Regional Review Article

Drug resistant *Mycobacterium tuberculosis* in Mexico

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Abstract

Tuberculosis (TB) remains a serious public health problem, worsened by an increased frequency of multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) launched the Global Project on Anti-Tuberculosis Drug Resistance Surveillance to measure the prevalence of drug resistance. Data from the global reports on resistance to anti-tuberculosis (anti-TB) drugs have shown that drug resistance still presents worldwide and that MDR-TB is present in almost all the world. Though the Global Project (WHO) has been operating since 1994, very few countries and states have reported new information. Data from repeated surveys employing comparable methodologies over several years are essential to determine with any certainty in which direction the prevalence of drug resistance is moving. Drug-resistant tuberculosis and MDR-TB have been identified in Mexico, even with the existence of a National Tuberculosis Program based on Directly Observed Treatment, Short-course (DOTS). This review discusses available surveillance data on drug susceptibility data for TB in different states of Mexico.

Key words: Drug, resistance, Tuberculosis, Mycobacterium, Mexico

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Introduction

The emergence of *Mycobacterium tuberculosis* strains resistant to anti-tuberculosis (anti-TB) drugs is a difficult problem to solve and is one of the greatest threats to public health worldwide [1,2]. The delays in diagnosis, therapy and treatment failures have complicated the epidemiology of this disease, and the emergence of multidrug-resistant *M. tuberculosis* strains mainly to the so-called first-line drugs have increased this problem [3-5]. The recent identification in 2006 of extensively drug-resistant (XDR) strains, which are resistant even to second-line anti-TB drugs, has increased the epidemiological magnitude of TB worldwide [6]. The control measure suggested by the World Health Organization (WHO), Directly Observed Treatment, Short-course (DOTS) [7], has demonstrated its effectiveness in preventing the emergence of drug-resistant TB [8]. This strategy has, however, presented failures of important magnitude in TB-resistant populations presenting a poor response to short-term treatment with standard first-line drugs. This often leads to treatment failure and higher mortality [8-10] as well as greater periods of transmissibility of TB [11].

The WHO estimates that about one third of the world's population (approximately 1.7 billion people) is infected with *M. tuberculosis* [12] and 9 million people develop active TB every year, with 3 million deaths [13,14]. Due to this epidemiological situation, in 1993 the WHO considered TB a global public health emergency. However, there are inconsistencies in the data, especially from developing countries [15,16]. This is in part due to extreme poverty and concomitant factors such as malnutrition, AIDS, diabetes and/or alcoholism. Developing countries account for 98% of cases and 95% of deaths from TB reported worldwide. Conversely, although resistance of *M. tuberculosis* was identified immediately after the initiation of therapy with anti-TB drugs (1950s) [17], it was not until the 1990s that this phenomena captured international attention due to multidrug-resistant TB outbreaks in countries such as United States [3] and then, in most geographical areas of the world [18,19]. The WHO estimates about 50 million people are infected with strains of resistant-TB [12] and according to surveillance of drug resistance, the

Table. Reports about *M. tuberculosis* resistance in several states of Mexico. 1974-2006

