Tuberculosis epidemiology and control in Veracruz, Mexico

Ma.de Lourdes García-García, Peter M Small, Cecilia Garcia-Sancho, Ma. Eugenia Mayar-Mayar, Leticia Ferreyra-Reyes, Manuel Palacios-Martinez, Sadoc Jiménez, Guadalupe Canales, Guadalupe Quiroz, Lucía Yáñez and José Luis Valdespino-Gómez

Background Tuberculosis (TB) rates remain high in regions of Southern Mexico despite the existence of a National Tuberculosis Program. Understanding TB epidemiology in such settings would assist in the design of improved TB control and highlight the challenges confronting TB control in developing countries.

Methods We conducted a retrospective review of treatment control cards from 1991 to 1994 in five municipalities in a semiurban region of Southern Mexico.

Results The relatively high rate of TB observed, 42.6 per 100,000 inhabitants, did not change significantly during the study period. Cure rates among new cases were 79% and significantly lower among retreatment cases (62%). Directly observed therapy (DOT) was administered to 84% of patients. Approximately one-half of the retreatment cases who were not cured were compliant with therapy, suggesting that drug resistance contributed to these poor results. Of particular concern was a core group of 16 patients who had received at least three treatments.

Conclusions This region of Mexico has persistently high TB rates despite a DOT-based TB control programme which achieves an overall cure rate of 77%. There exist many retreatment cases for whom cure rates are significantly lower. These cases may serve as a core group for the dissemination of drug resistant TB. The control programme is being reinforced by a nominal register of patients, decreasing administrative barriers for drug supply to individual patients and the availability of mycobacteria cultures. In addition to these measures, in regions which are approaching the levels of efficacy recommended by the WHO it may be appropriate to consider focusing efforts on the identification and treatment of chronic cases.

Keywords Tuberculosis, public health, Mexico, epidemiology, compliance, drug resistance

Accepted 17 March 1998

The National Tuberculosis Prevention and Control Program in Mexico follows the guidelines recommended by the World Health Organization. The programme was implemented nationally in 1973 and since 1986 its regulations are mandatory for all health services. This programme employs Bacille Calmette-Guérin (BCG) vaccination at birth, passive case detection with sputum microscopy, and prompt short course multidrug therapy administered under direct supervision for all identified cases.

Despite these efforts, tuberculosis (TB) remains a major public health problem. The incidence rate for tuberculosis (including smear positive and negative cases) in Mexico has been stated as 18.2 per 100,000 inhabitants, but some estimates suggest that the actual rates may be three times greater than this figure; 51.7 cases per 100,000 inhabitants. Most of these cases are considered to go undiagnosed, although undernotification may also constitute an important problem. Tuberculosis rates are particularly high in rural Southern states where limited resources, the dispersed population, poverty, and beliefs about disease complicate implementation of TB control.

We undertook the present study to evaluate the epidemiology and control of TB in a region which in many ways typifies these complexities in order to identify priorities for TB control intensification in the region.

Methods

Setting

Mexico is a country of 82 million inhabitants, located south of the US and formed by 32 states. The state of Veracruz, roughly the size of Portugal, has 6 million inhabitants. Tuberculosis is
a particularly important problem in this state, with morbidity
(30.9 cases per 100,000)\textsuperscript{3} and mortality rates (8.0 cases per
100,000)\textsuperscript{5} comparing unfavourably with the national rates
(18.2 cases per 100,000\textsuperscript{3} and 4.4 cases per 100,000\textsuperscript{5}). The state
is comprised of 207 municipalities which for public health
purposes have been aggregated into 11 jurisdictions. The study
was conducted in five municipalities of the Orizaba Health
Jurisdiction, (Figure 1), located in the centre of the state and
covering 216 km\textsuperscript{2}. These form an urban corridor of five urban
centres (Orizaba, Rio Blanco, Nogales, Ciudad Mendoza, and
Iztaczoquitlan) and the surrounding rural area, (population of
270,373, 11% rural). Most of the rural area is devoted to agri-
culture; however, the economic strength of the region is industrial
production of textiles, paper, foodstuffs, cement, oil and sugar.
Despite these industries, 13% of households have earthen floors,
8% don’t have access to municipal piped water and 9% of the
population is illiterate.\textsuperscript{6}

The local health care system is comprised of 13 primary
health care centres, 3 general hospitals, 10 private clinics, 114
private physicians, and 47 community health committees. These
committees are comprised of local personnel and charged with
monitoring diseases. This system is coordinated by the Health
Jurisdiction of the State Public Health Services.

