Salud Pública de México
ISSN: 0036-3634
spm@insp.mx
Instituto Nacional de Salud Pública
México

Flores-Treviño, Samantha; Mendoza-Olazarán, Soraya; Garza-González, Elvira
Drug resistance and molecular epidemiology of Mycobacterium tuberculosis in Mexico: A systematic review
Salud Pública de México, vol. 56, núm. 1, enero-febrero, 2014, pp. 63-77
Instituto Nacional de Salud Pública
Cuernavaca, México

Drug resistance and molecular epidemiology of *Mycobacterium tuberculosis* in Mexico: A systematic review

Samantha Flores-Treviño, MC,[1] Soraya Mendoza-Olazarán, MC,[2] Elvira Garza-González, D en C.[2]

Flores-Treviño S, Mendoza-Olazarán S, Garza-González E. Drug resistance and molecular epidemiology of *Mycobacterium tuberculosis* in Mexico: A systematic review. Salud Publica Mex 2014;56:63-77.

Abstract

Objective. To compare drug resistance (DR) rates and genetic diversity of *Mycobacterium tuberculosis* strains from different states of Mexico. **Materials and methods**. A systematic review of English and Spanish-language articles using MEDLINE and Google Scholar. Search terms included *Mycobacterium tuberculosis*, Mexico, resistance, mutation and epidemiology. **Results**. Fifteen studies for phenotypic DR rates (n=2 694), twelve studies for genotypic DR (n=748) and eleven studies for genetic diversity (n=2 044) met our inclusion criteria. Mean DR and multidrug resistance (MDR) rates were 37.5% and 20.6%, respectively. The most frequent mutations were *rpoB*531 (53.1%), *katG*315 (50.6%), *embB*306 (32.1%), *rpsL*43 (14.6%) and *pncA*359 (16.7%) in DR strains. Novel mutations were found. Predominant shared types were SIT53 (T1, n=188, 3.9%), SIT119 (X1, n=125, 6.9%), SIT19 (EAI2-Manila, n=80, 6.3%) and SIT42 (LAM9, n=77, 3.0%). SIT1 Beijing genotype has been reported in six states from Mexico. **Conclusions.** DR and MDR rates continue to increase. Genetic diversity of *M. tuberculosis* strains in Mexico is high. Reports of Beijing strains are increasing.

Key words: *Mycobacterium tuberculosis;* molecular epidemiology; drug resistance; mutation; Mexico

Flores-Treviño S, Mendoza-Olazarán S, Garza-González E. Farmacorresistencia y epidemiología molecular de Mycobacterium tuberculosis en México: una revisión sistemática. Salud Publica Mex 2014;56:63-77.

Resumen

Objetivo. Comparar los niveles de farmacorresistencia (FR) y la diversidad genética de cepas de *Mycobacterium tuberculosis* de diferentes estados de México. **Material y métodos**. Una revisión sistemática de artículos en inglés y español usando MEDLINE y Google Scholar. Los términos de búsqueda incluyeron *Mycobacterium tuberculosis*, México, resistencia, mutación y epidemiología. **Resultados**. Quince estudios de niveles de FR fenotípica (n=2 694), doce estudios de FR genotípica (n=748) y once estudios de diversidad genética (n=2 044) concordaron con nuestros criterios de inclusión. El promedio de los niveles de FR y multifarmacorresistencia (MFR) fue 37.5 y 20.6%, respectivamente. Las mutaciones más frecuentes fueron *rpoB*531 (53.1%), *katG*315 (50.6%), *embB*306 (32.1%), *rpsL*43 (14.6%) y *pncA*359 (16.7%) en cepas FR. Se encontraron nuevas mutaciones. Los tipos compartidos predominantes fueron SIT53 (T1, n=188, 3.9%), SIT119 (X1, n=125, 6.9%), SIT19 (EAI2-Manila, n=80, 6.3%) y SIT42 (LAM9, n=77, 3.0%). El genotipo Beijing SIT1 se ha reportado en seis estados de México. **Conclusiones.** Las tasas de FR y MFR siguen incrementando. La diversidad genética de las cepas de *M. tuberculosis* es alta. Los reportes de cepas Beijing están aumentando.

Palabras clave: *Mycobacterium tuberculosis;* epidemiología molecular; resistencia a medicamentos; mutación; Mexico

(1) Departamento de Microbiología, Facultad de Medicina, Universidad Autónoma de Nuevo León. Nuevo León, México.
(2) Servicio de Gastroenterología y Departamento de Patología Clínica, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León. Nuevo León, México.

Received on: July 22, 2013 • **Accepted on:** July 26, 2013
Corresponding author: Elvira Garza-González. Av. Madero s/n, col. Mitras Centro. 64460 Monterrey, Nuevo León, México.
E-mail: elvira_garza_gzz@yahoo.com

Almost one third of the global population is infected with *Mycobacterium tuberculosis*.[1] The TB rate in Mexico is 16.8 per 100 000 population in 2010. Every year, more than two thousand people die from tuberculosis (TB) in this country.[2] One of the most alarming trends worldwide concerning TB is the emergence of drug-resistant (DR) and multidrug-resistant strains of *M. tuberculosis* (MDR-TB). MDR strains are defined as those resistant to at least isoniazid (INH) and rifampicin (RIF). In *M. tuberculosis*, acquired drug resistance is caused mainly by spontaneous mutations in chromosomal genes, producing the selection of resistant strains during sub-optimal drug therapy.[3,4]

Molecular typing of *M. tuberculosis* strains has been used to understand the transmission dynamics of TB.[5] One genotyping technique is restriction fragment length polymorphism (RFLP) analysis, where the distribution and number of copies of an insertion sequence, IS*6110*, in a chromosome is monitored, with this event varying among different strains. However, PCR-based techniques have gradually been replacing RFLP analysis over the last decade. Spoligotyping detects polymorphisms present in a direct repeat locus, while molecular typing using mycobacterial interspersed repetitive units–variable number of DNA tandem repeats (MIRU–VNTRs) is also used.[6]

DR and MDR strains have been steadily increasing over the past years, making treatment of TB difficult. Thus, it is important to identify resistant strains as soon as possible in order to adjust treatment strategies and minimize disease transmission. However, determining the DR rate in the country has proven difficult. Several reports are available and yet, some use different drug susceptility testing (DST). A systematic review of phenotypic and genotypic data of DR in *M. tuberculosis* strains, as well as an analysis of current genotypes has not been performed before.

To analyze the circulating *M. tuberculosis* strains from Mexico, we reviewed studies that assessed DR using specific DST, evaluated DR-associated mutation frequency and/or determined genetic diversity of *M. tuberculosis* strains in patients with either pulmonary or extrapulmonary TB from different states of Mexico.

Materials and methods

Analysis methods were performed based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement (http://www.prisma-statement.org/).

Studies were identified by searching the electronic Databases MEDLINE and Google Scholar.

No limits were applied for language and foreign papers were translated. The last search was run on July 8, 2013. Search terms included *Mycobacterium tuberculosis*, Mexico, resistance, mutation, molecular epidemiology, spoligotyping, RFLP-IS*6110*, MIRU-VNTR.

Articles were screened on the basis of title, abstract and manuscript review, when available. Data extraction from included studies was performed by one reviewer and inserted in a data sheet. Studies of phenotypic DR rate evaluation of first line drugs were included. To minimize risk of bias across studies, studies evaluating DR with a DST method other than the proportion or radiometric method were excluded from the review. Data of genotypic DR was included exclusively from DR strains from the selected studies. As such, we excluded the frequency of mutations in drug susceptible strains, and the mean mutation rate was modified accordingly. As well, genotype frequency comparison among states was performed only when the same genotyping method was used.

The information extracted from each included study was: 1) type of study (including articles studying phenotypic DR, genotypic DR or genetic diversity. No language, publication date, or publication status restrictions were imposed); 2) type of participants (including *M. tuberculosis* strains from patients either with pulmonary or extrapulmonar TB from any Mexican state); 3) characteristics of phenotypic and/or genotypic DR rates and/or genetic diversity (including state, year, number of strains and population), and the article's inclusion and exclusion criteria; 4) type of intervention (including drug susceptibility testing (DST) method, drugs evaluated (isoniazid (INH) and/or rifampicin (RIF), including or not ethambutol (EMB), streptomycin (STR) and pyrazinamide (PZA)), DR-associated mutation frequency (in genes associated to either aforementioned drug: *rpoB, katG, inhA, oxyR-ahpC, embB, rss, rpsL* and *pncA*), specific site mutation and genotyping method (spoligotyping, RFLP-IS*6110* fingerprinting, MIRU-VNTR; 5) type of outcome measure (including the mean of phenotypic DR and MDR for each state, DR-associated genes mutation frequency, specific site (codon or nucleotide) mutation frequency, local sample total mutation rate, clustering rate, shared types, lineages and frequency of novel genotypes).

We performed three different analyses in our study. First, we compared DR and MDR levels, as well as resistance of each drug to *M. tuberculosis* strains among Mexican states. The mean rate was also obtained. Secondly, we compared the frequency of each site mutation associated to DR and obtained the most frequent. Thirdly, we obtained the frequency of shared types found in each study and compared it among Mexican states. Clustering rates were also determined (clustered shared type, representing two or more identical shared type found within study/state; unique, representing a single shared type found within study/state). As well,

we searched specifically for strains belonging to the Beijing genotype.

Additional data not included in the studies, such as spoligotype description and frequency and geographical distribution of DR associated mutations, was supplemented with the multimarker database for *M. tuberculosis* (SITVITWEB)[6] and the TB Drug Resistance Mutation Database (TBDReaMDB).[7]

Results

Because the study designs, participants, interventions, and reported outcome measures varied markedly, we focused on describing the studies, their results, their applicability, and their limitations and on qualitative synthesis rather than meta-analysis. Thirty studies selected for the review were published in English and three in Spanish (figure 1). The included studies involved 3 969 *M. tuberculosis* strains from TB patients. The main inclusion criteria entailed strains from Mexico with phenotypic DR and/or MDR rate evaluation, genotypic DR and/or genetic diversity analysis (supplemental table I).

