Drug resistance profiles of *Mycobacterium tuberculosis* isolates: five years' experience and insight into treatment strategies for MDR-TB in Lima, Peru

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_____ S U M M A R Y

SETTING: Lima, Peru.

OBJECTIVE: To describe drug resistance profiles of TB isolates from patients at risk for multidrug-resistant tuberculosis (MDR-TB), and to consider the implications of these findings for treatment.

DESIGN: Descriptive study of drug susceptibility testing (DST) results for TB isolates from 1680 patients referred for suspicion of MDR-TB between 1996 and 2001.

RESULTS: Of 1680 isolates tested, 1144 (68%) were resistant to at least one anti-tuberculosis drug and 926 (55%) were MDR-TB strains. Of 926 MDR isolates, 50 (5%) were resistant to INH and RMP alone, while 367 (40%) were resistant to at least five first-line drugs. We identified 146 unique drug resistance profiles, the most

common of which accounted for 11% of drug-resistant isolates. The annual prevalence of isolates with resistance to at least five first-line drugs rose significantly during the study period, from 29% to 37% ($P = 0.00086$).

CONCLUSIONS: This is a group of patients with TB disease among whom the prevalence of a broad spectrum of often highly drug-resistant strains appears to be increasing over time. A single standardized retreatment regimen may be inadequate to cure most patients. Capacity for drug sensitivity testing is essential for development of multiple standardized retreatment or individualized treatment regimens and epidemiological surveillance for planning.

KEY WORDS: MDR-TB; tuberculosis; multidrug resistance; drug susceptibility testing; Peru

THE DOTS STRATEGY, of which two of the main elements are directly observed therapy (DOT) and short-course chemotherapy (SCC), and which is endorsed by the World Health Organization (WHO) as the current standard for tuberculosis (TB) treatment, has been adopted for use by TB control programs in 148 countries.[1] The efficacy of DOTS in the treatment and control of TB is widely recognized.[2–5] However, treatment failures occur that are most often due to limited resources, inadequate retreatment regimens, and incomplete treatment, increasing the risk of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampin (RMP). In some settings, drug-resistant TB has become so prevalent that the efficacy of national DOTS campaigns may be compromised.[6–9]

In such settings, more timely identification of MDR-TB disease, knowledge of prevalent drug resistance (DR) patterns, and effective treatment strategies targeting drug-resistant strains are needed. Treatment regimens may need to include second-line drugs, which,

compared to SCC drugs, are often less effective, more expensive, and more toxic, and must be administered for up to four times as long.[10] Second-line drugs may be provided by WHO-sponsored DOTS-Plus programs, and are administered either in individualized treatment regimens (ITR), tailored to the resistance profile of the infecting strain, or in empiric standardized treatment regimens (STR).[11] ITR can be highly effective, with a cure rate of 83% observed in one population of chronic TB patients who had previously failed multiple treatments.[12] However, ITR-based strategies require resource-intensive capabilities and special laboratory facilities for drug susceptibility testing (DST), which are currently difficult or unfeasible to implement in resource-limited settings. STR for MDR-TB can also be highly effective, particularly in populations with little previous exposure to the drugs included in the regimen.[13–15] However, in settings of high-grade resistance, i.e., resistance to more than INH and RMP, cure rates for STR regimens may be less than 50%.[16,17] Knowledge of prevalent DR pat-

terns in these populations may enable the development of more effective treatment regimens.

Worldwide, there are more than 8 million new cases of TB each year, of which tens to hundreds of thousands may be infected with drug-resistant strains. MDR-TB incidence can vary widely with geographic location.[18,19] In Peru, the National Tuberculosis Program (NTP) operates a well-established, model DOTS program that has achieved remarkable improvements in coverage, diagnostic capability, and TB cure rates since 1991.[20] Nevertheless, in northern Lima, the prevalence of MDR-TB measured among patients failing DOTS exceeded 90%.[21] Beginning in 1996, DST was routinely performed on TB isolates from symptomatic patients referred for retreatment. In this study, we examine these DST data with the following objectives: to determine the prevalence of specific drug resistance profiles in this cohort between 1996 and 2001, and to consider the implications of these findings for the treatment of chronic MDR-TB in Lima.