Tuberculosis control is provided for most of the inhabitants of
the region by the Ministry of Health (SSA), which provides
care to the uninsured low-income population and the Mexican
Social Security Institute (IMSS), which cares for the insured
working population. In addition, other institutions provide care
for smaller groups; e.g. the State Worker’s Social Security and
Services Institute (ISSSTE) provides care for government
employees and Petroleos Mexicanos provides care for oil workers.
Overall, 9% of patients receive clinical care at these smaller
institutions. The majority of patients are diagnosed and treated
as outpatients. Hospitalization is rare and usually because of
comorbid conditions. There are 114 licensed private physicians
in the region serving the more affluent residents, however,
because anti-tubercular medications are available free of charge
through the health institutions these doctors manage relatively
few TB patients. Mycobacterial diagnostic facilities include 31
microscopy laboratories (26 private, 2 SSA, 2 IMSS, 1 ISSSTE)
and one culture laboratory in the regional SSA hospital.

Diagnosis of TB is based upon results of sputum microscopy.
The acid-fast bacilli (AFB) smear positive cases are treated with
isoniazid, rifampin and pyrazinamide for 2 months followed
by isoniazid and rifampin for an additional 4 months.
Ethambutol is added to the treatment of AFB smear positive
cases who have been previously treated for TB. Patients suspected
of having TB, but for whom sputum microscopy was not done
or failed to identify AFB are referred to specialized care at
hospital. Mycobacterial cultures and drug susceptibility testing
are generally not available due to lack of trained personnel,
appropriate equipment and reagents. Cure is not always
bacteriologically proven through smears or culture because of
administrative barriers.

Data sources
All treatment control cards for patients treated from January
1991 to December 1994 from the Orizaba Health Region avail-
able in the 13 health centres and three public hospitals were
reviewed. A structured questionnaire was used to collect social,
demographic, clinical, microbiological and treatment data. Follow-
up included a review of records verifying patient attendance
directly observed therapy (DOT) visits. Mycobacterial drug
susceptibility and retreatment regimens administered were not
available for most cases.

Definitions
The operational definitions used in the study are those
stipulated by the policy of the National Tuberculosis Program,\textsuperscript{2}
with the exception of abandonment and death for which the
definitions recommended by the WHO\textsuperscript{7} were used. Definitions
were as follows:

- **Classification of case at initiation of therapy**
  - **New case.** Patient in whom a first-time TB diagnosis is made and
    reported.
  - **Re-treatment case.** Treatment prescribed by a specialist in the case
    of multi-treated TB or when there was failure after short course
    treatment. These cases were further classified as re-entering the
    programme due to relapse (presenting with signs, symptoms, or
    microbiology consistent with TB after a bacteriological or prob-
    able cure) or due to abandonment or failure of the previous
    treatment.

- **Classification at completion of therapy**
  - **Bacteriological cure.** Completed treatment with the disappearance
    of signs and symptoms, with two or more AFB microscopies or
cultures with negative results at the end of therapy.
  - **Probable cure.** Completed treatment with the disappearance
    of signs and symptoms without at least two AFB microscopies or
cultures with negative results being performed before the end
    of therapy.
  - **Abandonment.** Attended less than 80% of planned appointments,
    clinical consultations or laboratory controls, or who stopped
    going to the clinic for \( \geq 60 \) days.
  - **Failure.** The AFB microscopies or cultures remain positive after
    the fifth month of treatment.
Death. Died of any cause during therapy.

Transfer. Management of patient transferred to another institution outside of the study region.

Other Definitions

Chronic case. Patient receiving three or more courses of antituberculous therapy from the institutional health services.

Directly observed therapy (DOT). Treatment provided in health units under the supervision of personnel who ensured ingestion of medication.

Socioeconomic level. According to the patient’s self reported occupation; professionals were classified as high, other patients in steady employment considered medium, and unstably or the unemployed were considered as low status.

Analysis

Annual TB incidence rates (including both pulmonary and extrapulmonary cases) were calculated according to the number of new cases which were found at all 13 primary health centres of SSA and IMSS clinics and the three general hospitals. A careful analysis was used to identify redundant reporting to ensure that each treatment episode was included once and only once in the analysis. Incidence rates were calculated by counting only new cases initiating therapy each year and dividing by the population established for the region. Population for the years 1991, 1992, 1993 and 1994 were expanded from the 1990 census according to the Mexican National Institute of Statistics, Geographics and Informatics recommended methodology.6

Socioeconomic comparisons were made between the study population and the 1990 census.6

Treatment courses were classified as either ‘new’ or ‘retreatment’. Outcomes were analysed by TB treatment courses as documented by control cards. Univariate analysis was performed to investigate association of variables to abandonment of treatment. Univariate analysis was performed to investigate association of variables to cure (both probable and bacteriological) among patients who completed therapy.