Phenotypic data was available for seven studies using the proportion method (n=800), seven using the radiometric (BACTEC) method (n=1 591) and one using both methods (n=303). In table I, phenotypic DR reports published between 1995 and 2013 are listed, and these represent a total of 2 694 isolates analyzed from 22 Mexican states.[8-22] The overall mean DR and MDR rates were 37.5% and 20.6%, respectively. The states with the highest DR rates were Chiapas (72.2%),[9] the Distrito Federal and the State of Mexico (68.3%),[12] and Nuevo Leon (53.5%).[14] As well, the highest MDR rates were reported in Chiapas (66.7%),[10] Chiapas (53%)[9] and Nuevo Leon (33.3%).[15] Moreover, the lowest DR rates were reported in Baja California, Oaxaca and Sinaloa (21%),[21]

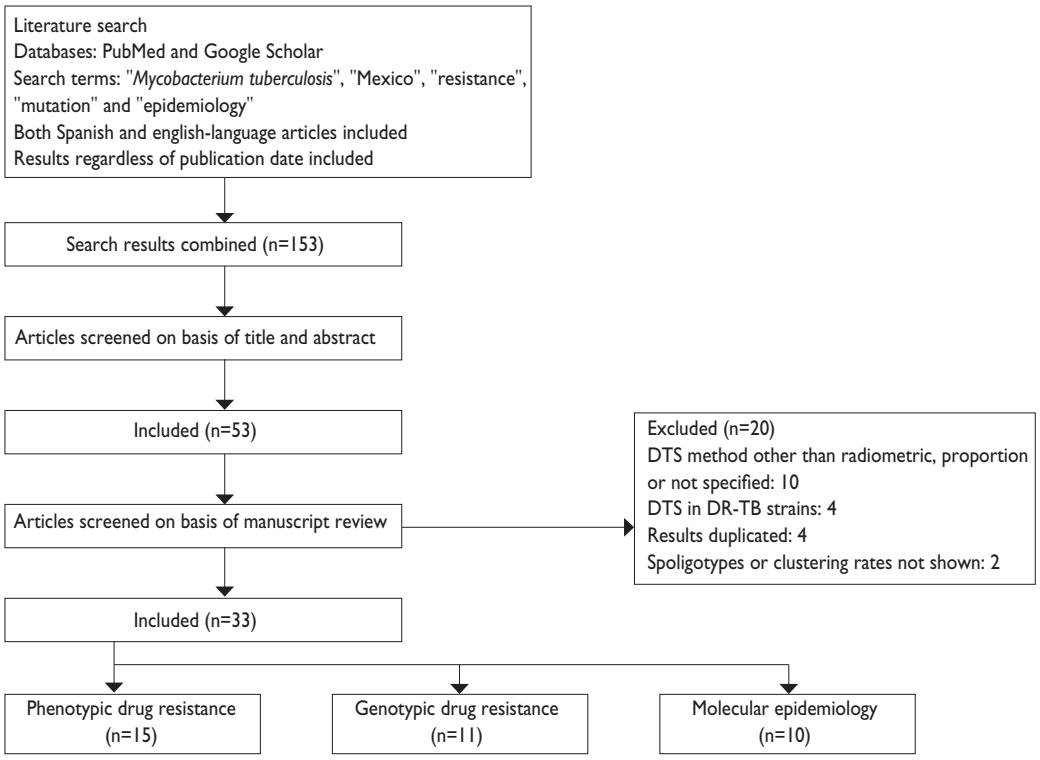


Figure 1. Flow diagram of study selection. A total of 33 studies involving 3 969 clinical strains were identified for inclusion in the review. The MEDLINE search provided a total of 153 citations: 92 citations were of phenotypic DR, 29 citations were of genotypic DR and 32 studies were of either spoligotyping, RFLP and MIRU-VNTR. Of those, 91 studies were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the criteria. Three additional studies were discarded because full texts of the studies were not available. The full texts of the remaining 59 citations were examined in more detail. It appeared that 31 studies did not meet the inclusion criteria as described. An additional five studies that met the criteria for inclusion were identified by checking the references of located, relevant papers and searching for studies that have cited these papers. No unpublished relevant studies were obtained

Table I
Reports of drug-resistant *M. tuberculosis* strains identified in several states of Mexico between 1995 and 2013

State[a]	Method	No. of isolates	Year	% Drug-resistant isolates[b]					Overall resistance (%)	MDR[c] rated (%)	Population/ criteria[d]	Ref. no.
				INH	RIF	EMB	STR	PZA				
BC	Radiometric	427	1998	28.8	-	12.2	-	-	41.0	17.0	Patients with pulmonary TB	8
CHP	Proportion	18	1995	76.9	69.2	46.2	53.8	15.4	72.2	53.0	Patients with pulmonary TB	9
	Proportion	61	1999	86.7	-	-	-	-	24.2	66.7	Patients with pulmonary TB	10
COAH±	Proportion	22	2004	13.6	4.5	0	18.1	9	32.0	4.5	Patients with pulmonary TB	11
DF, MEX±	Proportion, radiometric	303	2001	8.3	8.9	-	-	-	68.3	30.0	Patients with pulmonary TB	12
NL	Proportion	186	2001	24.0	22.0	13.0	22.0	-	32.0	18.0	Patients who attended the clinic	13
	Radiometric	101	2001	-	-	-	-	-	53.5	19.8	Patients with pulmonary TB	14
	Proportion	180	2010	18.9	18.9	-	-	-	52.2	33.3	Patients who attended the clinic	15
	Radiometric	139	2013	37.4	17.3	18.7	25.9	18.7	47.5	17.3	Patients with pulmonary TB	16
SLP±	Proportion	237	2013	3.8	0.84	-	-	-	9.7	4.22	Patients with pulmonary TB	17
SIN±	Radiometric	66	2006	27.2	18.1	18.1	21.2	15.1	37.8	18.1	Case-patients	18
TAM	Proportion	96	2010	13.5	8.3	-	-	-	19.8	2.1	Consecutive clinical isolates	19
VER	Radiometric	308	2001	12.0	8.1	3.9	4.9	-	25.0	6.2	Patients with persistent cough and AFB	20
BC, OAX, SIN±	Radiometric	460	2000	19.1	9.3	6.3	15.9	5.4	21.0	7.4	Patients with pulmonary TB	21
18 states*	Radiometric	90	2011	23.3	11.1	10.0	12.2	8.8	26.7	11.1	Patients with pulmonary and extrapulmonary TB	22
Mean				28.1	16.4	14.3	21.8	12.1	37.5	20.6		

[a] BC: Baja California; CHP: Chiapas; COAH: Coahuila; COL: Colima; DF: Distrito Federal; DUR: Durango; GUA: Guanajuato; GRO: Guerrero; HID: Hidalgo; JAL: Jalisco; MEX: State of Mexico; NAY: Nayarit; NL: Nuevo Leon; OAX: Oaxaca; PUE: Puebla; QUE: Queretaro; SLP: San Luis Potosi; SIN: Sinaloa; TAB: Tabasco; TAM: Tamaulipas; VER: Veracruz; YUC: Yucatan. *BC, CHP, COL, DF, DUR, GUA, GRO, HID, JAL, MEX, NAY, OAX, PUE, QUE, SIN, TAB, TAM, YUC. ±Quality tests included
[b] INH: Isoniazid, RIF: Rifampicin, EMB: Ethambutol, STR: Streptomycin, PZA: Pyrazinamide
[c] MDR: Multidrug resistant
[d] AFB: Acid-Fast Bacilli

Tamaulipas (19.8%)[19] and San Luis Potosi (9.7%).[17] The lowest MDR rates were reported in Coahuila (4.5%),[11] San Luis Potosi (4.2%)[17] and Tamaulipas (2.1%).[19]

Genotypic DR data were available for twelve studies (n=748). Table II lists the gene mutations currently associated with DR strains of *M. tuberculosis* reported in Mexico.[15, 19, 23-33] The most frequent mutations were *rpoB*531 (53.1%), *rpoB*526 (36.3%) and *rpoB*516 (19.5%) in RIF-resistant strains; *katG*315 (50.6%), position -15 of *inhA* (14.8%) and position -32 of *ahpC* (9.4%) in INH-resistant strains; *embB*306 (32.1%) and *embB*406 (8.1%) in ethambutol (EMB) resistant strains; *rpsL*43 (14.6%) and *rrs*513 (8.8%) in STR (streptomycin) resistant strains and *pncA*359 (16.7%) in pyrazinamide (PZA) resistant strains. In addition, a high number of previously unreported mutations in *rpoB*,[24, 26, 27, 29, 30] *katG*,[26, 29] *rrs*[26, 32] and *pncA*[33] were found, many of which are not included in the TBDReaMDB.

Genetic diversity data were available for ten studies. Three of them used RFLP analysis (n=807), and high clustering rates were discovered in Veracruz (36%)[20] and Nuevo Leon (39%)[13] for drug susceptible isolates. In contrast, the Mexican states of Tamaulipas and Chihuahua had a high clustering rate (46%) for MDR isolates.[34] Two of them reported an analysis of the genetic diversity of mycobacterial strains using MIRU-VNTR. One analysis included strains isolated exclusively from HIV-infected patients from the Distrito Federal,[30] and the other included only MDR strains from 23 different states.[35] A wide variability in the *M. tuberculosis* strains was observed in both studies, with most of the genotypes being unique.[30, 35]

Eight studies used spoligotyping for genetic diversity analysis (n=1 237). In table III, a description of the *M. tuberculosis* shared types reported in Mexico so far are listed, and 26 states of Mexico and the Distrito Federal were included.[15, 17, 22, 30, 34-37] The most predominant clades identified to date include the Haarlem (H) clade, the Latin American-Mediterranean (LAM) clade, the X

Table II

Mutations in genes associated with drug resistance in *M. tuberculosis* strains reported in seven states in Mexico from year 2001 to 2013

