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Presence of comorbidities and their association with antimicrobial resistance of tuberculosis, in a national reference center in the Bajío region and the north of Mexico

Presencia de comorbilidades y su asociación a la resistencia antimicrobiana de tuberculosis, en un centro de referencia nacional en la región del Bajío y norte de México

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ABSTRACT. Introduction: although tuberculosis is preventable and curable, this infection represents the leading cause of death from a single infectious agent. The interruption of public health services caused by the COVID-19 pandemic globally reversed the gradual progress that had been achieved in reducing mortality and the incidence of drug-resistant tuberculosis has not been completely determined. **Objective:** to determine the presence of comorbidities and their association with antimicrobial resistance in tuberculosis in 2022. **Material and methods:** a total of 480 cases diagnosed through molecular diagnosis (PCR), microbiological culture, M. tuberculosis isolation, and drug susceptibility testing, reported by UIBMZ-IMSS in the epidemiological surveillance laboratory during the period from January to December 2022. **Results:** a total of 480 tuberculosis cases diagnosed in Mexico in 2022 were analyzed, with 46.88% showing antimicrobial resistance. The most common resistance was to streptomycin (11.67%), followed by pyrazinamide (6.46%), while resistance to isoniazid and ethambutol was lower. It was found that 5.63% of the cases showed resistance to more than three drugs. Resistant tuberculosis was associated with comorbidities such as immunosuppression and drug use. **Conclusions:** the present study emphasizes the need to adjust health policies to control drug-

RESUMEN. Introducción: aunque la tuberculosis es prevenible y generalmente curable, esta infección representa la primera causa de muerte por un solo agente infeccioso. La interrupción de los servicios de salud pública causada por la pandemia de COVID-19 revirtió en el mundo los avances graduales que se habían logrado en la reducción de la mortalidad y la incidencia de tuberculosis farmacorresistente, causando estragos que a la fecha no se han determinado completamente. **Objetivo:** determinar la presencia de comorbilidades y su asociación con la resistencia antimicrobiana de tuberculosis en 2022. **Material y métodos:** un total de 480 casos diagnosticados a través de diagnóstico molecular, mediante cultivo microbiológico, aislamiento de *M. tuberculosis* y prueba de susceptibilidad a fármacos, emitido por la Unidad de Investigación Biomédica de Zacatecas perteneciente al Instituto Mexicano del Seguro Social en el laboratorio de vigilancia epidemiológica durante el período de enero a diciembre de 2022. **Resultados:** se analizaron 480 casos diagnosticados con tuberculosis en México en el año 2022, mostrando resistencia antimicrobiana 46.88%. La resistencia más común fue a la estreptomicina (11.67%), seguida de la pirazinamida (6.46%), mientras que la resistencia a la isoniazida y etambutol fue menor. Se encontró que 5.63% de los casos muestra resistencia a más de tres fármacos. La tuberculosis resistente está asociada con comorbilidades como la inmunosupresión

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resistant tuberculosis, focused on vulnerable populations, mainly immunosuppressed people, or people with addictions.

Keywords: tuberculosis, incidence, *Mycobacterium tuberculosis*, multidrug-resistance, comorbidity.

y el consumo de drogas. **Conclusiones:** el presente estudio enfatiza la necesidad de ajustar las políticas de salud para el control de la tuberculosis farmacorresistente, enfocado en poblaciones vulnerables, principalmente en personas inmunosuprimidas o con adicciones.

Palabras clave: tuberculosis, incidencia, *Mycobacterium tuberculosis*, multidrogorresistencia, comorbilidad.

Abbreviations:

95%CI = 95% Confidence Interval.
IMSS = *Instituto Mexicano del Seguro Social*.
WHO = World Health Organization.
RR = Relative risk.
TB = Tuberculosis.
DR-TB = Drug-resistant tuberculosis.
HIV = Human immunodeficiency virus.