Ref.	Year of publication	Period of study	states	All cases (%)							New cases (%)							Treated cases (%)						
				DR	MDR	H	R	E	S	Z	DR	MDR	H	R	E	S	Z	DR	MDR	H	R	E	S	Z
37	1976	1974	Federal District	-	-	-	-	-	-	-	-	-	3.9	-	-	14.3	-	-	-	-	-	-	-	-
38	1982	1982	Federal District	-	-	-	-	-	-	-	-	-	-	-	-	15.4	-	-	-	-	-	-	-	-
39	1985	1980-1985	Several states	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50.4	-	-	-	-	-	-
5	1994	1986-1990	Guanajuato, Hidalgo, Veracruz, Oaxaca	-	-	-	-	-	-	-	19.1	-	-	-	-	-	-	-	-	-	-	-	-	-
41	1995	1991-1993	Federal District and state of Mexico	30.0	64.0	24.0	19.0	10.0	12.0	-	17.0	6.0	9.0	6.0	2.0	2.0	-	46.0	35.0	44.0	35.0	19.0	24.0	-
40	1995	1992	Chiapas	72.2	53.0	76.9	69.2	46.2	53.8	15.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42	1998	1995-1996	Baja California	41.0	17.0	28.8	-	12.2	-	-	-	10.0	-	-	-	-	-	-	43.3					
31	2000	1993-1999	Jalisco	-	38.0	58.0	44.0	43.0	50.0	43.0	-	23.0	48.0	32.0	32.0	42.0	38.0	-	52.0	68.0	57.0	54.0	58.0	48.0
11	2000	1995-1998	Veracruz	28.4	10.8	7.3	1.7	0.4	2.6	0.0	20.7	3.3	8.4	0.6	0.6	2.8	0.0	54.7	35.8	3.8	5.7	0.0	1.9	0.0
32	2000	1995-1999	Veracruz	24.2	7.7	18.6	9.0	4.3	8.0	-	12.0	7.3	10.0	8.5	2.3	2.7	-	75.0	9.4	53.1	10.9	12.5	29.7	-
25	2000	1997	Sinaloa, Baja California, Oaxaca	21.5	7.4	19.1	9.3	6.3	15.9	5.4	12.9	2.4	12.0	3.0	3.0	12.0	1.5	50.5	22.4	43.0	29.0	16.8	29.0	17.8
43	2000	1998-1999	Baja California	25.8	13.3	24.1	13.3	13.3	11.6	8.3	8.4	1.8	8.9	1.8	1.8	3.6	1.8	48.9	30.6	44.8	28.6	30.6	24.2	19.6
		1991-1993		-	-	-	-	-	-	-	-	-	-	-	-	-	-	78.9	35.3	6.0	5.6	-	-	-
29	2001	1994-1996	Federal District and state of Mexico (principally)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	68.3	30.0	8.3	8.9	-	-	-
		1997-2000		-	-	-	-	-	-	-	-	-	-	-	-	-	-	15.8	12.5	1.0	0.5	-	0.6	-
4	2001	1995-1999	Veracruz	25.0	6.2	12.0	8.1	3.9	4.9	-	18.8	1.6	5.7	2.4	2.4	4.1	-	49.2	23.8	36.5	30.2	9.5	7.9	-
33	2001	2000	Nuevo Leon	53.5	-	-	-	-	-	-	16.8	-	-	-	-	-	-	27.7	71.4	-	-	-	-	-
34	2002	2001	Chihuahua	-	-	-	-	-	-	-	37.5	9.3	18.8	9.4	18.8	18.8	-	-	-	-	-	-	-	-
35	2004	1992-2000	Sonora	44.0	28.0	16.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30	2004	2000	Coahuila	-	-	-	-	-	-	-	32.0	4.5	-	-	-	13.6	4.5	-	-	-	-	-	-	-
36	2004	2000-2003	Federal District and state of Mexico (principally)	-	32.6	6.1	6.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	2006	2003-2004	San Luis Potosi	36.0	16.0	-	-	-	-	-	6.2	-	-	-	-	-	-	32.9	-	-	-	-	-	-
26	2006	2003-2004	Sinaloa	37.8	18.1	27.2	18.1	18.1	21.2	15.1	17.5	0.0	0.0	0.0	0.0	17.5	0.0	69.2	46.1	69.2	46.1	46.1	26.9	38.4
			Median	33.0	17.0	21.6	11.3	11.1	12.0	11.7	17.3	4.5	9.0	3.0	2.3	12.8	1.7	50.4	35.0	43.0	28.6	17.9	24.2	19.6
			Minimum	21.5	6.2	6.1	1.7	0.4	2.6	0.0	6.2	0.0	0.0	0.0	0.0	2.0	0.0	15.8	9.4	1.0	0.5	0.0	0.6	0.0
			Maximum	72.2	64.0	76.9	69.2	46.2	53.8	43.0	37.5	23.0	48.0	32.0	32.0	42.0	38.0	78.9	71.4	69.2	57.0	54.0	58.0	48.0

H: Isoniazid, R: Rifampin, E: Ethambutol, S: Streptomycin, Z: Pyrizinamide, DR: Resistance to at least one drug, MDR: Resistance to at least H and R
New Cases: Patients without treatment, Treated Cases: Patients with previous treatment, All Cases: All patients. Some figures were reported by authors as Primary-, Secondary- and combined-resistance.

problem persists in almost all geographical areas of the world and levels are rising [19-22].