Gene[a]	*Codon or Nucleotide*	*Mutation*[b]	*State*[c] *(Mutation rate in local sample, %)*	*Total mutation rate (%)*[d]	*Total codon mutation rate (%)*	*Ref.*
RIF Resistance						
rpoB	469	GAG→TCG[2]	DF (50*)	-*	50.0	30
	509	AGC→CAG[1]	VER (6.7)	6.7	6.7	29
	510	CAG→AAG[1]	VER (6.7)	6.7	6.7	29
	511	CTG→CCG	DUR (19), DF (18.8)	18.9	18.9	23
	513	CAA→AAA	DF (5.7)	5.7	8.6	24
		CAA→CCA	DF (2.9)	2.9		24
	516	GAC→GTC	TAM (25), DF (14.3), VER (6.7), NL (7.1, 5.4, 1.8)	10.1	19.5	15, 19, 24-26, 29
		GAC→TAC	VER (6.7)	6.7		29
		GAC→GAG	NL (2.7)	2.7		26
	522	TCG→TTG	NL (8.1), DF (2.9)	5.5	12.6	24, 26
		TCG→CAG	NL (7.1)	7.1		15
	524	TTG→TCG[1]	VER (6.7)	6.7	6.7	29
	526	CAC→TAC	NL (22.8, 21.4, 13.5), SON (15.4), DF (14.3)	17.5	36.3	15, 24-26, 31
		CAC→GAC	VER (13.4), DF (11.4), NL (9.1, 8.1, 7.0), DUR (4.8)	9.0		19, 23-26, 29
		CAC→CGC	TAM (50*), NL (3.0)	3.0*		19
		CAC→TGC	VER (6.7), NL (3.0, 2.7)	4.1		19, 26, 29
		CAC→AAC	NL (2.7)	2.7		26
	528	CGC→CCT[1]	VER (6.7)	6.7	6.7	29
	530	CTG→GCT[2]	DF/PUE/VER (1.6)	1.6	1.6	27
	531	TCG→TTG	NL (54.4, 48.5, 40.5, 28.6), VER (33.3) DF (50*, 28.6, 12.5), DF/PUE/VER (35.9), SON (30.8), DUR (14.3)	32.7*	53.1	15, 19, 23-27, 29-31
		TCG→TGG	VER (13.4), DF/PUE/VER(12.5), NL (6.1), DF (2.9)	8.7		19, 24, 27, 29
		TCG→CCG[2]	DF (2.9)	2.9		24
		TCG→GCG[2]	DF (5.8)	5.8		24
		TCG→TTC[2]	DF/PUE/VER (3.1), DF (2.9)	3.0		24, 27
	533	CTG→CCC	DF/PUE/VER (1.6)	1.6	6.1	27
		CTG→GCG	DF/PUE/VER (1.6)	1.6		27
		CTG→CCG	DF (2.9), NL (2.7, 3.0)	2.9		19, 24, 26
	561	ATC→GTC[1]	NL (2.7)	2.7	2.7	26
	572	ATC→TTC	DF (2.9), DF/PUE/VER (1.6)	2.3	2.3	24, 27
INH Resistance						
katG	29-353	Deletion[1]	NL (2.7)	2.7	2.7	26
	249	CGC→TGC[1]	NL (5.4)	5.4	5.4	26
	271	ACC→S[3]	NL (7.1)	7.1	14.2	15
		ACC→P[3]	NL (7.1)	7.1		15
	275	ACC→TCC[1]	NL (2.7)	2.7	2.7	26
	307	GGA→GAA[1]	NL (2.7)	2.7	2.7	26
	311	GAC→GAG[1]	VER (5.9)	5.9	5.9	29
	315	AGC→ACC	DF (100*), NL (64.9, 53.7, 35.7), VER (52.9), SON (42.9)	47.9*	50.6	15, 25, 26, 29-31
		AGC→ACA	NL (2.7)	2.7		26
	318	GAG→GTA[1]	VER (5.9)	5.9	5.9	29
	328	TGG→TGC	VER (5.9)	5.9	5.9	29
	331	AGT→TGT[1]	VER (5.9)	5.9	5.9	29
	727	GCC→GAC[1]	NL (2.7)	2.7	2.7	26
inhA	-15	C→T	SON (28.6), NL (8.1), TAM (7.7)	14.8	14.8	19, 26, 31
oxyR-ahpC	-39	C→T	NL (3.1)	3.1	3.1	19
	-32	G→A	NL (9.4)	9.4	9.4	19
	-17; -12	+A; +CCA[2]	SON (8.3)	8.3	8.3	31
	-10	C→T	NL (3.1)	3.1	3.1	19
EMB Resistance						
embB	306	ATG→ATA	NL (18.9), DF/PUE/VER (5.9)	12.4	32.1	26, 28
		ATG→CTG	DF/PUE/VER (11.8), NL (2.7)	7.3		26, 28
		ATG→ATC	DF/PUE/VER (5.9), NL (2.7)	4.3		26, 28
		ATG→GTG	NL (2.7)	2.7		26
		ATG→ATT	NL (5.4)	5.4		26
	406	GGC→GAC	NL (5.4)	5.4	8.1	26
		GGC→GCC	NL (2.7)	2.7		26
STR Resistance						
rrs	189	G→A[1]	NL (2.7)	2.7	2.7	26
	426	G→T[1]	NL (2.7)	2.7	2.7	26
	483	A→T[2]	VER (2.2)	2.2	2.2	32

continúa…

	485	A→G[2]	VER (2.2)	2.2	2.2	32
	491	C→T	NL (8.1)	8.1	8.1	26
	496	G→A[2]	VER (2.2)	2.2	2.2	32
	513	A→C	VER (8.8)	8.8	8.8	32
	516	C→T	VER (6.6), NL (2.7)	4.7	4.7	26
	795	C→T[2]	VER (6.6)	6.6	6.6	32
	870	C→T[2]	VER (3.3)	3.3	3.3	32
	907	A→C[2]	VER (3.3)	3.3	3.3	32
	1238	T→C[1]	NL (8.1)	8.1	8.1	26
rpsL	43	AAG→AGG	NL (16.2), VER (13)	14.6	14.6	26
	88	AAG→AGG	VER (4)	4.0	6.0	32
		AAG→CAG	VER (2)	2.0		32
PZA Resistance						
pncA	35	A→C	VER (4.8)	4.8	4.8	33
	139	A→G	VER (2.4)	2.4	2.4	33
	141	+GGCAACC[2]	VER (2.4)	2.4	2.4	33
	145	G→C	VER (2.4)	2.4	2.4	33
	161	C→T	VER (2.4)	2.4	2.4	33
	188	A→C[2]	VER (2.4)	2.4	2.4	33
	202	T→G	VER (2.4)	2.4	2.4	33
	211	C→T	VER (2.4)	2.4	2.4	33
	225	T→C	VER (4.8)	4.8	4.8	33
	226	A→C	VER (2.4)	2.4	2.4	33
	281	T→C[2]	VER (2.4)	2.4	2.4	33
	287	A→G[2]	VER (9.5)	9.5	9.5	33
	305	C→T	VER (2.4)	2.4	2.4	33
	359	T→C	VER (16.7)	16.7	16.7	33
	374	G→T[2]	VER (2.4)	2.4	2.4	33
	375	+C[2]	VER (2.4)	2.4	2.4	33
	379-408	-30 bp [2]	VER (2.4)	2.4	2.4	33
	380-388	-9 bp[2]	VER (2.4)	2.4	2.4	33
	390	+CGG	VER (2.4)	2.4	2.4	33
	391	+C	VER (2.4)	2.4	2.4	33
	415	G→C	VER (2.4)	2.4	2.4	33
	427	G→C[2]	VER (2.4)	2.4	2.4	33
	440	-1 pb[2]	VER (2.4)	2.4	2.4	33
	479	C→A[2]	VER (2.4)	2.4	2.4	33
	487-496	-10 bp[2]	VER (2.4)	2.4	2.4	33
	515	T→C	VER (2.4)	2.4	2.4	33

[a] INH: Isoniazid; RIF: Rifampicin; EMB: Ethambutol; STR: Streptomycin; PZA: Pyrazinamide

[b] 1Novel mutation; 2 Novel mutation not reported in the Tuberculosis Drug Resistance Mutation Database; 3 Mutations reported at the amino acid level. +: Insertion; -: Deletion

[c] DF: Distrito Federal; DUR: Durango; NL: Nuevo Leon; PUE: Puebla; SON: Sonora; TAM: Tamaulipas; VER: Veracruz

[d] *Mutation rate from local sample was not included in the total mutation rate as the number of isolates analyzed was too low

clade, and the T clade, which were detected in almost all of the states analyzed (table III, supplemental figure S1). The associated sublineages include T1, LAM9, H3, and H1. Specifically, the most predominant shared types were SIT53 (T1, n=188, 3.9%), SIT119 (X1, n=125, 6.9%), SIT19 (EAI2-Manila, n=80, 6.3%) and SIT42 (LAM9, n=77, 3.0%). As well, clustering of spoligotypes is frequent. SIT1 Beijing genotype has been reported in Puebla,[36] Jalisco,[22] Baja California, Sinaloa, Veracruz[35] and San Luis Potosi.[17] A high number of spoligotypes previously unreported in the global database were detected (58% in Guerrero,[37] 34% in Distrito Federal[30]), which were not included in our results.

Discussion

Some acceptable evidence from comparison of DR and MDR levels of *M. tuberculosis* strains from Mexico indicated higher rates than those presented in a nationally representative survey conducted during 2008-2009 in nine states (DR=7.8% and MDR=2.8%).[38] This indicates that the prevalence of DR and MDR is a remaining issue.

The evidence regarding genotypic DR analysis is weak. Currently, only seven states (Nuevo Leon, Veracruz, Distrito Federal, Sonora, Tamaulipas, Puebla, and Durango) in Mexico have been studied to detect mutations associated with DR-TB strains. As such, the

Table III

DESCRIPTION OF *M. TUBERCULOSIS* SHARED TYPES REPORTED FOR TB STRAINS ISOLATED IN MEXICO IN 26 STATES AND DISTRITO FEDERAL FROM 2002 TO 2013

