Dynamics of multidrug resistant tuberculosis in Veracruz, México between 2002 and 2008

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According to the World Health Organization (WHO), approximately 500,000 of the tuberculosis (TB) cases reported in 2007 were identified as multidrug-resistant tuberculosis (MDR-TB). This large number of multidrug resistant cases complicates the control of TB, making the disease a serious concern for global public health [1]. In 2006, morbidity and mortality rates of TB in Mexico were estimated to be 14 and 2.5 cases per 100,000 individuals, respectively [2]. In the same year, the state of Veracruz reported 1,800 cases and 250 deaths from TB. As a result, this state is one of the largest contributors of TB in the country [3]. However, information regarding MDR-TB in Mexico is scarce [4-5]. The last national survey in 1997 showed a prevalence of 2% in new cases and 22% in previously treated cases [5].

The national health system, through the National Program for Prevention and Control of Tuberculosis, has established the State Committees of Drug-Resistant Tuberculosis (SCDR-TB) to monitor and supervise drug resistance to tuberculosis in close collaboration with the state tuberculosis programs. In Veracruz, the SCDR-TB is comprised of representatives from all the institutions that provide medical attention within the state, with a patient base of close to seven million inhabitants. The information provided by the SCDR-TB will help to analyze the situation of MDR-TB in Veracruz, Mexico.

Through the review of clinical records of patients reported as MDR-TB carriers by the SCR-TB, the demographics of the population affected by this disease from 2002 to 2008 were evaluated.

Patients suspected of having drug-resistant tuberculosis based on the results of their drug susceptibility tests were included in the analysis. Respiratory sample decontamination was achieved according to Petroff´s method, and primary isolation was performed in Löwenstein-Jensen slants medium. Susceptibility testing for first-line drugs including isoniazid, streptomycin, rifampin, ethambutol and pyrazinamide, was performed in duplicate according to the radiometric method (BACTEC 460, Becton-Dickinson, Sparks, MD) in the Veracruz public health laboratory. Clinical record data from 173 individuals were analyzed, including age; gender; date of diagnosis as an MDR-TB case; the start date of standardized, individualized treatment; and treatment outcome.

The annual mean number of cases in the study period was 25; the maximum number of cases was 35 in the year 2002, while the minimum was 16 in 2007 (Table 1). Sensitivity tests to first-line drugs showed that all isolates had resistance to rifampin and isoniazid; additionally, 122 (70%) isolates were resistant to ethambutol, 109 (62%) to streptomycin, and 70 (40%) to pyrazinamide (Table 1).

The MDR-TB prevalence for new TB cases was calculated at 1.6%. This number is lower than the 2.6% and 2% reported for Mexico by the WHO [1] and Granich [5]. For the previously treated cases, the MDR prevalence was 26%, which was higher than

the national estimates of 22% and 17% by Granich [5] and Zazueta-Beltran [4].

Resistance to three drugs was observed in 115 (66%) individuals, while 112 (64%) showed resistance to four or more drugs. No susceptibility tests were done for fluoroquinolones or any second-line drugs (amikacin, kanamycin and capreomycin) because limited economic resources within the state TB program prevented the acquisition of second-line drug resistance detection kits. One implication of this limitation of the study is that some patients could have had extensive drug-resistant TB (XDR-TB); this information has important epidemiological value because the first cases of XDR-TB have been recently reported in Mexico [1].
A total of 107 of the subjects were males (60%), with a mean age of 45 years; 68 of the subjects were females (40%), with a mean age of 40 years. The mean age of the entire population was 43 years. These results concur with the fourth global report on anti-tuberculosis drug resistance, where middle-aged men were found to be the main affected group [1].

In relation to the treatment outcomes, recovery from infection was observed in 47 (27%) individuals, while 42 (24%) died. Unfortunately, it was not possible to identify whether TB was the main cause of death. Neglect was observed in eight (5%) subjects while two (1%) refused to continue treatment. To date, 74 (43%) individuals are still awaiting treatment: 21 (12%) for retreatment, 35 (21%) for standardized treatment and 18 (10%) for individualized treatment. This last finding is a concern because according to both Mexican and WHO control programs [1,6-7], all patients must be treated with specific drugs. This lack of treatment is the result of second- and third-line drugs not being included in the national basic drug regimen, forcing the TB state programs to acquire them. However, considering the high costs and scarcity of the resources, only a limited number of drugs and treatments can be acquired and administered. According to the WHO and the Stop TB Partnership, this is a common problem within the TB programs in developing countries [1,8], and is considered one of the most serious challenges to reduce the generation and expansion of MDR-TB by 2015 [9].