Statistical significance was tested using t test, \( \chi^2 \) and Fisher exact tests. SAS, EPI-INFO (version 5), and STATA programs were used for analysis of data.

Results

Investigation of treatment control cards identified 466 incident TB cases and 40 retreatment TB cases during 1991–1994. We obtained outcome of treatment information on all of these 506 patients who received 553 courses of therapy (466 courses administered to new cases and 87 courses administered to retreatment cases) during this period.

Passive case surveillance during 1992–1994 (number of reported cases for 1991 was not available) reported 293 new cases from this area to the National Program. Through review of treatment cards, we located 371 treatment cards for new patients during this same period, finding therefore 78 additional cases who were not officially reported during 1992–1994 (Table 1).

Selected demographic characteristics of the 506 patients are compared with those determined for the region by the 1990 census in Figure 2 and Table 2. These TB patients are older than

<table>
<thead>
<tr>
<th>Year</th>
<th>Notified cases (/100 000)a</th>
<th>New cases</th>
<th>Retreatment courses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>NA</td>
<td>95</td>
<td>35.9</td>
<td>18</td>
</tr>
<tr>
<td>1992</td>
<td>77</td>
<td>122</td>
<td>45.1</td>
<td>22</td>
</tr>
<tr>
<td>1993</td>
<td>115</td>
<td>124</td>
<td>44.8</td>
<td>17</td>
</tr>
<tr>
<td>1994</td>
<td>101</td>
<td>125</td>
<td>44.2</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>293</td>
<td>466</td>
<td>42.6</td>
<td>87</td>
</tr>
</tbody>
</table>

NA = Not available.

Using treatment cards, \( r \) Pearson = 0.72, \( P \) NS.

Figure 2 Age distribution of tuberculosis cases (circles) contrasted with that of the general population (squares), demonstrating the disproportionate impact of disease on middle-aged people

![Figure 2](image)

Table 1 Tuberculosis in the Orizaba Health Region, Veracruz, 1991–1994

<table>
<thead>
<tr>
<th>Study population</th>
<th>1992 populationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total = 506</td>
<td>Total = 270 373</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
</tr>
<tr>
<td>Age (Ave, SD)</td>
<td>41 (18)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>267 (53)</td>
</tr>
<tr>
<td>Socioeconomic level</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>119 (24)</td>
</tr>
<tr>
<td>Geographics</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>122 (24)</td>
</tr>
<tr>
<td>Site of clinical care</td>
<td></td>
</tr>
<tr>
<td>Orizaba</td>
<td>293 (58)</td>
</tr>
<tr>
<td>Ciudad Mendoza</td>
<td>56 (11)</td>
</tr>
<tr>
<td>Rio Blanco</td>
<td>53 (11)</td>
</tr>
<tr>
<td>Nogales</td>
<td>35 (7)</td>
</tr>
<tr>
<td>Iztaacoquitlan</td>
<td>69 (14)</td>
</tr>
</tbody>
</table>

a Estimated from 1990 census.

b \( \chi^2 \).
the general population, of lower socioeconomic status and more likely to live at a rural address. Patients tend to seek medical care in Orizaba, which has the biggest primary care centre in the region.

Of these cases, 87% of patients were smear positive cases. Sites in which TB was diagnosed were known for 503 patients and included: pulmonary only 433 (87%), pulmonary and extrapulmonary 19 (4%) and extrapulmonary 51 (10%). Of the 70 cases with extrapulmonary involvement the most common sites were renal (28), lymphatic (17), miliary (8) meningeal (5). Patients with extrapulmonary TB were more frequently cared for at one of the institutions (SSA) (odds ratio (OR) = 23.5, 95% CI : 5.6–14.7, P < 0.001). Comorbid conditions such as diabetes, cirrhosis, and malnutrition were noted in 94 patients. Of the courses of therapy, 84% were DOT.

The outcome at the completion of treatment is shown in Table 3. Of all cases, 77% successfully completed therapy. Among courses administered to new cases the proportion of cure (bacteriological and probable), 79%, was significantly different to that of second courses, 71%, and third or fourth courses, 35% (P < 0.001). Proportion of failures was significantly different among third or fourth courses (30%), second courses (6%) and first time courses (3%) (P < 0.001). Proportion of deaths, was also different among the three groups: 15% for third and fourth courses, none for second courses and 3% for first time courses (P < 0.01).