SIT[a]	*Spoligotype description*	*Octal number*	*Clade*[b]	*Cluster patterns*[c]	*Mexican state (%)*[d]	*Mean rate (%)*	*Total strains*	*Ref.*
1	□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□■■■■■■■■■	000000000003771	Beijing	Clustered	PUE (5.9), SLP (1.3), JAL (1.1), BC (0.9), SIN (0.9), VER (0.9)	1.8	9	17, 22, 35, 36
2	□□□□□□□□□□□□□□□□□□□□□□□■□□□□□□■□□□□■■■■■■■■■	000000004020771	H2	Clustered	CHH/TAM (3.2), DF (2.1), SLP (0.9), GRO (0.8)	1.8	12	17, 30, 34, 37
3	□□□□□□□□□□□□□□□□□□□□□□□□■■■■■■□■□□□□■■■■■■■	000000007720771	H3	Clustered	CHH/TAM (4.1), JAL (1.1), NL (1.1)	2.1	16	15, 22, 34
4	□□□□□□□□□□□□□□□□□□□□□□□□■■■■■■■■□□□□■■■■■■■	000000007760771	U	Unique	SLP (0.4)	0.4	1	17
8	■□□□□□□□□□□□■■■■■■■■■■■■■■■□□□□■□■■■■■■■■■	400037777413771	EAI5	Clustered	GRO (6.7), JAL (0.9)	3.8	34	35, 37
17	■■□■■■■■■■■□■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	677737607760771	LAM2	Clustered	SLP (1.3), JAL (1.1), PUE (0.9), GRO (0.4)	0.9	6	17, 22, 35, 37
19	■■□■■■■■■■■■■■■■■□□■■■■■■■□□□□■□■■■■■■■■■	677777477413771	EAI2 Manila	Clustered*	GRO (13.5), PUE (8.8), SLP (1.7), NL (1.1)	6.3	80	15, 17, 35-37
20	■■□■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	677777607760771	LAM1	Clustered	SLP (3), NL (2.8), GRO (1.2), HID (1.1)	2.0	18	15, 17, 22, 35, 37
33	■■■■■■■■□□□■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	776177607760771	LAM3	Clustered	JAL (1.1), SIN (1.1), SLP (0.9), NL (0.6), GRO (0.4)	0.8	6	15, 17, 22, 37
34	■■■■■■■■□□■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	776377777760771	S	Clustered	GRO (1.9), TAB (1.1), NL (0.6)	1.2	7	15, 22, 37
37	■■■■■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	777737777760771	T3	Clustered	SLP (0.9)	0.9	2	17
42	■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	777777607760771	LAM9	Clustered*	DF (11.5), CHH/TAM (6.1), SLP (6.0), GRO (2.9), JAL (2.2), SIN (2.2), TAM (2.2), GUA (1.1), MEX (1.1), NL (1.1), PUE (1.1), CHP (1.0), YUC (0.9)	3.0	77	15, 17, 22, 30, 34-37
46	■■■■■■■■■■■■■■■■■■■■■■■□□□□□□□□□□□□□□□□□□□	777777770000000	U	Clustered	GRO (0.8), NL (0.6)	0.7	3	15, 37
47	■■■■■■■■■■■■■■■■■■■■■■■□□□□□□■□□□□■■■■■■■	777777774020771	H1	Clustered	DF (4.2), CHH/TAM (3.2), GUA (2.2), NL (2.2), GRO (1.5), BC (1.1), SIN (1.1), MICH (0.9), SLP (0.4)	1.9	26	15, 17, 22, 30, 34, 35, 37
49	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□■□□□□■■■□■■■	777777777720731	H3	Unique	MEX (1.1), SIN (1.1), NL (0.6)	0.9	3	15, 22
50	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□■□□□□■■■■■■■	777777777720771	H3	Clustered	DF (4.2), SLP (2.2), BC (1.1), COL (1.1), NL (1.1), PUE (1.1), COAH (0.9), GRO (0.9)	1.6	15	15, 17, 22, 30, 35, 37
51	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■□□□□	777777777760700	T1	Unique	GRO (0.4), SLP (0.4)	0.4	2	17, 37
52	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■□■■■	777777777760731	T2	Clustered	NL (2.8), GRO (1.1), HID (0.9), SLP (0.9)	1.4	10	15, 17, 35, 37
53	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	777777777760771	T1	Clustered*	SLP (29.3), NL (23.9), GRO (5.9), DF (5.7), CHP (2.8), DUR (2.8), NAY (2.8), GUA (2.2), CHH/TAM (1.9), COAH (1.8), SON (1.8), BC (1.6), JAL (1.6), PUE (1.1), SIN (1.1), OAX (1.0), AGS (0.9), BCS (0.9), COL (0.9), HID (0.9), MEX (0.9), MICH (0.9), TAM (0.9), YUC (0.9)	3.9	188	15, 17, 22, 30, 34-37
54	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□■■■■■■■■■	777777777763771	Manu2	Clustered	GRO (1.5), SLP (0.4)	1.0	5	17, 37
60	■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■□■■■	777777607760731	LAM4	Unique	GRO (0.4), SLP (0.4)	0.4	2	17, 37
64	■■■■■■■■■■■■■■■■■■■□□□□■■■■□■■■□□□□■■■■■■■	777777607560771	LAM6	Clustered	NL (1.1),CHH/TAM (1.0), NAY (0.9)	1.0	6	15, 34, 35
70	■■■□□□□□□□□□■■■■■□■■■■■■■■■■■■■■□□□□■■□■■■■	700076777760671	X3	Clustered	GUA (2.2), BC (1.1), NL (1.7)	1.7	6	15, 22
73	■■■■■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■□■■■	777737777760731	T3-T2	Clustered	NL (2.2)	2.2	4	15
78	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■□□■■	777777777760711	T	Unique	SLP (0.4)	0.4	1	17
81	■■■■■■■■■□■■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	777377607760771	LAM9	Unique	JAL (1.1), GRO (0.4)	0.8	2	22, 37
91	■■■□□□□□□□□□■■■■■□■■■■■■■■■■■■■■□□□□■■■■■■■	700036777760771	X3	Unique	BC (1.1), GRO (0.4)	0.8	2	22, 37

continúa…

92		700076777760771	X3	Clustered	CHH/TAM (3.8), NL (4.4), TAM (1.1), GRO (0.8)	2.5	23	15, 22, 34, 37
93		77773760776071	LAM5	Unique	TAB (0.9)	0.9	1	35
95		777777607560731	LAM6	Unique	NAY (1.1), GRO (0.4)	0.8	2	22, 37
97		777777760760771	T1	Unique	SLP (0.4)	0.4	1	17
100		777777777773771	Manu1	Clustered	GRO (1.1)	1.1	3	37
106		776177400000171	U	Unique	SLP (0.4)	0.4	1	17
111		776167607760771	LAM3	Unique	CHP (0.9)	0.9	1	35
118		777767777760771	T1	Clustered	NAY (1.8), MICH (0.9), GRO (0.9, 0.4)	1.0	5	35, 37
119		777776777760771	X1	Clustered*	CHH/TAM (28.4), NL (15.6), DF (6.3), JAL (1.1), SIN (1.1), TAM (1.1), YUC (1.1), SLP (0.4)	6.9	125	15, 17, 22, 30, 34
120		777777577760771	T1	Unique	NL (0.6)	0.6	1	15
125		000000007760731	LAM3	Clustered	SLP (0.9)	0.9	2	17
130		776177607760731	LAM3	Unique	BC (1.1)	1.1	1	22
137		777776777760601	X2	Clustered	DF (4.2), NL (0.6)	2.4	3	15, 30
150		777767607760771	LAM9	Unique	SLP (0.4)	0.4	1	17
151		777767774020771	H1	Unique	SLP (0.4)	0.4	1	17
154		757777777760771	T1	Unique	SLP (0.4)	0.4	1	17
168		777777777720671	H3	Unique	NL (0.6)	0.6	1	15
173		777767677760771	T1	Unique	SLP (0.4)	0.4	1	17
175		777777677760731	T2	Unique	GUA (0.9)	0.9	1	35
176		777737607560771	LAM6	Clustered	NL (1.1)	1.1	2	15
194		677737607760731	LAM2	Clustered	SLP (0.9)	0.9	2	17
197		700036777760731	X3	Unique	SLP (0.4)	0.4	1	17
205		737777777760771	T1	Unique	PUE (0.9), SLP (0.4)	0.7	2	17, 35
207		767777777720771	H3	Clustered	NL (1.7)	1.7	3	15
209		776017607760771	LAM12-Madrid1	Unique	JAL (0.9)	0.9	1	35
211		776137607760771	LAM3	Clustered	NL (3.3), CHH/TAM (1.3), GRO (0.4), SLP (0.4)	1.4	12	15, 17, 34, 37
215		777703777360771	T	Unique	SLP (0.4)	0.4	1	17
217		777736777760771	X1	Clustered	NL (1.7), TAB (0.9)	1.3	4	15, 35
221		777766777760771	X1	Clustered	SLP (3)	3	7	17
232		777777760000171	U	Unique	DUR (0.9), NL (0.6), SLP (0.4)	0.6	3	15, 17, 35
236		777777777413771	EAI5	Clustered	GRO (0.8)	0.8	2	37
239		777777777760031	T2	Clustered	SLP (2.6), NL (1.7), GRO (1.1), CHH/TAM (0.6)	1.5	12	15, 17, 22, 34
244		777777777760601	T1	Unique	SLP (0.4)	0.4	1	17
245		777777777760671	T1	Unique	SLP (0.4)	0.4	1	17
258		000000177760771	T	Clustered	SLP (1.3)	1.3	3	17
274		777777600000371	U	Unique	DF (2.1)	2.1	1	30
281		777775777760771	T1	Unique	MICH (0.9)	0.9	1	35