INTRODUCTION

Tuberculosis (TB) is a disease caused by the bacillus *Mycobacterium tuberculosis*. The infection is transmitted almost exclusively through the air, through the inhalation of aerosols generated when a person with active lung disease speaks, coughs, or sneezes. It has been estimated that about a quarter of the world's population is infected by the bacillus in a latent state. It is important to highlight that people infected with the bacillus have a 5-10% chance of becoming ill with TB throughout their life. This risk is increased in people with compromised immune systems, as occurs in cases of human immunodeficiency virus (HIV) infection, diabetes *mellitus*, or in users of tobacco and other drugs.[1] Although TB is preventable and generally curable, this infection represents the first cause of death due to a single infectious agent, causing more than one million deaths and more than 10 million new cases reported by the World Health Organization (WHO) each year.[2]

As a result of the recent COVID-19 pandemic, coupled with the ongoing challenges facing the global health sector, the WHO reported a global reduction of -18% in the number of patients diagnosed with active TB during 2020 compared to 2019, which appears to be due to a lack of funding for TB prevention, diagnosis, and treatment services.[3] In Mexico, the observed reduction in the number of new cases was -22.9% in 2020, with a partial recovery of -9.4% in 2021. This ultimately leads to an increase in deaths, transmission of the infection, and, over time, an increase in the number of patients.[4]

On the other hand, the constant increase in drug resistance has emerged as a significant challenge in recent decades. People with drug-resistant tuberculosis (DR-TB) require treatment with regimens that include second-line drugs such as bedaquiline and fluoroquinolones. The WHO recommends different regimens for rifampicin - single-resistant tuberculosis (RR-TB) or multidrug-resistant tuberculosis (DR-TB, defined as resistance to both rifampicin and isoniazid) and XDR-TB (resistance to rifampicin, any fluoroquinolone, and at least one of bedaquiline or linezolid).[5] Globally, a 15% reduction in the number of people starting treatment for drug-resistant TB was reported during the COVID-19 pandemic.[3] This decline can be attributed to several factors, such as the disruption of health services, the diversion of resources to the COVID-19 response, and mobility restrictions that affected access to health centers.

Therefore, it is essential to conduct targeted epidemiological studies on TB resistance in order to determine the observed local and national impact of the increase in FRTB cases and to demonstrate epidemiological changes following the COVID-19 epidemic.

MATERIAL AND METHODS

This observational, descriptive, and retrospective study was conducted at the Unidad de Investigaciones Biomédica-Zacatecas (UIBMZ) of the Instituto Mexicano del Seguro Social (IMSS) through the diagnostic and epidemiological surveillance program. From a database of 1,900 samples received by the Epidemiological Surveillance Service, 480 cases with primary TB confirmed by molecular diagnosis (PCR) using GeneXpert MTB/RIF™ and microbiological culture on solid Lowenstein-Jensen medium were selected, excluding those that did not present positivity.

Phenotypic susceptibility testing for first-line drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin) was performed using a BD BACTEC™ MGIT™ 960, following the supplier's instructions. The results were subsequently issued by the UIBMZ-IMSS epidemiological surveillance laboratory. The cases analyzed during the period from January to December 2022 came from various states in Mexico and all corresponded to patients with IMSS benefits. The protocol was approved by the IMSS National Ethics Committee under registration number R-2024-785-014.

Sociodemographic data and the presence of comorbidities, including type II diabetes *mellitus*, HIV, neoplasia, immunosuppression (derived from transplants, use of interferon inhibitors and immunosuppressants), drug use such as alcoholism, smoking, and other substances

(referred to by the physician as recreational substances), were collected as described in the patients' medical records and finally analyzed using SPSS version 24 statistical *software*. Variables were summarized by determining absolute and relative frequencies, which were used as summary measures for analysis and presentation of results. Relative risk (RR) was calculated with its confidence intervals (CI) using Pearson's χ^2 test and Fisher's exact test. Finally, statistical significance was established for p values less than or equal to 0.05.

RESULTS

Total diagnosed cases

The study included a total of 480 individuals diagnosed with TB, of which 37.2% (n = 179) were women and 62.7% (n = 301) were men. Furthermore, the age of the participants was analyzed separately for men and women. In men, the average age was 47.7 ± 17.04 years. On the other hand, the average age of women was 42.98 ± 16.98 years. The distribution of the sample by age and sex is presented in *Table 1*. Finally, the age ranges were categorized as follows: 0-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years, and ≥ 65 years. The absolute number of participants is presented for each range. The majority of individuals were between the ages of 45 and 64, representing 43.12% of the total population (n = 207). The specific distribution by sex and age range was as follows: the highest number of women with TB was found in the age range of 25 and 44, representing 35.19% of the sample of female patients with TB (n = 63). The lowest representation was observed in the 5 and 14 age group, excluding younger ages, with 0.55% of the sample of female patients (n = 1). Similarly, the highest number of men with TB was found in the age range of 45 and 64, representing 48.83% of the sample of male patients (n = 147). The lowest representation of these groups was the 5 and 14 age group, representing 0.33% of the sample (n = 1), excluding unrepresented groups. The distribution of the sample according to age range and sex is presented in *Figure 1*.