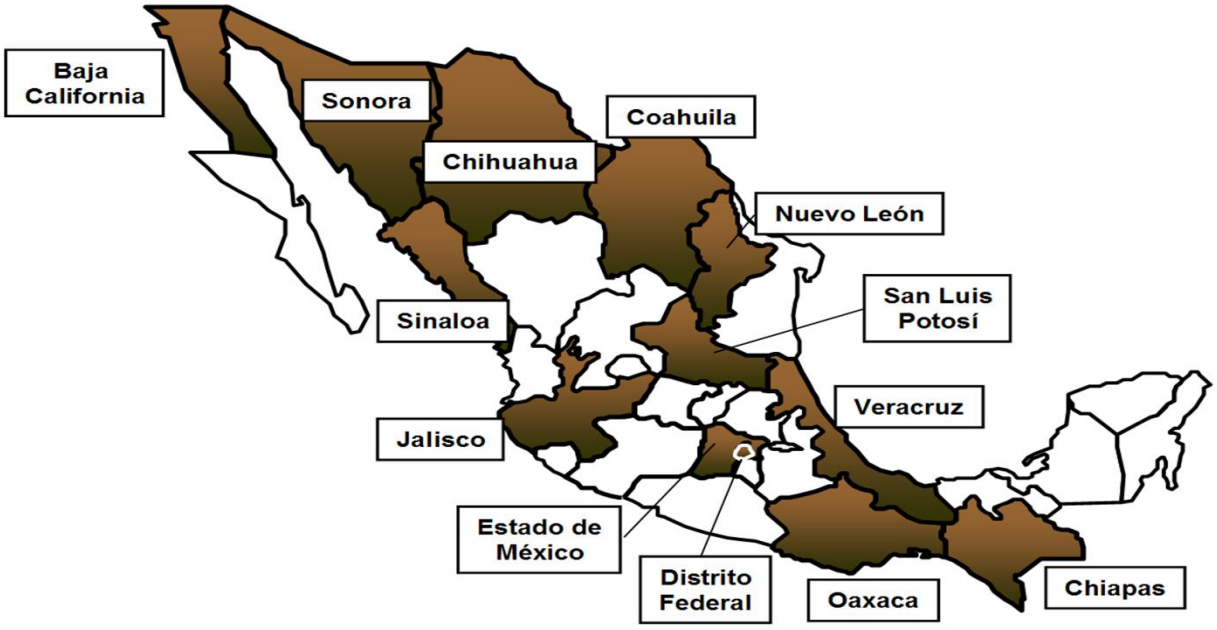
In Mexico, TB remains endemic and approximately three thousand people die of this disease every year. The TB incidence rate was in decline until the end of the 1980's. Since then, the national incidence rate has remained almost stable, with slight variations [23]. The TB rate per 100,000 population declined from 16.5 cases in 1984 to 14.3 cases in 1990. From 1991 to 2002, the rate increased from 14.4 to 15.1 cases. Finally, in 2006 the rate decreased to 12.8 cases (http:/www.dgepi.salud.gob.mx).

The WHO has defined terms for classifying resistance depending upon treatment outcomes. Thus, the term "*resistance among new cases*" refers to patients with pulmonary TB who have never received anti-TB drugs or have received less than 1 month of treatment. The term "*resistance among previously treated cases*" is used to refer to patients who had previously received anti-TB drugs for at least 30 days. This group includes patients with relapse, treatment failures, and chronic cases. Finally, the term "*resistance among all cases*" refers to all TB patients without considering the history of tuberculosis treatment. However, in Mexico as in many countries, several reports still use the classical terminology. Thus, the "*resistance among new cases*" is also called "*primary or initial resistance*." The "*resistance among previously treated cases*" is also known as "*secondary or acquired resistance*" and the "*resistance among all cases*" is also named as "*combined resistance*." In this review we will cite the terms used by the authors of the respective publications. Likewise, we will use the term "*multidrug-resistant*" (MDR) to define an *M. tuberculosis* strain recovered from a patient who presents resistance to at least isoniazid (H) and rifampin (R). Similarly, the term "*drug-resistant*" (DR) will be used to define resistance to at least one (any) of the first-line anti-TB drugs used in Mexico: H, R, ethambutol (E), pyrazinamide (Z) and streptomycin (S) [24].

Until now, studies about resistance in Mexico have included several geographic areas around the country (Fig. 1). However, some of these areas presented significant biases, because outcome-based measures have some significant limitations (different studies, methods, and population involved), which resulted in high degrees of variability between resistance levels found among different settings (Table 1). Only the survey conducted in 1997 attempted to be representative of the population throughout the country but included only three states (Sinaloa, Baja California and Oaxaca) [25]. While these efforts have helped to understand and to control this infection, some recent studies have shown that drug-resistant *M. tuberculosis* remains in Mexico, and might still be increasing in some settings [26-36].