continúa…

287	■■■■■■■■■■■■■■■■■■■■■■□□■■■■■■■■□□□□■□■■■■■■■□■■	677777477413751	E A I 2 - Manila	Clustered	GRO (0.8)	0.8	2	37
291	■■■■■■■■■■■■■■■■■■■■■□■■■■■■■■■■□□□□■■■■■■■	777777677760771	T1	Unique	CHP (0.9), GRO (0.4)	0.7	2	35, 37
334	■□■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	577777777760771	T1	Clustered	PUE (2.9), COAH (0.9), NAY (0.9), TAM (0.9), SLP (0.4)	1.2	5	17, 35, 36
336	■■■■■■■■■■■■■■■■□■■■■■■■■■■■■■■□□□□■■■□■■■	777776777760731	X1, T2	Clustered	NL (1.1)	1.1	2	15
342	■■□■■■■■■■■■■■■■■■■■■■■■■■■□□□□■□■■■■■■■■■	677777777413771	EAI5	Clustered	GRO (3)	3.0	8	37
344	■■■□□□□□□□□■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	700077777760771	T1	Unique	CHP (0.9)	0.9	1	35
373	■■■■■■■■■■■■■■■■■■■■■■■□■■■■■■■■□□□□■■■■■■■	777777767760771	T1	Unique	TAM (1.1)	1.1	1	22
389	■□■■■■■■■■■■■■□■■■■■□□□□■■■■■■■■□□□□■■■■■■■	677767607760771	LAM1	Unique	SLP (0.4)	0.4	1	17
398	■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■□□■■■	777777607760631	LAM4	Clustered	GRO (1.5), GUA (1.1)	1.3	5	22, 37
449	■■■■■■■■■■■■■■■■■□■■■■□■■■■■■■■□□□□■■■■■■■	777776757760771	X1, T5	Unique	NL (0.6)	0.6	1	15
450	■■■■■■■■■■■■■■■■■□■■■■■■□□□□□□□□□□□□□□□□□□	777776770000000	U	Clustered	DF (1.1), CHH/TAM (0.6), NL (0.6)	0.8	4	15, 22, 34
453	■■■■■■■■■■■■■■■■■■■■□■■■■■■■■□■■■□□□□■■■■■■■	777777677560771	T1	Unique	SLP (0.4)	0.4	1	17
457	■■■■■■■■■■■■■■■■■■■■■■■■■□■■□■□□□□■■■■■■■	777777777320771	H3	Unique	SLP (0.4)	0.4	1	17
478	■■□□□■■■■■■■■■■■□■■■■■■■■■■■■■□□□□■■□□□□■	617776777760601	X2	Clustered	CHH/TAM (3.5), NL (2.2)	2.9	15	15, 34
508	■■■■■■■■■■■■■■■■■□□■■■■■■■■■■■■■□□□□■■■■■■■	777776377760771	T1	Clustered	DF (8.3)	8.3	4	30
519	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□□□■■■■■■	777777777740371	T1	Unique	NL (0.6)	0.6	1	15
522	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■□	777777777760770	T1	Unique	NL (0.6)	0.6	1	15
535	■■■■■■■■■■■■■■■■■■■■■■□□□■■■■■■■■□□□□■■■■■■■	777777770760771	T1	Unique	SLP (0.4)	0.4	1	17
573	■■■■■■■■■■■■■■■■■■■■□■■□□■■■□■■■□□□□■■■■■■■	777777663560771	T1	Unique	NL (0.6)	0.6	1	15
732	■■■■■■■■■■■■■■□□■■■■■■■■■■■■■■■■□□□□■■■■■■■	777763777760771	T1	Clustered	DF (4.2)	4.2	2	30
756	■■□■■■□■■■■■■■■■■■■□□■■■■■■■□□□□■□■■■■■■■■■	673777477413771	E A I 2 - Manila	Unique	GRO (0.4)	0.4	1	37
787	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□□□■■■■■	777777777760071	T1	Clustered	SLP (2.2), MEX (0.9)	1.6	6	17, 35
804	■□□■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	477777777760771	T1	Unique	JAL (1.1)	1.1	1	22
866	■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	577777607760771	LAM9	Unique	SIN (0.9)	0.9	1	35
879	■■■■■■■■■■■■■■□■■■■■■■■■■■■■■■■□□□□■■□■■■■	777767777760671	T1	Unique	SLP (0.4)	0.4	1	17
880	■■■■■■■■■■■■■■■■■□□□□□□□□■■■■■□□□□■■■■■■■	777777000760771	T1	Clustered	GRO (0.8)	0.8	2	37
888	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□■■□□■■■	777777777760631	T2	Unique	COAH (0.9)	0.9	1	35
892	■■■■■■■■■■■■■■■■■■□□■■■■■■■■□□□□■□■■■■■■■■■	777777477413771	EAI5	Clustered	GRO (1.5), TAM (0.9)	1.2	5	35, 37
894	■■□■■■■■■■■■■■■■■■□□■■■■■■■■□□□□■□■■■■■□■■■	677777477413731	E A I 2 - Manila	Unique	GRO (0.4)	0.4	1	37
913	■■■■■■■■■■■■■□□□■■■■■■■■■■■■■■■■□□□□■■■■■■■	777743777760771	T1	Unique	BCS (0.9)	0.9	1	35
948	■■■■■■■■■■■■■■■■■■■■■□□□□□□□□■□□□□■■□□□■■	777777760020611	H3	Unique	DF (2.1)	2.1	1	30
1053	■■■■■■■■■■■■■□■■■■■□□■■■■■■■■■■□□□□■■■■■■■	777767637760771	T1	Unique	COAH (0.9), SLP (0.4)	0.7	2	17, 35
1060	■■■■■■■■■■■■■■■■■■■■■■■■□□□■■■□□□□■■■■■■■	777777776160771	T1	Unique	GRO (0.9)	0.9	1	35
1142	■■■■■■■■■■■■■■■■■■■■■■■■■■■■■□■□□□□□□■■■■■	777777777720071	H3	Unique	SLP (0.4)	0.4	1	17
1166	■■■■■■■■■□■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	777377777760771	T1	Unique	MEX (1.1)	1.1	1	22
1193	■■■■■■■■■■■■■■■■■■■■□■■■■■■■■■■■□■■■■■■■■■	777777677773771	Manu1	Clustered	GRO (1.1), MEX (1.1), YUC (1.1)	1.1	5	22, 37

continúa…

1210	□□□□□■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	01777760776071	LAM1	Clustered	CHH/TAM (0.6)	0.6	2	34
1211	■□■■■■■■□□■■■■■■■■■■■■■■■■■■■■■□□□□■■■■■■■	576377777760771	S	Clustered	NL (5)	5.0	9	15
1215	■■□■■■■■■■■□■■■□■■■□□□□■■■■■■■■□□□□■■■■■■■	67773560776071	LAM2	Clustered	NL (1.7)	1.7	3	15
1219	■■■□■■■■■■■■■■■■■■□□□■□□■■■□■■■□□□□■■■■■■■	737777423560771	T1	Clustered	CHH/TAM (1.3)	1.3	4	34
1221	■■■■□■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	757767777760771	T1	Unique	SLP (0.4)	0.4	1	17
1224	■■■■■■■■□□□■■■■■■■■■□□□□■■■■■■■■□□□□■■■□□□□	776177607760700	LAM3	Clustered	GRO (0.8), NL (0.6)	0.7	3	15, 37
1236	■■■■■■■■■■■■■■■■■■■■■■■□□□□□□□□□□□□□■■□□□■■	777777760000611	U	Clustered	NL (1.1)	1.1	2	15
1243	■■■■■■■■■□■■■■■■■■■■■■■■■■■□■□□□□■■■■■■■	777377777720771	H3	Unique	DF (1.1), JAL (1.1)	1.1	2	22
1277	■■■■■■■■■■■■■■■■■□■□□□□■■■■■■■■□□□□■■■■■■■	777777207760771	LAM9	Clustered	TAB (1.1), SLP (0.9), NL (0.6)	0.9	4	15, 17, 22
1318	■□■■■■■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	577767777760771	T1	Unique	SLP (0.4)	0.4	1	17
1321	■■□■■■■■■■■■■■■■■■■□□□□■■■■■■■■□□□□■■■□■■■	677777607760731	LAM1, LAM4	Unique	SLP (0.4)	0.4	1	17
1329	■■■■■■■■■■■■■■■■□■■■■■■■■■□■■■□□□□■■■■■■■	777776777560771	X1	Unique	NL (0.6)	0.6	1	15
1394	■■■■■■■■■■■■■■■■□■■■■■■■■■■■■■■■□□□□■■□■■■■	777776777760671	X1	Unique	NAY (0.9)	0.9	1	35
1574	■■■■■□□□□□□□□□□□□□□□□□■■■■■■■■□□□□■■■■■■■	760000007760771	LAM3	Unique	SLP (0.4)	0.4	1	17
1626	■■■■■■■■■■■■■■■■■■■■■■■■■□■■■■■□□□□■■■■■■■	777777776760771	T1	Unique	DF (2.1), SIN (1.1)	1.6	2	22, 30
1629	■■■■■■■■■■■■■■■■■■■■■■■■■□□□□□□■□□□□■■■■□■■	777777774020751	H1	Unique	NL (0.6)	0.6	1	15
1679	■■■■■■■■■■■■■■□■■■■■■□■■■■■■■■■■□□□□■■■■■■■	777767737760771	T1	Unique	CAM (0.9)	0.9	1	35
1711	■■□■■■■■■□■■■□■■■■■■■□□□□■■■■■■■■□□□□■■■■■■■	677337607760771	LAM2	Unique	JAL (1.1)	1.1	1	22
1751	■■■□□□□□□□□■■□■■□■■■■■■■■■■■■■■■□□□□■■■■■■■	700066777760771	X3	Unique	BCS (0.9)	0.9	1	35
1905	■■■■■■■■■■■■■■■■■■■■■■■■■■■□□■■□□□□■■■■■■■	777777777460771	T1	Unique	SLP (0.4)	0.4	1	17
1916	■■■■■■■■■■■■□□□□□■■■■■■■■■■■■■■■□□□□■■■■■■■	777701777760771	T1	Unique	SIN (0.9)	0.9	1	35
1952	■■■■■■■■■■■■■■■■■■■■■■■■■□□□□□□□□□□■■■■■■■	777777774000771	U	Unique	GUA (0.9)	0.9	1	35
1979	■■■■■■■■■■■■■■■■■■■■■■■■■■□□□□□□□■■■■■■■	777777777400771	U	Unique	TAB (0.9)	0.9	1	35
2070	■■■■■■■■■■■■■■■■■■■□□■■■■■■■■■□□□□■■■■■■■	777777637760771	T1	Clustered	SLP (0.9)	0.9	2	17
2111	■■■□□□□■■■■■■■■■■■■■■■■■■■■■□■□□□□■■■■■■■	701777777720771	H3	Clustered	SLP (1.3)	1.3	3	17
2188	■■■■■■■■■□■■■■■■■■■■■■■■■■■■■■■□□□□■■■□■■■	777377777760731	T2	Unique	OAX (1.1)	1.1	1	22
2337	■■■■■■■■■□■■■■■■■■■■■■■■■□□□□□□■□□□□■■■■■■■	777377774020771	H1	Unique	BC (1.1)	1.1	1	22
2356	■■■□□■■■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	717776777760771	X1	Unique	NL (0.6)	0.6	1	15
2403	■■□■■■■■■■■□■■■■■■■□□□□□□■■■■■■□□□□■■■■■■■	677737601760771	LAM	Unique	NL (0.6)	0.6	1	15
2496	■■■■■■■■■□■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	777367777760771	T1	Unique	HID (1.1)	1.1	1	22
2914	■■□■■■■■■■■■■■■■□■■■■■■■■■■■■■■■■■□□□□■■■■■■■	677776777760771	X1	Clustered	NL (1.7)	1.7	3	15

[a] In the SITVIT2 database, the spoligo international type (SIT) numbers designate spoligotypes shared by two or more patient isolates. In contrast, "orphan" designates patterns reported for a single isolate

[b] Clade designations according to the SITVIT2 database: Beijing clade, East African-Indian (EAI) clade and 9 sublineages, Haarlem (H) clade and 3 sublineages, Latin American-Mediterranean (LAM) clade and 12 sublineages, the ancestral "Manu" family and 3 sublineages, the S clade, the IS6110-low-banding X clade and 3 sublineages, and an ill-defined T clade with 5 sublineages. U: Unknown patterns

[c] *High clustering rate reported

[d] AGS: Aguascalientes; BC: Baja California; BCS: Baja California Sur; CAM: Campeche; CHP: Chiapas; CHH: Chihuahua; COAH: Coahuila; COL: Colima; DF: Distrito Federal; DUR: Durango; GUA: Guanajuato; GRO: Guerrero; HID: Hidalgo; JAL: Jalisco; MEX: State of Mexico; MICH: Michoacan; NAY: Nayarit; NL: Nuevo Leon; OAX: Oaxaca; PUE: Puebla; SIN: Sinaloa; SLP: San Luis Potosí; SON: Sonora; TAB: Tabasco; TAM: Tamaulipas; VER: Veracruz; YUC: Yucatan

assessment of the actual mutation frequency in the country is difficult.