METHODS

Study population

The study population comprised residents of Lima referred by the NTP for evaluation for MDR-TB between September 1996 and August 2001. Initially, only residents of northern Lima were included, but in 1998 eligibility was expanded to include residents referred from all parts of Lima. All participants had active pulmonary TB disease, and had either failed previous TB treatment regimens administered through the Peruvian NTP, or were known contacts of someone with documented MDR-TB. The treatment regimens included Category I, consisting of INH, RMP, ethambutol (EMB), and pyrazinamide (PZA); Category II, consisting of INH, RMP, EMB, PZA, and streptomycin (SM); and STR for MDR-TB, consisting of kanamycin (KM), ciprofloxacin (CPX), ethionamide (ETH), EMB and PZA.[20]

Laboratory methods

Sputum specimens underwent initial processing and culture at a regional Ministry of Health laboratory in Lima or at the Massachusetts State Laboratory Institute (MSLI), using standard protocols.[22] DST was performed at the MSLI using the proportion method[23] on 7H10 agar plates for the following drugs at the concen-

trations indicated: INH (0.2, 1, 5 μg/ml), RMP (1 μg/ml), EMB (5 μg/ml), SM (2, 10 μg/ml), KM (5 μg/ml), capreomycin (CM, 10 μg/ml), ETH (5 μg/ml), cycloserine (CS, 30 μg/ml), and CPX (2 μg/ml). The BACTEC method was used for DST of PZA (100 μg/ml). DST for second-line drugs used the critical drug concentrations described by Pfyffer et al,[24] and the methods and media specified by the guidelines of the National Committee for Clinical Laboratory Standards.[25]

Statistical analysis

DST data were analyzed only for the first isolate from each patient. Descriptive analyses were performed to examine the prevalence of resistance to individual drugs, the distribution of the number of drugs to which patients were resistant, and the frequency of specific combinations of drug resistance. Analyses were performed using χ^2 tests for categorical data and the Wilcoxon rank-sum test for ordinal data. Trends in prevalence of drug resistance over 5 years were analyzed using χ^2 tests for trend. Analyses were performed using Epi Info version 6.04d (CDC, Atlanta, GA, 2001) or SAS version 8.2 for Windows (SAS Institute, Cary, NC, 2001).

RESULTS

Between September 1996 and August 2001, 1680 patients were referred for evaluation for MDR-TB, all of whom had *Mycobacterium tuberculosis* isolated from their sputum specimen; 1144 (68%) were resistant to at least one drug and 536 (32%) were pansusceptible (Table 1). The median number of drugs to which each isolate was resistant was three (range 0–9). Of the 1680 isolates, resistance to INH and RMP was most frequent, with INH resistance detected in 1068 (64%), RMP in 951 (57%) and both INH and RMP in 926 (55%). After INH and RMP, resistance to the other first-line drugs was most frequent: EMB in 789 (47%), SM in 773 (46%), and PZA in 626 (37%) (Table 1). MDR including at least INH, RMP, EMB, and PZA occurred in 471 (28%) isolates, and in 367 (22%) isolates included at least INH, RMP, EMB, PZA, and SM.

Among the 1144 drug-resistant isolates, there were 146 distinct profiles (data not shown), with the 10 most common profiles accounting for 555 isolates (49%), and 60 profiles for 1034 isolates

Table 1 Prevalence of resistance to INH, RMP, EMB, SM, and PZA in the study population, Lima, Peru, 1996–2001

		Patients with resistance (*n* = 1680)									
		INH		RMP		EMB		SM		PZA	
Patients tested	Any resistance % (*n*)	Mono % (*n*)	Any % (*n*)	Mono % (*n*)	Any % (*n*)	Mono % (*n*)	Any % (*n*)	Mono % (*n*)	Any % (*n*)	Mono % (*n*)	Any % (*n*)
1680	68.1 (1144)	1.8 (31)	63.5 (1068)	0.5 (9)	56.6 (951)	0.2 (3)	47.0 (789)	1.3 (22)	46.0 (773)	0.5 (9)	37.3 (626)

INH = isoniazid; RMP = rifampin; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide.