One of the first antecedents for the investigations of drug-resistant TB in Mexico is the report by Herrera *et al*., in 1974, in which 126 TB cases with primary resistance to H and S were studied. The prevalence of resistance in the Federal District was 3.9% and 14.3% to H and S respectively [37]. Another study on primary resistance, carried out in 1982, included several first-line anti-TB drugs which reported 19% resistance to one, two or three drugs, including 15.4% resistance to S [38]. From 1980 to 1994, according to the National Diagnostic and Epidemiologic Reference Institute (InDRE), high levels of resistant-*M. tuberculosis* strains were reported in several states [39]. From 1980 to 1985, a 50.4% secondary DR was reported. The primary DR increased from 10.6% in 1989 to 27.7% in 1994 and, although the secondary DR was stable, it was very high (74.3%). The trend of the combined DR increased from 59.4% in 1989 to 74.8% in 1994. In addition, the primary MDR increased: in 1989 it was 8.5% and in 1994 it reached 11.1%. The secondary MDR was 40% on average. Another study performed between 1986 and 1990 by Laszlo and Kantor [5] reported 19.1% primary DR. In the 1990s, other studies were conducted in different parts of the country reporting alarming rates of resistance. For example in Chiapas, Alvarez-Gordillo and colleagues [40] reported rates of 72% DR in 1995, possibly attributed to an inadequate local program of infection control. In the same year, Sifuentes-Osornio and colleagues [41] reported rates of 30%, 17% and 46% for combined, primary and secondary DR, respectively, in the population from the Federal District and State of Mexico. A high prevalence of drug resistance has also been documented in the state of Veracruz. In fact, Garcia-Garcia and colleagues in 2000 [11] reported a prospective study performed from 1995 to 1998 in this state, where the combined, primary and secondary DR were 28.4%, 20.7% and 54.7%, respectively, while primary and secondary MDR were 3.3% and 35.8% respectively. In 1999, a slight decrease in resistance rates was found: down to 25% for combined DR, 18.8% for primary DR, and 42.9% for secondary DR. A similar decline was also

Figure 1. States of Mexico reporting resistance of *M. tuberculosis* to first-line anti-TB Drugs up to and including 2006.



observed for MDR with rates of 1.6% and 23.8% for primary and secondary MDR, respectively [4].

In 1996, Peter and colleagues [42] conducted a binational study in San Diego California (United States) and Tijuana, Baja California (Mexico) reporting 41% combined DR and 17% MDR. In 1999, another study by Laniado-Laborin and colleagues [43] in Baja California reported rates of 25.8% and 13.3% for combined DR and MDR, respectively.

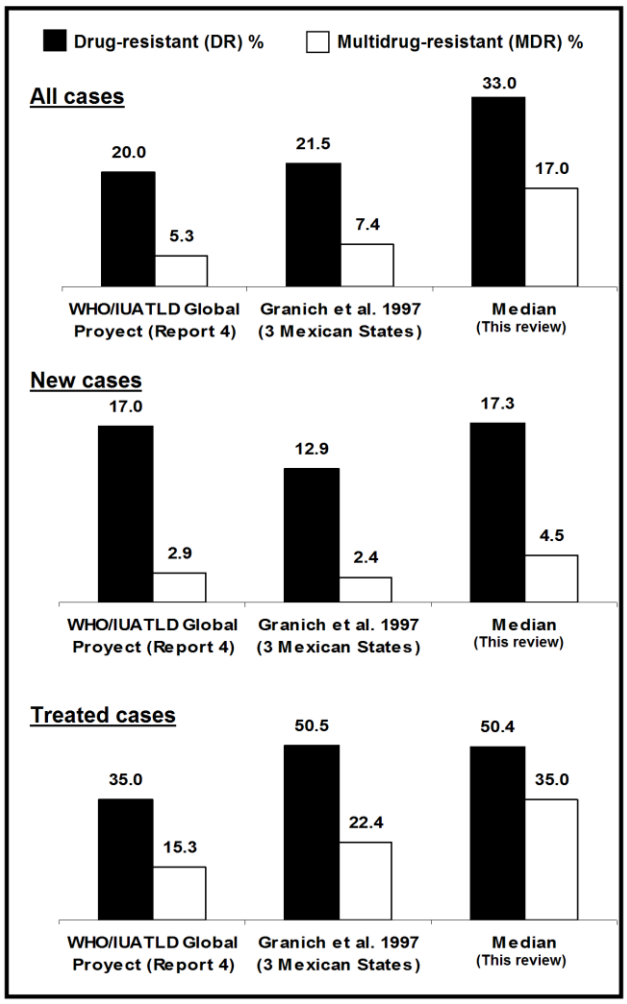
Mycobacterium tuberculosis drug resistance has serious consequences for both the patient and the TB control program. Drug resistance increases the rate of treatment failure and the costs of TB control. Due to the problem of drug resistance and because previous studies considered only a small number of subjects in some settings of Mexico or had important methodological limitations, in 1997, the Secretary of Health of Mexico took action. In collaboration with The Centers for Disease Control and Prevention (CDC), a national survey of drug resistance for TB was developed and implemented as part of the WHO/IUATLD (International Union Against Tuberculosis and Lung Disease) global project on TB drug resistance. Their report describes results for three states in Mexico and presents the first population-based TB drug-resistance data available for the country [21, 25]. This was a prospective study in which Sinaloa (high incidence of TB), Baja California (high incidence) and Oaxaca (median incidence) states were selected. Patterns of drug resistance of 460 strains of *M. tuberculosis* were studied; finding 12.9%, 50.5% and 21.5% DR among new cases, treated cases and all cases, respectively. MDR was 2.4%, 22.4% and 7.4%, respectively. In this study, the overall resistance rate (21.5%) and MDR (7.4%) were higher than the median WHO/IUATLD global project figures (20% and 5.3%, respectively,) as shown in Figure 2 [22, 25]. This population-based study of *M. tuberculosis* demonstrated moderately high levels of drug resistance in Mexico [25].