The evidence regarding genetic diversity is acceptable enough only for spoligotyping, given that few studies using RFLP and MIRU-VNTR analysis were found. The detection of high clustering rates for spoligotypes suggests that a high transmission rate of *M. tuberculosis* clones exists in the country. As well, the detection of a high number of spoligotypes previously unreported in the global database, highlights the need for further spoligotyping analyses to be conducted in Mexico.

Beijing *M. tuberculosis* strains have been reported to have an increased ability to spread and cause disease, and accordingly, are considered hypervirulent strains. In addition, although these strains are highly prevalent throughout Asia, they have also been detected worldwide.[39] The SIT1 genotype, which belongs to the Beijing genotype of East-Asian lineage, has been reported in several states in Mexico.

Understanding the nature and frequency of mutations associated with DR-TB, as well as the distinct *M. tuberculosis* genotypes that are responsible for TB in different settings, are important for control of this disease. However, our study has several limitations. The quality, the methodology and population of the studies varied. Five of the studies did not explicitly state that evaluation of phenotypic DR data included quality control, which could lead to overestimation of actual DR levels in these studies. As well, nine studies did not include DR data for all five drugs, thus actual mean DR rate for these drugs may vary. As well, different methodologies used in the studies can difficult DR rate levels comparison. Consequently, this resulted in high degrees of variability between resistance levels found among different settings, as reported before.[40]

Conclusion

This represents the first systematic review of phenotypic and genotypic DR, and genetic diversity of *M. tuberculosis* strains from Mexico. DR-TB still remains in Mexico, and might still be increasing in some settings. The alarming lack of genotyping information available for clinical isolates of *M. tuberculosis* from Mexico, specifically MIRU-VNTR data, as well as the detection of a high number of spoligotypes previously unreported in the global database, highlights the need for additional analyses to be conducted in Mexico. Importantly, further information regarding the current genotypes that exist is needed. For example, the status of Beijing TB strains in Mexico also needs to be monitored, particularly to determine whether they are expanding. Some Beijing genotypes have been associated with MDR and the incidence rate of MDR strains and their associated mutations have not been decreasing over the past few years. Thus, additional emphasis must be placed on the search for these genotypes. Furthermore, considering that a meaningful decrease in the incidence rate of TB in Mexico has not been observed in recent years, additional studies are needed to better evaluate the transmission dynamics of TB and DR-TB.

Acknowledgements

We thank Sergio Lozano-Rodríguez, M.D., from Hospital Universitario for his review of the manuscript.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. World Health Organization. Global Tuberculosis Report 2012. WHO/HTM/TB/2011.16. Geneva, Switzerland: WHO, 2012.
2. Secretaría de Salud. Perfil Epidemiológico de la Tuberculosis en México [online monograph]. México. Sistema Nacional de Vigilancia Epidemiológica, 2012 [Accessed 2012 November 20]; Available from: http://www.dgepi.salud.gob.mx/2010/PDFS/PUBLICACIONES/2012/Monografias5_Tuberculosis_Mex_junio12.pdf.
3. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update. Tuber Lung Dis 1998;79(1):3-29.
4. Almeida Da Silva PE, Palomino JC. Molecular basis and mechanisms of drug resistance in *Mycobacterium tuberculosis*: classical and new drugs. J Antimicrob Chemother 2011;66(7):1417-1430.
5. Barnes PF, Cave MD. Molecular epidemiology of tuberculosis. N Engl J Med 2003;349(12):1149-1156.
6. Demay C, Liens B, Burguiere T, Hill V, Couvin D, Millet J *et al.* SITVITWEB--a publicly available international multimarker database for studying *Mycobacterium tuberculosis* genetic diversity and molecular epidemiology. Infect Genet Evol 2012;12(4):755-766.
7. Sandgren A, Strong M, Muthukrishnan P, Weiner BK, Church GM, Murray MB. Tuberculosis drug resistance mutation database. PLoS Med 2009;6(2):e2.
8. Peter CR, Schultz E, Moser K, Cox M, Freeman R, Ramirez-Zetina M *et al.* Drug-resistant pulmonary tuberculosis in the Baja California-San Diego County border population. West J Med 1998;169(4):208-213.
9. Alvarez-Gordillo GC, Halperin-Frisch D, Blancarte-Melendres L, Vazquez-Castellanos JL. Risk factors for antitubercular drug resistance in Chiapas, Mexico. Salud Publica Mex 1995;37(5):408-416.
10. Alvarez-Gordillo GC, Sandoval-Trujillo H, Bojalil-Jaber LF. Tuberculosis resistant to treatment with antitubercular drugs. A study in the state of Chiapas, Mexico. Aten Primaria 1999;24(4):209-214.
11. Velasco-Rodriguez VM P-GA, Esquivel-Molina C, Sanchez-Cabral O, Martinez-Ordaz V, Cicero-Sabido R. Epidemiología y resistencia primaria a farmacos en casos incidentes de tuberculosis pulmonar. Rev Med IMSS 2004;42:301-306.
12. Olvera-Castillo R. Farmacorresistencia secundaria en tuberculosis. Tendencia en el Instituto Nacional de Enfermedades Respiratorias. Rev Inst Nal Enf Resp Mex 2001;14:151-159.
13. Yang ZH, Rendon A, Flores A, Medina R, Ijaz K, Llaca J *et al.* A clinic-based molecular epidemiologic study of tuberculosis in Monterrey, Mexico. Int J Tuberc Lung Dis 2001;5(4):313-320.