Table 1: Distribution of study participants by age and sex (N = 480).

Sex, n (%)	
Male	301 (62.7)
Female	179 (37.2)
Edad (años), media ± DE	
Male	47.70 ± 17.04
Female	42.98 ± 16.98

SD = standard deviation.

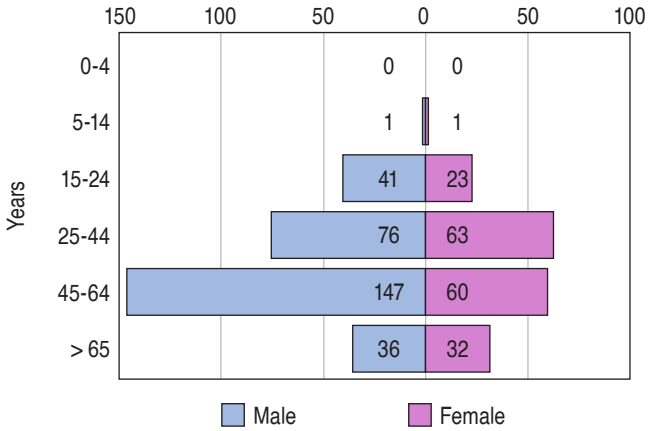

Figure 1: Distribution of diagnosed tuberculosis cases by age group and sex in 2022 (N = 480).

Prevalence of tuberculosis cases

The distribution of cases diagnosed by the tuberculosis epidemiological surveillance laboratory in 2022 shows a marked concentration in Nuevo León, which reported 316 of the 480 total cases, representing 66% of the total reported. Other states with relevant prevalence include Tamaulipas, Veracruz, and San Luis Potosí, with 45, 25, and 23 cases, respectively. Most of the remaining states report fewer than 10 cases, indicating a lower prevalence of cases reported by the unit. States such as Baja California, Campeche, Chiapas, Coahuila, Mexico City, Jalisco, Michoacán, Oaxaca, Quintana Roo, Yucatán, and Zacatecas report between two and 10 cases each. States such as Baja California Sur, Chiapas, Sonora, Nayarit, Puebla, Sinaloa, and Tabasco only reported one to two cases of the total evaluated at the UIBMZ-IMSS *(Figure 2A)*.

Distribution of DR-TB cases in Mexico in 2022

Of the total diagnosed TB cases, 225 (46.88%) were resistant to anti-TB drugs. The geographic distribution of these resistant cases showed a notable concentration in certain states. According to the data analyzed, the state of Nuevo León has the highest number of cases, with a total of 154, representing a considerable concentration of the disease burden in this region. In contrast, most states report considerably lower numbers of cases. Tamaulipas (17 cases) and San Luis Potosí (16 cases) are the states with the highest number of reports, followed by Veracruz and Zacatecas, both with six cases each. Other states such as Jalisco and Michoacán reported four cases each, while Mexico City recorded three cases. States such as Coahuila and Oaxaca recorded two cases each. Finally, the states of Baja California, Baja California Sur, Campeche, Chiapas, Quintana Roo,

and Yucatán have only one reported case. Sonora, Nayarit, Puebla, Sinaloa, and Tabasco reported TB cases overall, but no cases of drug-resistant TB were recorded. It is important to note that data on the incidence of drug-resistant TB are not available in other states in the country *(Figure 2B)*.

These results suggest that drug-resistant TB affects the entire country; however, in the present study, we can only make inferences about those who send samples to the UIBMZ/LAVE-IMSS. *Figure 2C* presents the distribution of total and drug-resistant cases in different states of Mexico, along with the percentage of drug-resistant cases in each state.

Percentage of DR-TB cases during 2022

Streptomycin resistance has a resistance rate of 11.67%, indicating that a considerable percentage of TB strains in the country are resistant to this key drug. Pyrazinamide resistance shows a relatively high resistance rate of 6.46%, suggesting a significant prevalence of strains resistant to this essential drug in the initial phase of treatment. On the other hand, the resistance rates to isoniazid and ethambutol were 3.96 and 0.83%, respectively, while resistance to rifampin was 0.83%. Analyzing drug combinations, resistance to rifampin in combination with streptomycin is 4.38%, to pyrazinamide 0.42%, and to isoniazid 2.91%. Combinations with isoniazid show a resistance rate of 3.75% with streptomycin. Finally, 5.63% of cases show resistance to more than three drugs, the most common drug being rifampicin with 2.5% of the total representation, which is substituted as a marker of DR-TB *(Figure 3)*.