Among patients who finished treatment, cure (bacteriological and probable) was significantly associated with first time treatment versus subsequent treatments (OR = 3.8, 95% CI : 1.8–7.8, P < 0.001) and absence of comorbid conditions (OR = 2.3, 95% CI : 1.1–4.9, P = 0.03). One of the institutions (SSA) documented bacteriological cures more frequently than the social security system (IMSS) (OR = 1.98, 95% CI : 1.38–2.84, P < 0.001). Relapses occurred with similar frequency after bacteriological cures (5%) than after probable cures (3%).

Trends of outcomes by annual cohorts were stable (Figure 3). Stratified analysis of pulmonary and extrapulmonary courses according to new or retreatment courses did not show significant differences between annual cohorts (data not shown).

In a univariate model age, sex, socioeconomic level, municipality of diagnosis, access to social security, socioeconomic level, year of diagnosis, associated diseases, DOT, or receiving a retreatment course were not associated with abandonment of therapy.

During the study period, 87 (16%) of the 553 regimens initiated were for patients who had been previously treated. The reasons for retreatment included prior relapse (45%), abandonment (33%) and failure (16%). Of those who abandoned therapy the median time to abandonment was 72 days (SD = 49, range 1–177). In relapsed cases the median time to relapse was 341 days (SD = 311, range 61–1298).

Seventeen cases identified during this 4-year period had received ≥3 courses of anti-tuberculous therapy. These patients received 56 courses of treatment; 64% of these courses were administered to patients with a positive AFB smear. Their clinical histories were notable for the duration and complexity of their disease, and are shown for 16 patients in Figure 4. Dates for initiation of first and second course were not available for one patient who was omitted from the Figure and who received three courses of therapy. The 16 patients have been divided into three groups, according to their compliance to therapy. Group A includes patients who were compliant with therapy, group B includes patients who were not compliant with therapy and group C includes patients with mixed histories. Group B included five patients among whom failures were primarily due to inability to complete prescribed regimens as they received 16 courses of which they abandoned 10. However, group A includes eight chronic cases who had been repeatedly compliant with prescribed therapy and apparently cured. This group received 26 courses of therapy, and were compliant to all treatment courses. Sixteen of these courses were apparently cured (six of which were bacteriologically proven). Group C included three patients who received 11 courses, two of which were apparently cured.

**Table 3** Outcomes at completion of antituberculous treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All courses</th>
<th>First course</th>
<th>Second course</th>
<th>Third and fourth course</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriological cure</td>
<td>258 (47)</td>
<td>226 (48)</td>
<td>28 (42)</td>
<td>4 (20)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probable cure</td>
<td>167 (30)</td>
<td>145 (31)</td>
<td>19 (29)</td>
<td>3 (15)</td>
<td>0.3</td>
</tr>
<tr>
<td>Subtotal cure</td>
<td>425 (77)</td>
<td>371 (79)</td>
<td>47 (71)</td>
<td>7 (35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abandon</td>
<td>75 (13)</td>
<td>58 (12)</td>
<td>14 (21)</td>
<td>3 (15)</td>
<td>0.2</td>
</tr>
<tr>
<td>Failure</td>
<td>22 (4)</td>
<td>12 (3)</td>
<td>4 (6)</td>
<td>6 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>17 (3)</td>
<td>13 (3)</td>
<td>1 (1)</td>
<td>3 (15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transfer</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (2)</td>
<td>7 (2)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>553</td>
<td>466</td>
<td>67 (20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²x², comparing first, second and third/fourth courses.

**Discussion**

Despite having a National Control Program, TB continues to be a public health problem in Mexico. It is the leading cause of death from a single infectious agent, and is particularly problematic in the Southern region of the country. Although the HIV/AIDS epidemic has increased in Mexico during the last 10 years, it has not reached the same magnitude as in other
regions. The cumulative AIDS rate in Veracruz for 1995 was 14.6 per 100,000, below the national rate of 30.8 per 100,000, and the HIV/AIDS epidemic has not yet had an impact on TB rates in the study area. This study, the first detailed examination of TB epidemiology and control in one such region, was conducted to assist in the prioritization and further intensification of control programmes.