14. Said-Fernandez S C-OG, Becerril-Montes P, Navarro-Marmolejo L, Valdovinos-Chavez S. Perfiles de resistencia a medicamentos antituberculosos de primera y segunda elección en cepas de *Mycobacterium tuberculosis* aisladas de enfermos con tuberculosis pulmonar radicados en el sector noroeste de la ciudad de Monterrey y atendidos por el IMSS. RESPYN 2001;4.
15. Molina-Torres CA, Moreno-Torres E, Ocampo-Candiani J, Rendon A, Blackwood K, Kremer K *et al. Mycobacterium tuberculosis* spoligotypes in Monterrey, Mexico. J Clin Microbiol 2010;48(2):448-455.
16. Becerril-Montes P, Said-Fernandez S, Luna-Herrera J, Caballero-Olin G, Enciso-Moreno JA, Martinez-Rodriguez HG *et al.* A population-based study of first and second-line drug-resistant tuberculosis in a high-burden area of the Mexico/United States border. Mem Inst Oswaldo Cruz 2013;108(2):160-166.
17. Lopez-Rocha E, Juarez-Alvarez J, Riego-Ruiz L, Enciso-Moreno L, Ortega-Aguilar F, Hernandez-Nieto J *et al.* Genetic diversity of the *Mycobacterium tuberculosis* Complex in San Luis Potosi, Mexico. BMC Res Notes 2013;6:172.
18. Zazueta-Beltran J, Muro-Amador S, Flores-Gaxiola A, Llausas-Magana E, Leon-Sicairos N, Canizalez-Roman A. High rates of multidrug-resistant *Mycobacterium tuberculosis* in Sinaloa State, Mexico. J Infect 2007;54(4):411-412.
19. Garza-Gonzalez E, Gonzalez GM, Renteria A, Cruz-Pulido W, Rivera G, Bocanegra-Garcia V. A pyrosequencing method for molecular monitoring of regions in the *inhA*, *ahpC* and *rpoB* genes of *Mycobacterium tuberculosis*. Clin Microbiol Infect 2010;16(6):607-612.
20. Garcia-Garcia ML, Sifuentes-Osornio J, Jimenez-Corona ME, Ponce-de-Leon A, Jimenez-Corona A, Bobadilla-del Valle M *et al.* Drug resistance of *Mycobacterium tuberculosis* in Orizaba, Veracruz. Implications for the tuberculosis prevention and control program. Rev Invest Clin 2001;53(4):315-323.
21. Granich RM, Balandrano S, Santaella AJ, Binkin NJ, Castro KG, Marquez-Fiol A *et al.* Survey of drug resistance of *Mycobacterium tuberculosis* in 3 Mexican states, 1997. Arch Intern Med 2000;160(5):639-644.
22. Macias-Parra M, Kumate-Rodriguez J, Arredondo-Garcia JL, Lopez-Vidal Y, Castanon-Arreola M, Balandrano S *et al.* Mycobacterium tuberculosis Complex Genotype Diversity and Drug Resistance Profiles in a Pediatric Population in Mexico. Tuberc Res Treat 2011;2011:239042.
23. Alvarado-Esquivel C, Rossau R, Martinez-Garcia S, Cisneros-Martinez JA, Mijs W, Nevarez-Najera A *et al.* Characterization of *rpoB* gene mutations in rifampicin resistant *Mycobacterium tuberculosis* strains isolated from pulmonary tuberculosis patients at 5 Mexican public hospitals. Rev Invest Clin 2001;53(6):526-530.
24. Bobadilla-del-Valle M, Ponce-de-Leon A, Arenas-Huertero C, Vargas-Alarcon G, Kato-Maeda M, Small PM *et al. rpoB* gene mutations in rifampin-resistant *Mycobacterium tuberculosis* identified by polymerase chain reaction single-stranded conformational polymorphism. Emerg Infect Dis 2001;7(6):1010-1013.
25. Viader-Salvado JM, Luna-Aguirre CM, Reyes-Ruiz JM, Valdez-Leal R, del Bosque-Moncayo Mde L, Tijerina-Menchaca R *et al.* Frequency of mutations in *rpoB* and codons 315 and 463 of *katG* in rifampin- and/or isoniazid-resistant *Mycobacterium tuberculosis* isolates from northeast Mexico. Microb Drug Resist 2003;9(1):33-38.
26. Ramaswamy SV, Dou SJ, Rendon A, Yang Z, Cave MD, Graviss EA. Genotypic analysis of multidrug-resistant *Mycobacterium tuberculosis isolates* from Monterrey, Mexico. J Med Microbiol 2004;53(Pt 2):107-113.
27. Varma-Basil M, El-Hajj H, Colangeli R, Hazbon MH, Kumar S, Bose M *et al.* Rapid detection of rifampin resistance in *Mycobacterium tuberculosis* isolates from India and Mexico by a molecular beacon assay. J Clin Microbiol 2004;42(12):5512-5516.
28. Hazbon MH, Bobadilla del Valle M, Guerrero MI, Varma-Basil M, Filliol I, Cavatore M *et al.* Role of embB codon 306 mutations in Mycobacterium tuberculosis revisited: a novel association with broad drug resistance and IS6110 clustering rather than ethambutol resistance. Antimicrob Agents Chemother 2005;49(9):3794-3802.
29. Zenteno-Cuevas R, Zenteno JC, Cuellar A, Cuevas B, Sampieri CL, Riviera JE *et al.* Mutations in *rpoB* and *katG* genes in *Mycobacterium* isolates from the Southeast of Mexico. Mem Inst Oswaldo Cruz 2009;104(3):468-472.
30. Lopez-Alvarez R, Badillo-Lopez C, Cerna-Cortes JF, Castillo-Ramirez I, Rivera-Gutierrez S, Helguera-Repetto AC *et al.* First insights into the genetic diversity of *Mycobacterium tuberculosis* isolates from HIV-infected Mexican patients and mutations causing multidrug resistance. BMC Microbiol 2010;10:82.
31. Bolado-Martinez E, Perez-Mendoza A, Alegria-Morquecho FM, Candia-Plata M del C, Aguayo-Verdugo M del R, Alvarez-Hernandez G. DNA mutations associated to rifampicin or isoniazid resistance in *Mycobacterium tuberculosis* clinical isolates from Sonora, Mexico. Salud Publica Mex 2012;54(2):167-170.
32. Cuevas-Cordoba B, Cuellar-Sanchez A, Pasissi-Crivelli A, Santana-Alvarez CA, Hernandez-Illezcas J, Zenteno-Cuevas R. *rrs* and *rpsL* mutations in streptomycin-resistant isolates of *Mycobacterium tuberculosis* from Mexico. J Microbiol Immunol Infect 2013.
33. Cuevas-Cordoba B, Xochihua-Gonzalez SO, Cuellar A, Fuentes-Dominguez J, Zenteno-Cuevas R. Characterization of *pncA* gene mutations in pyrazinamide-resistant *Mycobacterium tuberculosis* isolates from Mexico. Infect Genet Evol 2013;46(1):30-34.
34. Quitugua TN, Seaworth BJ, Weis SE, Taylor JP, Gillette JS, Rosas, II *et al.* Transmission of drug-resistant tuberculosis in Texas and Mexico. J Clin Microbiol 2002;40(8):2716-2724.
35. Martinez-Guarneros A, Rastogi N, Couvin D, Escobar-Gutierrez A, Rossi LM, Vazquez-Chacon CA *et al.* Genetic diversity among multidrug-resistant *Mycobacterium tuberculosis* strains in Mexico. Infect Genet Evol 2013;14:434-443.
36. Martinez-Gamboa A, Ponce-de-Leon A, Galindo-Fraga A, Bobadilla-del-Valle M, Kato-Maeda M, Robertson BD *et al.* Molecular analysis of *Mycobacterium tuberculosis* strains with an intact *pks*15/1 gene in a rural community of Mexico. Arch Med Res 2008;39(8):809-814.
37. Nava-Aguilera E, Lopez-Vidal Y, Harris E, Morales-Perez A, Mitchell S, Flores-Moreno M *et al.* Clustering of *Mycobacterium tuberculosis* cases in Acapulco: Spoligotyping and risk factors. Clin Dev Immunol 2011;2011:408375.
38. Bojorquez-Chapela I, Backer CE, Orejel I, Lopez A, Diaz-Quinonez A, Hernandez-Serrato MI *et al.* Drug resistance in Mexico: results from the National Survey on Drug-Resistant Tuberculosis. Int J Tuberc Lung Dis 2013;17(4):514-519.
39. Hanekom M, Gey van Pittius NC, McEvoy C, Victor TC, Van Helden PD, Warren RM. *Mycobacterium tuberculosis* Beijing genotype: a template for success. Tuberculosis 2011;91(6):510-523.
40. Zazueta-Beltran J, Leon-Sicairos C, Canizalez-Roman A. Drug resistant *Mycobacterium tuberculosis* in Mexico. J Infect Dev Ctries 2009;3(3):162-168.

Supplemental table S1

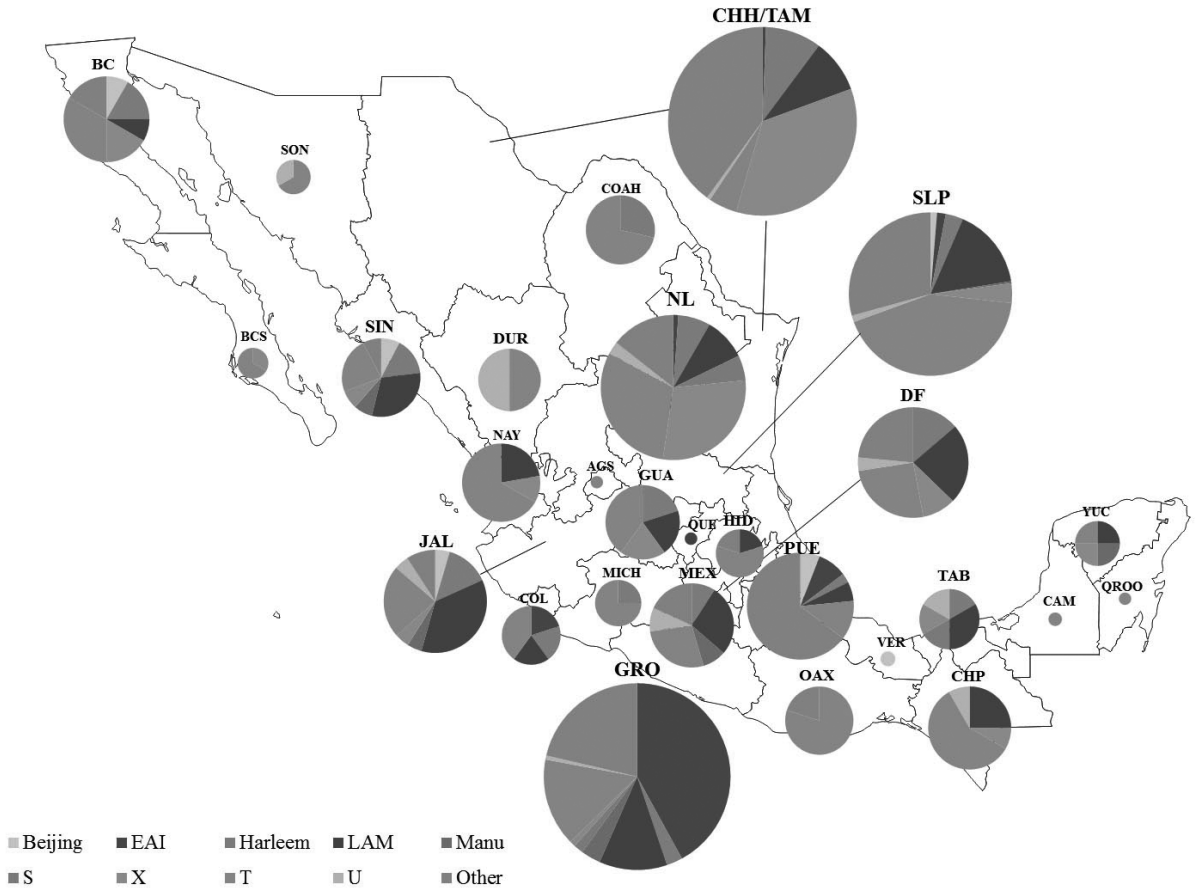
SUMMARY OF INCLUDED STUDIES EVALUATING PHENOTYPIC DRUG RESISTANCE, GENOTYPIC DRUG RESISTANCE AND MOLECULAR EPIDEMIOLOGY OF *M. TUBERCULOSIS* STRAINS FROM MEXICO

Source	*State*[a]	*No. of isolates*	*Population characteristics*	*Method*	*Data available*
Phenotypic drug resistance					
Alvarez-Gordillo *et al*., 1995[9]	CHP	18	Patients with pulmonary TB	Proportion	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Alvarez-Gordillo *et al*., 1999[10]	CHP	61	Patients with pulmonary TB	Proportion	DR, MDR and INH-resistance
Becerril-Montes *et al*., 2013[16]	NL	139	Patients with pulmonary TB	Radiometric	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Garza-Garcia *et al*., 2001[20]	VER	308	Patients with persistent cough and AFB	Radiometric	DR, MDR, INH-resistance, RIF-resistance, STR-resistance and EMB-resistance
Garza-Gonzalez *et al*., 2010[19]	TAM	96	Consecutive clinical isolates	Proportion	DR, MDR, INH-resistance and RIF-resistance
Granich *et al*., 2000[21]	BC, OAX, SIN	460	Patients with pulmonary TB	Radiometric	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Lopez-Rocha *et al*., 2013[17]	SLP	237	Patients with pulmonary TB	Proportion	DR, MDR, INH-resistance and RIF-resistance
Macias-Parra *et al*., 2011[22]	BC, CHP, COL, DF, DUR, GUA, GRO, HID, JAL, MEX, NAY, OAX, PUE, QUE, SIN, TAB, TAM, YUC	90	Pediatric patients with pulmonary and extrapulmonary TB	Radiometric	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Molina-Torres *et al*., 2010[15]	NL	180	Patients who attended the clinic	Proportion	DR, MDR, INH-resistance and RIF-resistance
Olvera-Castillo, 2001[12]	DF, MEX	303	Patients with pulmonary TB	Proportion, radiometric	DR, MDR, INH-resistance and RIF-resistance
Peter *et al*., 1998[8]	BC	427	Patients with pulmonary TB	Radiometric	DR, MDR, INH-resistance and EMB-resistance
Said-Fernandez *et al*, 2001[14]	NL	101	Patients with pulmonary TB	Radiometric	DR and MDR
Velasco-Rodriguez *et al*., 2004[11]	COAH	22	Patients with pulmonary TB	Proportion	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Yang *et al*., 2001[13]	NL	186	Patients who attended the clinic	Proportion	DR, MDR, INH-resistance, RIF-resistance, STR-resistance and EMB-resistance
Zazueta-Beltran *et al*., 2007[18]	SIN	66	Case-patients	Radiometric	DR, MDR, INH-resistance, RIF-resistance, STR-resistance, EMB-resistance and PZA-resistance
Genotypic drug resistance					
Alvarado-Esquivel *et al*., 2001[23]	DF	35	Isolates with undetermined DR	PCR and line probe assay	rpoB mutation frequency
Bobadilla-del-Valle *et al*., 2001[24]	DF	46	DR isolates	PCR Single-Stranded Conformational Polymorphism	rpoB mutation frequency
Bolado-Martinez *et al*., 2012[31]	SON	13	DR isolates	PCR and sequencing	rpoB, katG, inhA and oxyR-ahpC mutation frequency
Cuevas-Cordoba *et al*., 2013[32]	VER	91	DR isolates	Sequencing	rrs and rpsL mutation frequency
Cuevas-Cordoba *et al*., 2013[33]	VER	42	DR isolates	Sequencing	pncA mutation frequency