In conclusion, the rates of MDR-TB observed were constant throughout the years of the study and were not the product of uncontrolled or sporadic outbreaks. This observation indicates that the actions of the Veracruz TB program, which are based on national regulations, effectively control and reduce to a minimum the dispersion of MDR-TB [3,6]. This deduction is confirmed by the low prevalence of MDR in new TB cases (1.6%). The authors are now conducting a study, whose aim is to genotype and sequence the genes associated with the MDR-TB strains to determine how these strains are generated and dispersed in the population.
Limited funding was the main factor that affected the correct control and management of the MDR-TB patients in this study. Inadequate control and management measures could have serious consequences in the future of this disease and the generation of new cases of MDR-TB and XDR-TB in this region of the country.

Table 1. Distribution of multidrug resistant tuberculosis patients, 2002-2008, Veracruz, Mexico.

Drug \ Years and number of cases	2002 n=35 (%)	2003 n= 26 (%)	2004 n= 28 (%)	2005 n= 20 (%)	2006 n= 20 (%)	2007 n=16 (%)	2008 n= 28 (%)	Total 173(%)
Isoniazid (H)	35 (100)	26 (100)	28 (100)	20 (100)	20 (100)	16 (100)	28 (100)	173 (100)
Rifampin (R)	35 (100)	26 (100)	28 (100)	20 (100)	20 (100)	16 (100)	28 (100)	173 (100)
Pyrazinamide (Z)	15 (42)	9 (34)	9 (30)	7 (35)	6 (30)	9 (56)	15 (53)	70 (40)
Streptomycin (S)	26 (74)	16 (61)	10 (33)	14 (70)	13 (65)	14 (87)	16 (57)	109 (63)
Ethambutol (E)	22 (62)	20 (76)	19 (63)	12 (60)	15 (75)	12 (75)	22(78)	122 (70)

Acknowledgments

References

1. World Health Organization (2008) Anti tuberculosis drug resistance in the world: fourth global report (WHO/HTM/TB/2008.394).
2. Pan-American Health Organization (2004) Epidemiological tuberculosis situation (región de las Américas 2004). Available: http://www.paho.org/common/Display.asp?Lang=S&RecID=6432. Accessed 15 January 2010.
3. Tuberculosis state program (2010) Servicios de Salud de Veracruz, México. Available: http://sesver.ssaver.gob.mx/portal/page?_pageid=%20693,6992673&_dad= portal&_schema=PORTAL]. Accessed 15 January 2010.
4. Zazueta-Beltran J, León-Sicairos C, Canizalez-Roman A (2009) Drug resistant Mycobacterium tuberculosis in México. J Infect Dev Ctries 3: 162-8.
5. Granich RM, Balandrano S, Santaella AJ, Binkin NJ, Castro KG, Marquez-Fiol A, Anzaldo G, Zarate M, Jaimes ML, Velazquez-Monroy O, Salazar L, Alvarez-Lucas C, Kuri P, Flisser A, Santos-Preciado J, Ruiz-Matus C, Tapia-Conyer R, Tappero JW (2000) Survey of drug resistance of Mycobacterium tuberculosis in 3 Mexican states, 1997. Arch Intern Med 160: 639-44.
6. Modification to the National regulations for prevention and control of tuberculosis (NOM-006SSA2-1993) (2000). Secretaria de Salud. *Diario Oficial de la Federación,* pp. 9-33.
7. World Health Organization (2002) An expanded DOTS Framework for Effective Tuberculosis Control: WHO report 2002. (WHO/CDS/TB/2002.297).
8. Stop TB Partnership (2006) The global plan to stop TB, 2006-2015. Available: http://www.stoptb.org/global/plan/ Accessed 27 October 2010.
9. Stop TB Partnership (2010date?) About the funding gaps.. Available:http://www.stoptb.org/global/plan/funding/default.asp. Accessed 27 October 2010.

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