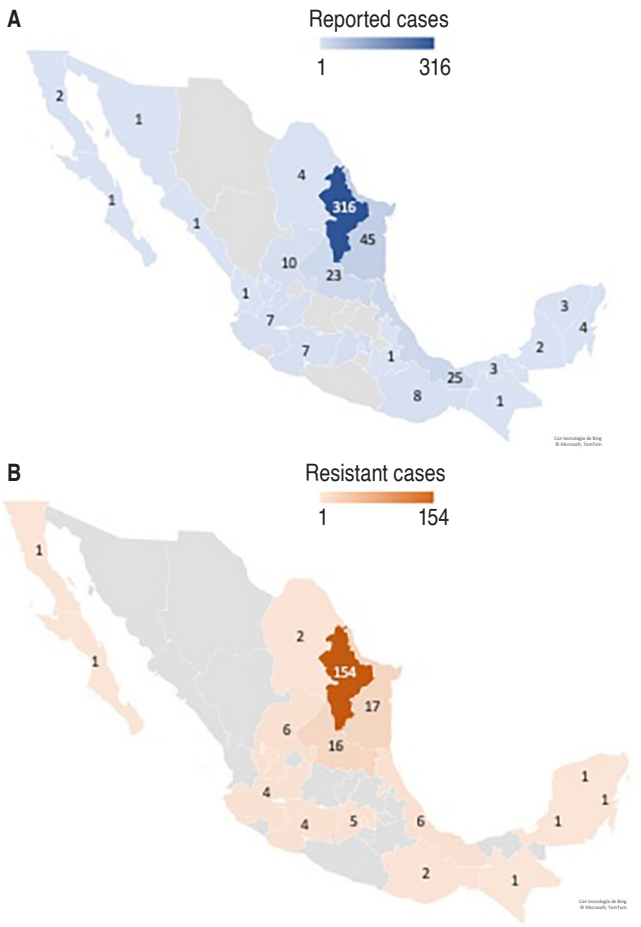

Figure 2: Distribution of total and resistant cases by state in 2022. The map shows the total number of cases per state. **A)** Number of cases with reported antimicrobial resistance. **B)** The gray areas indicate states for which data are unavailable (N = 480). **C)** The percentage of treatment-resistant cases in various states of Mexico.

C

	Cases	
State	Total	Resistant n (%)
Baja California	2	1 (50.00)
Baja California Sur	1	1 (100.00)
Campeche	2	1 (50.00)
Chiapas	1	1 (100.00)
Coahuila	4	2 (50.00)
CDMX	4	3 (75.00)
Jalisco	7	4 (57.14)
Mexico	11	5 (45.45)
Michoacán	7	4 (57.14)
Nuevo León	316	154 (48.73)
Oaxaca	8	2 (25.00)
Quintana Roo	4	1 (25.00)
San Luis Potosí	23	16 (69.57)
Tamaulipas	45	17 (37.78)
Veracruz	25	6 (24.00)
Yucatan	3	1 (33.33)
Zacatecas	10	6 (60.00)
Sonora	1	0 (0.00)
Nayarit	1	0 (0.00)
Puebla	1	0 (0.00)
Sinaloa	1	0 (0.00)
Tabasco	3	0 (0.00)