Garza-Gonzalez *et al*., 2010[19]	TAM	96	DR isolates	Sequencing	rpoB, inhA and oxyR-ahpC mutation frequency
Hazbon *et al*., 2005[28]	DF, PUE, VER	197	DR isolates	PCR and sequencing	embB mutation frequency
Lopez-Alvarez *et al*., 2010[30]	DF	5	DR isolates	PCR and sequencing	rpoB and katG mutation frequency
Molina-Torres *et al*., 2010 [15]	NL	14	IS6110 low copy number DR isolates	PCR and sequencing	rpoB and katG mutation frequency
Ramaswamy *et al*., 2004 [26]	NL	37	DR isolates	PCR and sequencing	rpoB, katG, inhA, rrs,rpsL and embB mutation frequency
Varma-Basil *et al*., 2004[27]	DF, PUE, VER	64	DR isolates	PCR and sequencing	rpoB mutation frequency
Viader-Salvado *et al*., 2003[25]	NL	76	DR isolates	PCR and line probe assay	rpoB and katG mutation frequency
Zenteno-Cuevas *et al*., 2009[29]	VER	20	DR isolates	PCR and sequencing	rpoB and katG mutation frequency
Molecular Epidemiology					
Garza-Garcia *et al*., 2001[20]	VER	308	Patients with persistent cough and AFB	RFLP-IS6110	Clustering rate
Quitugua *et al*., 2002[34]	CHH, TAM	303	Patients with DR-TB	Spoligotyping and RFLP-IS6110	Spoligotypes, shared types and clustering rates
Lopez-Alvarez *et al*., 2010[30]	DF	48	HIV-infected patients	Spoligotyping and MIRU-VNTR	Spoligotypes, shared types, MIRU-VNTR patterns and clustering rates
Lopez-Rocha *et al*., 2013[17]	SLP	237	Patients with pulmonary TB	Spoligotyping	Spoligotypes, shared types and clustering rates
Macias-Parra *et al*., 2011[22]	BC, CHP, COL, DF, DUR, GUA, GRO, HID, JAL, MEX, NAY, OAX, PUE, QUE, SIN, TAB, TAM, YUC	90	Pediatric patients with pulmonary and extrapulmonary TB	Spoligotyping	Spoligotypes, shared types and clustering rates
Martinez-Gamboa *et al*., 2008[36]	PUE	34	Patients who attended the clinic	Spoligotyping and RFLP-IS6110	Spoligotypes, shared types and clustering rates
Martinez-Guarneros *et al*., 2013[35]	AGS, BC, BCS, CAM, CHP, COAH, COL, DF, DUR, GUA, GRO, HID, JAL, MEX, MICH, NAY, OAX, PUE, QROO, SIN, SON, TAB, TAM, VER, YUC	109	MDR isolates	Spoligotyping	Spoligotypes, shared types and clustering rates
Molina-Torres *et al*., 2010 [15]	NL	180	Patients who attended the clinic	Spoligotyping and RFLP-IS6110	Spoligotypes, shared types and clustering rates
Nava-Aguilera *et al*., 2011[37]	GRO	267	Consecutive TB patients	Spoligotyping	Spoligotypes, shared types and clustering rates
Yang *et al*., 2001[13]	NL	186	Patients who attended the clinic	RFLP-IS6110	Clustering rate

[a] GS: Aguascalientes; BC: Baja California; BCS: Baja California Sur; CAM: Campeche; CHP: Chiapas; CHH: Chihuahua; COAH: Coahuila; COL: Colima; DF: Distrito Federal; DUR: Durango; GUA: Guanajuato; GRO: Guerrero; HID: Hidalgo; JAL: Jalisco; MEX: state of Mexico; MICH: Michoacan; NAY: Nayarit; NL: Nuevo Leon; OAX: Oaxaca; PUE: Puebla; QROO: Quintana Roo; SIN: Sinaloa; SLP: San Luis Potosi; SON: Sonora; TAB: Tabasco; TAM: Tamaulipas; VER: Veracruz; YUC: Yucatan

[b] DR: drug resistance, MDR: multidrug resistance, INH: isoniazid, RIF: rifampicin, STR: streptomycin, EMB: ethambutol, PZA: pyrazinamide



AGS (Aguascalientes, n=1)35: T1=100%; BC (Baja California, n=12)22, 35: Beijing=8.3%, H1=8.3%, H3=8.3%, LAM3=8.3%, T1=33.3%, X3=16.7%, Other=16.7%; BCS (Baja California Sur, n=3)35: T1=66.7%, X3=33.3%; CAM (Campeche, n=2)35: T1=100%; CHP (Chiapas, n=12)22, 35: LAM3=8.3%, LAM9=16.7%, T1=58.3%, X3=8.3%, U=8.3%; CHH/TAM (Chihuahua and Tamaulipas, n = 325)22, 34, 35: EIA2-Manila=0.3%, EIA5=0.3%, H1=3.1%, H2=2.5%, H3=4%, LAM1=0.6%, LAM3=1.2%, LAM6=0.9%, LAM9=6.5%, T1=4.3%, T2=0.6%, X1=27.7%, X2=3.4%, X3=4%, U=0.6%, Other=40%; COL (Colima, n=5)22, 35: EAI5=20%, H3=20%, LAM9=20%, T1=40%; COAH (Coahuila, n=7)35: H3=28.6%, T1=57.1%, T2=14.3%; DF (Distrito Federal, n=51)22, 30: H1=3.9%, H2=2%, H3=7.8%, LAM9=23.5%, T1=25.5%, X1=5.9%, X2=3.9%, U=3.9%, Other=23.5%; DUR (Durango, n=6)35: T1=50%, U=50%; GRO (Guerrero, n=295)22, 35, 37: EAI2-Manila=25.8%, EAI5=16.3%, H1=1.4%, H2=0.7%, H3=0.7%, LAM1=1.7%, LAM2=0.3%, LAM3=1.4%, LAM4=1.7%, LAM6=0.3%, LAM9=6.4%, Manu1=2%, Manu2=1.4%, S=1.7%, T1=13.6%, T2=1.7%, X3=1%, U = 0.7%, Other=21.4%; GUA (Guanajuato, n=9)22, 35: H1=20%, LAM4=10%, LAM9=10%; T1=30%, T2=10%, X3=20%; HID (Hidalgo, n=5)22, 35: LAM1=20%, T1=40%, T2=20%, Other=20%; JAL (Jalisco, n=23)22, 35: Beijing=4.3%, EAI-5=4.3%, H1=4.3%, H3=8.7%, LAM2=8.7%, LAM3=4.3%, LAM8=4.3%, LAM9=13%, LAM12=4.3%, Manu2=4.3%, T1=21.7%, X1=4.3%, U=4.3%, Other=8.7%; MEX (State of Mexico, n=11)22, 35: H3=9.1%, LAM4=9.1%, LAM9=18.2%, Manu1=9.1%, T1=27.3%, U=9.1%, Other=18.2%; MICH (Michoacan, n=4)35: H1=25%, T1=75%; NAY (Nayarit, n=9)22, 35: LAM6=22.2%, X1=11.1%, T1=66.7%; NL (Nuevo Leon, n=180)15: EAI2-Manila=1.1%, H1=2.2%, H3=5%, LAM1=2.8%, LAM2=1.7%, LAM3=1.7%, LAM6=2.2%, LAM9=1.1%, S=5.6%, T1=26.1%, T2=4.4%, X1=20%, X2=2.8%, X3=6.1%, U=2.8%, Other=14.4%; OAX (Oaxaca, n=5)22: T1=60%, T2 = 20%, Other=20%; PUE (Puebla, n=34)22, 36: Beijing=5.9%, EAI2-Manila=8.8%, H3=2.9%, LAM2=2.9%, LAM9=2.9%, T1=11.8%, Other=64.7%; QROO (Quintana Roo, n=1)35: T1=100%; QUE (Queretaro, n=1)22: LAM6=100%; SIN (Sinaloa, n=12)22, 35: Beijing=7.7%, H1=7.7%, H3=7.7%, LAM3=7.7%, LAM9 = 23.1%, Manu2=7.7%, X1=7.7%, T1=23.1%, Other = 7.7%; SLP (San Luis Potosi, n=232) 17: Beijing=13%, EAI2-Manila=1.7%, H1=0.9%, H2=0.4%, H3=2.2%, LAM1=3.5%, LAM2=2.2%, LAM3=2.6%, LAM4=0.4%, LAM9=7.3%, Manu2=0.4%, T1=38.8%, T2=3%, T3=0.9%, X1=3.5%, X3=0.4%, U=1.3%, Other=29.3%; SON (Sonora, n=3)35: T1=66.7%, U=33.3%; TAB (Tabasco, n=6)22, 35: H3=16.7%, LAM5=16.7%, LAM9=16.7%, S=16.7%, U=16.7%, X1=16.7%; VER (Veracruz, n=1)35: Beijing=100%; YUC (Yucatan, n=4)22, 35: LAM9=25%, Manu1=25%, T1=25%, X1=25%.

Supplemental figure S1. Geographical distribution of major *M. tuberculosis* lineages