Table 2 The five most prevalent drug resistance patterns identified among isolates from 1680 patients in Lima, Peru, 1999–2001

Pattern	Isolates n (%)	Resistant isolates %
INH+RMP+EMB+PZA+SM	130 (7.7)	11.4
INH+RMP+EMB+SM	83 (4.9)	7.3
INH+RMP+EMB+PZA+SM+ETH	72 (4.3)	6.3
INH+RMP+EMB+PZA	53 (3.2)	4.6
INH+RMP	50 (3.0)	4.4

INH = isoniazid; RMP = rifampin; EMB = ethambutol; PZA = pyrazinamide; SM = streptomycin; ETH = ethionamide.

(90%). The five most frequently observed resistance profiles are shown in Table 2. Prevalence of drug resistance was higher for isolates that were resistant to a greater number of drugs; 4.7% of the isolates were resistant to only one drug compared with 33.8% of isolates resistant to five or more drugs (Table 3).

Among the drug-resistant isolates, there was an increase in prevalence of resistance to each drug tested when trends were analyzed over the 5-year study period, with the exception of INH, ETH, and CS (Figure 1). These increases were statistically significant despite the uniform decrease in prevalence of resistance to each drug that occurred between the first and second years of the study. The increase was most pronounced for SM (64–77%, $P = 0.00001$), EMB (69–75%, $P = 0.00004$), and PZA (52–59%, $P = 0.00096$). The prevalence of isolates with resistance to at least five first-line drugs also rose significantly during this time period, from 29% to 37% ($P = 0.00086$), and concomitantly the median number of drugs to which isolates were resistant increased from four to five (Figure 2).

DISCUSSION

In this report, we present the drug resistance profiles of a large cohort of chronic patients at high risk for MDR-TB who were frequently found to have high-grade MDR-TB. In this population, 55% of all isolates were MDR; 28% of all isolates were resistant to at least INH, RMP, PZA and EMB, and 22% were resistant to at least all five first-line drugs. In comparison to the countrywide data reported for Peru in the WHO Global Project on Anti-tuberculosis Drug Resistance

Surveillance,[26] the prevalence of any drug resistance among patients in this study was dramatically higher overall than among the previously treated patients in the WHO study (63.3% compared to 36.0% for 1996 countrywide data and 13.5% for 1999). The trend for prevalence of isolates resistant to an increasing number of drugs was downward in the 1999 countrywide survey data for one to three drugs (10.0%, 6.2% and 2.7%, respectively), and it was 4.0% for four-drug resistance, compared to the consistently upward trend for Lima data for 1996–2001 (Table 3). As noted in a study of TB patients in Peru,[16] patients with resistance to five first-line drugs compared to those with strains resistant to four or fewer drugs were at a three-fold greater risk for failing STR for MDR-TB. Therefore, the observation that resistance occurred most frequently to the five first-line drugs included in the WHO Category I and II treatment regimens used in Peru is likely to be the result of resistance amplification, whereby resistance to additional drugs accrues with successive exposure to ineffective or inconsistently administered drug regimens.[26–31] These comparative data underscore the need for at least contemporary DST data, including locale-specific information sufficient to determine likely effective STR, if not adequate capability for determining ITR for areas with a high prevalence of high-grade drug-resistant TB strains.

The most pronounced trend observed was an increase in the frequency of resistance to SM, a trend also identified by the Peruvian national laboratory.[32] This trend was temporally associated with the introduction of the Category II treatment regimen in the 1990s. The Category II regimen, in which SM alone was added to the four drugs included in the Category I regimen, had a success rate of only 55% among Peruvian patients with pre-existing drug resistance.[33] Resistance amplification probably also occurred during treatment with the STR for MDR-TB, which cured less than 50% of patients.[16,17] The use of the STR between 1997 and 2001 in patients with a history of multiple treatment failures likely contributed to the observed increases in resistance to EMB, PZA, KM and CPX, and possibly CM, via cross-resistance to KM.[34]

Pre-existing resistance to drugs included in a regimen has been associated with an increased risk of failure of first-line four- and five-drug regimens[33] and of the STR used in Peru for treatment of MDR-TB.[16] Development of new STRs should therefore be guided by the DR profiles of a sample of patients in the target

Table 3 Prevalence of resistance in the study population ($n = 1680$)