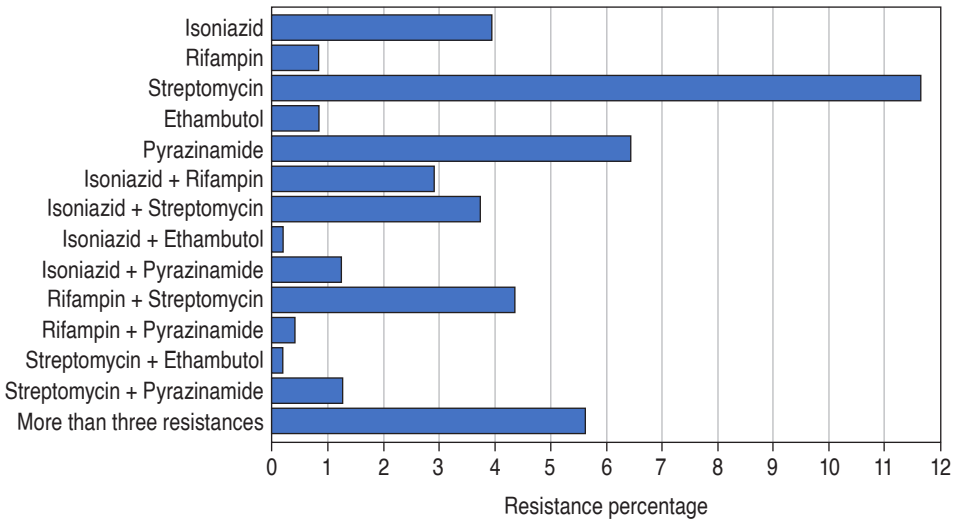

Figure 3:

Percentage distribution of resistance to anti-tuberculosis drugs and drug combinations in tuberculosis cases reported in Mexico during 2022. The figure shows the proportion of resistance to different anti-tuberculosis drugs and their combinations, each segment represents the percentage of resistance to a specific drug or drug combinations.

Prevalence of comorbidities

In this study, the frequency of various comorbidities in patients with TB resistant and sensitive to anti-tuberculosis drugs was evaluated. RR with 95%CI was calculated to compare the prevalence of each comorbidity between both groups as shown in *Table 2*. Most of the comorbidities evaluated were more frequent among cases of resistant TB compared to sensitive cases. In the case of HIV, it was observed that 2.86% of patients with drug-resistant TB also had this infection, compared to 1.86% of sensitive patients. The RR calculated for HIV was 1.553 (95% CI 0.453-4.509), suggesting that HIV infection is more common among patients with resistant TB, although the difference was not statistically significant. Diabetes was another common comorbidity in this study, present in 24.76% of drug-resistant patients and 18.59% of drug-sensitive patients. The RR for diabetes was 1.332 (95% CI 0.945-1.875), indicating that diabetes is common among patients with drug-resistant TB, although the difference was not significant. Regarding malnutrition, 7.14% of drug-resistant TB patients presented this comorbidity, compared with 7.06% of drug-sensitive patients. The RR of 1.015 (95% CI 0.533-1.925) suggests that malnutrition is equally common in both groups, with no notable difference in prevalence. Regarding neoplasia, only 0.48% of drug-resistant patients and 0.74% of drug-sensitive patients were diagnosed with this condition. The calculated RR was 0.642 (95% CI 0.084-4.875), indicating a lower prevalence of malignancies in patients with drug-resistant TB, although this difference was not statistically significant. Immunosuppression showed a more marked difference between the two groups. It was observed that 4.76% of patients with resistant TB also had some degree of immunosuppression, compared to only 1.49% of susceptible patients, with an RR of 3.214 (95% CI 1.083-9.581). This suggests that immunosuppressed patients are more than three times more likely to develop drug-resistant TB compared to those who are not immunosuppressed. This may imply that immunosuppression is a significant risk factor for TB resistance. Alcoholism was a relatively common comorbidity, present in 13.81% of resistant patients and 14.50% of susceptible patients. The calculated RR was 0.956 (95% CI 0.613-1.484), suggesting that alcoholism was equally prevalent in both groups. Smoking was observed in 15.24% of patients with DR-TB and 13.01% of patients with sensitive TB. The RR of 1.207 (95% CI 0.732-2.043) indicates a slightly higher prevalence of smoking among patients with resistant TB. Finally, the use of other drugs showed a significant difference between the groups; 6.67% of patients with drug-resistant TB also reported use of other drugs, compared to only 2.23% of sensitive patients. The RR of 3.000 (95% CI 1.213-7.449) suggests that the use of other drugs is considerably more common among patients with drug-resistant TB, which could indicate an additional risk factor for the development of resistance to anti-TB drugs. The analysis reveals comorbidities, such as immunosuppression and use of other drugs, are significantly more frequent in patients with drug-resistant TB, which could have important implications for the clinical management and treatment strategies of these patients. As shown in *Table 2*, comorbidity analysis revealed that immunosuppression and use of other drugs are significantly associated with an increased risk of drug-resistant TB, with a RR of 3.214 (95% CI 1.083-9.581, $p = 0.05$) and 3.00 (95% CI 1.213-7.449, $p = 0.0203$), respectively. These associations suggest that immunosuppressed patients and those who use drugs should be considered at high risk for developing resistance to anti-tuberculosis treatment.

