by the computational model done at the Harvard School of Public Health, in which a 5% increase in children who enter treatment will create a 25% reduction in pediatric TB cases and a 16% reduction in pediatric TB deaths after 10 years, compared with a control in which there was no change in children who entered treatment, while similar improvements in therapeutic and preventive measures for adults could not achieve a 1% improvement for pediatric TB [31]. A child with active TB represents a sentinel event, typically reflecting ongoing transmission in the community [8]. These characteristics may prove useful to define TB control in Mexico as a measurement of *M. tuberculosis* incidence in children through a TST evaluation [32]. In the US, the CDC released a report describing a 29% increase in TB rates for children younger than 5 years in 2022 [33], this is alarming considering that a phenomenon

Table 3. Pediatric TB-HIV co-infection studies

Authors	Krauss MR, et al., 2015*	Viani RM, et al., 2008*
Study period, Age range (mean), Location, Sample size,	2002 – 2011, Birth – 22 (−), Latin America (Mexico 10.1%), 69 patients	1998 – 2007, (3.6 years), Tijuana, Baja California, 13 patients
Most common clinical forms %	Pulmonary 47.8, miliary 34.8, lymphadenitis 13.0	All patients had pulmonary form Disseminated 54: Abdominal 23, miliary 15, meningeal, miliary, abdominal and splenic 8 and meningeal 8
Most common Symptoms (%)	Fever (70), Cough (65), Weight loss (36.7)	Cough (92), Anorexia (85), Fever (77)
Diagnostic tool positivity % Microbiological confirmation % BCG vaccine % Confirmed contact %	CXR and/or CT scans: 78.3% were abnormal, Laboratory confirmed 52.2, clinically confirmed 15.9, Presumed 31.9 BCG 84.1 Confirmed contact 46.4 (24.6% unavailable information)	Suggestive radiograph all cases, AFB 92, TST 17, Culture 33 BCG 46 Confirmed contact 62
Treatment outcome %	63.8 positive response 11.6 information unavailable	61.5 completed treatment 39 mortality

BCG: Bacillus Calmette-Guérin, TST: Tuberculin Skin Test, CXR: Chest X-ray, CT: Computed Tomography.

like this was observed in the mid-1980s, in which the resurgence of TB in adults followed the rise of pediatric TB [3], Due to geographical proximity, there is reason to suspect that a similar phenomenon is currently ongoing in Mexico under the radar, as a consequence of the COVID-19 pandemic disruption of epidemiological surveillance, and reports made by the Mexican government fail to represent the current epidemiological situation in Mexico.

The main effects of the COVID-19 pandemic had on the surveillance, treatment, and prevention of TB are diverse, and there has been controversy about the multiple factors which played a role during the pandemic: fewer visits to hospitals and clinics because of the fear of catching COVID-19, health professionals and resources from TB programs focused on dealing with the COVID-19 pandemic, less available health professionals because those who were members of vulnerable populations to COVID-19 were allowed to stay at home, lockdown of people living in overcrowded conditions increased the risk of TB infection, reduction in the search for contact TB cases, and interruption of communitarian activities for the prevention of diseases, such as BCG immunization (effects can be observed on the government data presented in this review), and difficulty in applying Directly Observed Treatment. Although different alternatives were implemented, such as administration of drugs for longer courses, treatment delivery, phone calls, video calls, and messages, they were useless in regions of the country that lack access to these communication facilities. Overall, this phenomenon ultimately caused decreased communication between patients and health professionals, which could had been one of the factors contributing to an increase of treatment abandonment [34]. The solution is not just re-establishing the old epidemiological control and measures that were used before the disruption caused by the COVID-19 pandemic, but to improve upon them and create specific epidemiological surveillance to directly deal with pediatric TB in Mexico. In this review, most of the studies consulted were retrospective, the current situation requires prospective and cross-sectional approach to evaluate the evolution of TB disease that happened during the pandemic. An integral approach to the problem may shed some light on the necessities required to take care of both the pediatric and non-pediatric TB. Most studies were conducted either in Mexico City, Tijuana, or Guadalajara, meaning that a single study concerning pediatric TB has been carried out in one of the top 10 Mexican states with the highest TB incidence. Epidemiological and clinical trials in the pediatric population are necessary in those Mexican states with high TB incidence.

FUTURE RESEARCH DIRECTION

The first step for future research is the publishing of more prospective and cross-sectional studies of TB on children as a measurement of current TB transmission and TB epidemiological studies localized in high incidence Mexican states. There is also a need for research with the purpose to aid physicians in the decision making between complete pharmacological treatment, prophylaxis, or just close observation of children with probable latent TB and the development of diagnosis protocols for the interpretation of discordant results to improve the evaluation of pediatric TB.

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