	Overall resistance		Resistance to					Polyresistance	
Patients tested	Susceptible % (n)	Resistant % (n)	1 drug % (n)	2 drugs % (n)	3 drugs % (n)	4 drugs % (n)	≥5 drugs % (n)	Any % (n)	MDR % (n)
1680	31.9 (536)	68.1 (1144)	4.7 (80)	6.0 (100)	8.9 (150)	14.7 (247)	33.8 (567)	63.3 (1064)	55.1 (926)

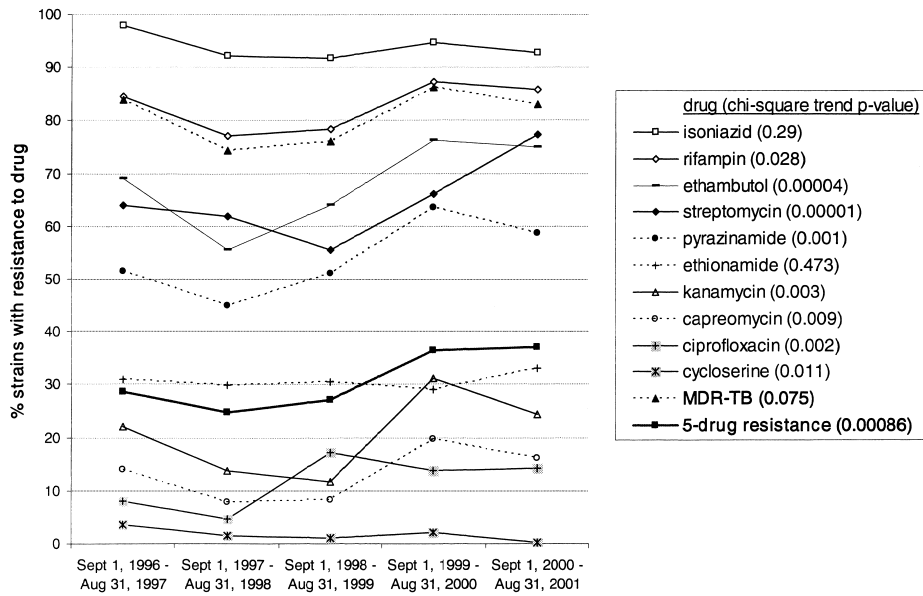MDR = multidrug-resistant tuberculosis (defined as resistance to at least isoniazid and rifampin).

Figure 1 Annual trends in resistance to anti-tuberculosis drugs, 1 September 1996–31 August 2001.

population. Furthermore, DST on a sampling of patients should continue to be performed on an ongoing basis, to identify changes that might necessitate modifications to existent STRs. In our cohort, we identified 146 unique DR profiles, the most common of which accounted for only 11% of all drug-resistant isolates. Although many profiles have common elements and most isolates have one of the more frequently observed profiles, it is still improbable that any single STR would be adequate in this population, as multiple empiric regimens have already failed. It may be more effective to develop a set of STRs, one of which is chosen for each patient on the basis of treatment history or contact exposure, and to use individual DST results to guide treatment for some patients. A related question needing further study is, 'What algorithm is most appropriate to ensure high cure rates of TB disease, and is sustainable in resource-limited settings?'.[35]
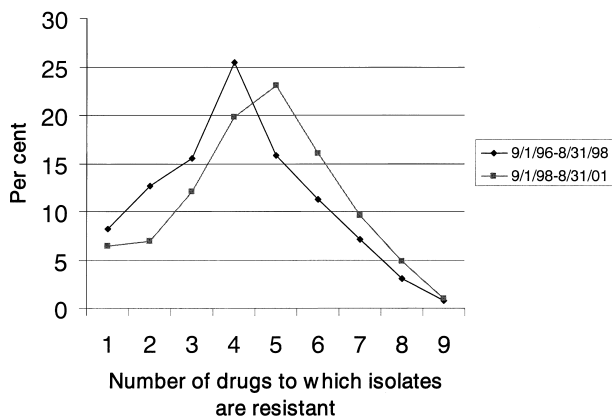

Figure 2 Number of drugs to which isolates were resistant before 31 August 1998 and after 1 September 1998.