During the years 1991–1994 TB case rates in this region were (42.6/100 000), twice the nationally reported rate. Unlike some settings which have shown rapid decreases in rates of TB and drug resistance with the implementation of good control practices, in this area, and most of Mexico, rates have not decreased. Since no significant changes were made to the control programme during this period, the persistently high case rate is not likely due to an artifact of improved surveillance. Tuberculosis in this region disproportionately affects poor, illiterate, rural, and indigenous populations. Thus, this region exemplifies the challenges of implementing TB control in many high prevalence regions. The conclusions of this study are limited by the retrospective nature of the study design and the inaccessibility of some records (e.g. those treated by private practitioners).

We found that considerable undernotification of cases existed during the study period. Of cases treated during 1992–1994, 21% had not been officially reported. These cases were diagnosed, treated and followed within the different health systems, however they were not officially notified. Therefore, one of the problems which we have identified is lack of completeness of reporting which hinders adequate evaluation of the programme at the state and national level. According to officials from the state programme, undernotification of cases existed mainly among cases receiving care at the social security system (IMSS) which cares for the largest number of patients. Since 1995 a nominal register which includes patients from all the institutions has been initiated. This strategy will improve communication between institutions and reduce undernotification. The comparison of incidence data from this study (based on all diagnosed cases) with national data (based only on reported cases) may be somewhat biased. This demonstrates the general phenomena that differential rates of underreporting may result in inflated case rates in areas with better reporting systems.

Complex clinical courses of the 16 people who were treated for tuberculosis on at least three occasions. Failure or relapse among the eight compliant patients (Group A) suggest that they may have been infected with drug resistant strains: C cure; AB abandoned therapy; D patient died; FR patient failed therapy.
in higher cure rates. Supervision of therapy has been shown to
decrease resistance rates, therefore this is the most important
strategy to be implemented in the short term to improve the
TB prevention and control programme. Uncertainty about the
impact of chronic cases on TB rates makes it difficult to know
when public health resources should be diverted to the man-
agement of chronic cases. If these cases are not a significant
source of infection in a community then efforts should continue
to be exerted on improving case cure rates. However, priorities
would need to be adjusted if these individuals account for a
disproportionate amount of ongoing transmission. This issue is
particularly important in settings such as this where the pro-
gramme is approaching the benchmarks set by the WHO.
Prospective evaluation utilizing molecular epidemiological ap-
proaches are underway to further define transmission dynamics
in this setting.

Acknowledgements

This project was funded by NIH grant number AI35969. The
authors would like to thank the health care providers through
whose efforts this study was possible. Dra. Edit Rodriguez, Dra.
Yolanda Jaramillo, local health authorities of IMSS, and the
directors of primary health care centers for essential support
and guidance; Carlos Arce, Josefa Rangel, Luisa Castillo, Sergio
Canizales, Raul Cruz, and Felipe Arroyo who assisted with data
collection; and Arturo Salcedo for assistance with data analysis.
Finally, we would like to thank the two anonymous reviewers
whose detailed and thoughtful comments have greatly
improved this manuscript.

References

1 Pacheco C, Olvera R. Control de la Tuberculosis en México. Bol Sanit
Panam 1988;105:34–44.

2 Secretaría de Salud. Norma Oficial para el Control y Prevención de la
Tuberculosis en la Atención Primaria a la Salud. Norma No. NOM-

3 Dirección General de Epidemiología. Anuario Estadístico de Morbilidad.

4 Valdespino JL. Enfermedades Tropicales en México. Diagnóstico, Tratamiento


6 Instituto Nacional de Estadística, Geografía e Informática. Anuario
Estadístico del Estado de Veracruz. México: Talleres Gráficos del Instituto

7 Chaulet P, Zibouni N. Evaluation of applied strategies of tuberculosis
control in the developing world In: Reichman L, Hershfield E (eds).

8 Consejo Nacional de Prevención y Control del SIDA (CONASIDA).
Situación del SIDA en México. Datos actualizados hasta el primer

9 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in

10 Weiss SE, Slocum PC, Blais FX et al. The effect of directly observed
therapy on the rates of drug resistance and relapse in tuberculosis.

11 Kim SJ, Hong YP. Drug resistance of Mycobacterium tuberculosis in

12 Grzybowski S, Enarson DA. The fate of cases of pulmonary tuber-
culosis under various treatment programmes. Bull Int Union 1978,
53:70–75.

13 Datta, M, Radhamani MP, Selvaraj R et al. Critical assessment of
smear-positive pulmonary tuberculosis patients after chemotherapy
under the district tuberculosis programme. Tuberc Lung Dis 1993;74:
180–86.

Ann Allergy 1990;64:325.

15 Yáñez-Velasco L, Quiroz G, Rodriguez J. Use of dots in pilot areas of