In 2001 a retrospective study was published by the National Institute of Respiratory Diseases in Mexico [29]. This study included patients from several states. Although these results indicate that the proportion among previously treated case-patients increased during the period from 1997 to 2000, the study was not representative of the statewide population.

In the state of Coahuila in 2004, a study reported only 32% primary DR [30]. In the states of San Luis Potosi and Sinaloa, data was reported about drug-resistance during 2003-2004. Fragoso-Morales and colleagues [27] reported 6.2%, 88.9% and 36% for primary, secondary and combined DR respectively in San Luis Potosi, while the combined MDR was 50%. We have previously reported the prevalence of resistance to the five first-line drugs in Sinaloa State; resistance to at least one anti-tuberculosis drug was

17.5%, 69.2% and 37.8% among new cases, previously treated cases and combined prevalence, respectively [26]. MDR among new cases was not detected, but MDR of previously treated cases was

Figure 2. Comparison of DR and MDR level from monitoring studies of drug-resistance by the WHO (report No.4) [22]. The national level studied in Mexico [25] and the median of the Mexican studies on resistance included in this review.



46.1% and MDR of all cases was 18.1%.

Thus, the rates presented here (see Table 1), show variability among the proportions of DR and MDR in different geographical areas of the country. The potential causes of this variability have been discussed above. The median ratios for the DR of the studies included in this review were 17.3%, 50.4% and 33.0% among new cases, treated cases, and all cases; MDR was 4.5%, 35.0% and 17.0% respectively. The states with higher rates of DR were Chihuahua with 37.5% (new cases), Federal District and State of Mexico with 78.9% (previously treated cases), and Chiapas with 72.2% (all cases). The MDR among new cases, previously treated cases, and all cases were higher in Jalisco (23.0%), Nuevo Leon (71.4%) and the Federal District and State of Mexico (64.0%). Lastly, the TB resistance studies in Mexico compared with the rate of drug-resistance surveillance conducted by the WHO/IUATLD suggest that the Mexican rate is higher than those reported worldwide (global project, report No.4; see figure 2). However, these data should be interpreted with caution because different studies, methods, and populations were involved in these reports.

Recently, at least one case of XDR-*M. tuberculosis* has been reported in Mexico [22], indicating the inappropriate use of second-line drugs in a patient for whom first-line drugs are failing. This alarming finding is a public health emergency, but population-based surveillance data are needed to describe the magnitude and trends of XDR TB in Mexico.

Conclusion

Tuberculosis, declared a global emergency by the WHO, remains a serious public health problem. Drug resistance and multidrug-resistance (MDR) in particular are a substantial threat to TB control in some countries. Despite the existence of DOTS, Mexico is not exempt from the problems that represent the emergence of drug-resistant *M. tuberculosis* strains. Resistance rates from first-line drug-resistance studies in Mexican populations suggest higher levels than those reported by the WHO in all four phases of global surveillance and, in some cases, reach alarming levels. Moreover, patients with MDR-TB in Mexico are especially worrying, since such cases are significantly more difficult to treat, and mortality is higher than for drug-susceptible cases. The results discussed in this review suggest that Mexico needs to strengthen strategies to prevent the emergence of new drug-resistant *M. tuberculosis* strains. Therefore, it is necessary and urgent to estimate the magnitude of the resistance of *M. tuberculosis* at a national level in order to evaluate the progress of DOTS under recent health care reforms and to follow trends in high-risk populations identified in the course of the surveys.

According to WHO/IUATLD (report No.4, 2008), Mexico has started a nationwide survey and has plans to test MDR-TB isolates for second-line drug resistance at a Supranational Reference Laboratory. This survey will be a priority to consider the future management of MDR-TB in Mexico.

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