DISCUSSION

The disruption of public health services caused by the COVID-19 pandemic reversed the gradual progress made globally in reducing TB mortality and incidence, causing havoc that has yet to be fully determined. According to results reported by the Instituto Nacional de Salud Pública, Mexico saw a 23% decrease in diagnoses in 2022 compared to the average of the previous five years, and a 42% decrease in mortality, suggesting an underestimation of actual cases.[6] Other determinants, such as timely treatment, have been disrupted, as suggested in the WHO's global tuberculosis report. This document reported that treatment coverage in 2022 was only 58%, compared to 70% in 2019, triggering the spread of the disease and thus facilitating the development of antibiotic resistance.[1] In the present study, we found that 43.75% of the cases diagnosed during 2022 at the UIBMZ-IMSS showed resistance to a first-line drug. It is important to highlight that this value is well above that observed with the national average, which is around 3% of total diagnoses. This arrival bias could be due to the fact that the data collected belong to a laboratory specialized in the evaluation of the susceptibility profile, highlighting the need to implement this strategy nationally, since the lack of specific methodologies and knowledge of this service would provide an overview of the drug resistance situation in Mexico.[6]

It is important to note that the overrepresentation observed in Nuevo León is significant, given that Monterrey, being an urban center with a more developed healthcare system, may have better diagnostic capabilities and greater access to healthcare services, which could explain the higher representation of cases in this region.[7] In contrast, other states with high TB rates, such as Sinaloa and Baja California, may face significant challenges in TB identification and treatment. Populations in these states often face barriers to accessing healthcare services, such as lack of documentation, language, fear of arrest, mistrust, and/or access to the healthcare system.[8]

Table 2: Distribution of comorbidities according to resistance or sensitivity to anti-tuberculosis treatments.

	Resistant N = 210 n (%)	Sensitive N = 270 n (%)	RR (95% CI)	p
HIV				
Yes	6 (2.86)	6 (2.22)	1.54	0.469
No	204 (97.14)	264 (97.7)	(0.453-4.509)	
Diabetes				
Yes	52 (24.76)	51 (18.88)	1.33	0.115
No	158 (75.24)	219 (81.11)	(0.945-1.875)	
Malnutrition				
Yes	15 (7.14)	19 (7.06)	1.015	> 0.999
No	195 (92.86)	251 (93.31)	(0.533-1.925)	
Neoplasms				
Yes	1 (0.48)	2 (0.74)	0.6429	> 0.999
No	209 (99.52)	268 (99.63)	(0.084-4.875)	
Immunosuppression				
Yes	10 (4.76)	4 (1.49)	3.214	0.050
No	200 (95.24)	266 (98.88)	(1.083-9.581)	
Alcoholism				
Yes	29 (13.80)	39 (14.50)	0.9560	0.895
No	181 (86.20)	231 (85.87)	(0.613-1.484)	
Smoking				
Yes	32 (15.24)	35 (13.01)	1.207	0.508
No	178 (84.76)	235 (87.36)	(0.732-2.043)	
Other drugs				
Yes	14 (6.67)	6 (2.23)	3.000	0.020
No	196 (93.33)	264 (98.14)	(1.213-7.449)	

RR = relative risk. 95%CI = 95% confidence interval.
p values ≤ 0.05 are considered statistically significant.

These factors may result in underdiagnosis of the disease, since the diagnostic service is aimed exclusively at IMSS beneficiaries, and the study population is limited to this population.

It is essential to consider the influence of associated factors in the development of resistant TB, including comorbidities, socioeconomic and cultural factors.[9]

In perspective, it is necessary to improve the diagnosis and epidemiological surveillance of DR-TB in at-risk populations, adapting treatments to local resistance patterns. The need to focus on vulnerable populations, such as immunosuppressed individuals or those with drug addiction, with specialized care programs is emphasized. Furthermore, it is proposed to strengthen public policies to prioritize TB after the impact of the pandemic. It is also proposed to expand research into the genetic and environmental factors that influence drug resistance, in order to optimize control and treatment strategies.

CONCLUSION

The present study described that the relative risk of developing drug-resistant tuberculosis was mainly associated with the presence of immunosuppression resulting from the use of biological agents and recreational drug use.

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