Although this population was selected using criteria to maximize the enrollment of patients with drug resistance, one third were infected with pan-susceptible TB strains. These patients would ideally be treated with DOTS, rather than any regimen targeting MDR-TB. If an empiric treatment strategy is used, reliable historical or clinical predictors of pan-susceptible disease must also be identified to ensure selection of an appropriate treatment regimen. Alternatively, limited DST (namely, testing only for resistance to INH and RMP) could be used to guide the selection of empiric regimens.[36]

One important limitation of this study is that previous treatment histories, demographics, and other data were not available for analysis, restricting our ability to describe characteristics of patient sub-strata and to identify confounders. Furthermore, our ability to interpret findings was limited by the absence of specific, consistent selection criteria applied throughout the 5-year study period. We know, for example, that a relatively higher percentage of patients with recalcitrant TB were enrolled in the first year, presumably because patients had been accumulating in the absence of viable treatment options during the years prior to the introduction of a DOTS-Plus program in Peru. However, this would only have resulted in underestimation of the increases observed in the number of drugs to which strains were resistant. Finally, it is beyond the scope of this study to demonstrate an association between the observed increase in resistance and any specific cause. Whether the increase resulted from failure of previous empiric treatment regimens, or from some other cause, remains to be determined.

In conclusion, patients referred for evaluation for MDR-TB in Lima present with a wide spectrum of

DR profiles. In such populations, effective treatment may require a combination of clinical, laboratory and epidemiological information to assess patient risk of MDR-TB to select one of several possible STRs, or to use DST results to select drugs for individualized treatment. Unfortunately, predictors of patient risk and ready access to DST are often unavailable. Furthermore, even if an empiric strategy is chosen, DST must still be made available to evaluate treatment failures, and methods must be developed to accurately identify patients with pan-susceptible isolates, to avoid inappropriate treatment with STRs designed for MDR-TB.

Access to validated DST in resource-poor settings must therefore be provided, by conventional methods or by simpler rapid methods that are now becoming available. The feasibility of this goal is currently being demonstrated in a collaboration with the Peru Ministry of Health.[12] International political commitment and public health advocacy is required to support laboratory infrastructure for DST and provide adequate treatment for patients infected with resistant TB. In the interim, until DST is widely available in resource-poor settings, improving STRs based on local epidemiological data on drug resistance profiles may improve treatment outcomes for standardized regimens. However, the potential for increasing the prevalence of high-grade resistance may limit the utility of this strategy if programs wait too long to develop local STRs. Among the patients in Lima referred to our program with drug-resistant TB, the frequency of high-grade resistance appears to be increasing over time. This observation is not entirely unexpected, as failure of retreatment regimens in this setting is common; indeed, initially resistant strains are more likely to survive an ineffective regimen, and a failed multidrug regimen may select for strains resistant to a greater number of drugs. Routine surveillance of DR profiles found in specific populations of previously treated patients provides information that is useful for adapting strategies for effective retreatment within NTPs, and is essential for the care of persons with chronic active tuberculosis disease.

Acknowledgements

References

1 World Health Organization. An expanded DOTS framework for effective tuberculosis control. WHO/CDS/TB/2002.297. Geneva, Switzerland: WHO, 2002.

2 Weis S E, Slocum P C, Blais F X, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994; 330: 1179–1184.

3 Chaulk C P, Kazandjian V A. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. JAMA 1998; 279: 943–948.

4 Chaulk C P, Moore-Rice K, Rizzo R, Chaisson R E. Eleven years of community-based directly observed therapy for tuberculosis. JAMA 1995; 274: 945–951.

5 Collaboration CTC. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. Lancet 1996; 347: 358–362.

6 Coninx R, Mathieu C, Debacker M, et al. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. Lancet 1999; 353: 969–973.

7 Primary multidrug-resistant tuberculosis—Ivanovo Oblast, Russia, 1999. Morbidity and Mortality Weekly Report 1999; 48: 661–664.

8 Kimerling M E, Kluge H, Vezhnina N, et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. Int J Tuberc Lung Dis 1999; 3: 451–453.

9 Portaels F, Rigouts L, Bastian I. Addressing multidrug-resistant tuberculosis in penitentiary hospitals and in the general population of the former Soviet Union. Int J Tuberc Lung Dis 1999; 3: 582–588.

10 Mukherjee J, Rich M, Socci A, et al. Programs and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004; 363: 474–481.

11 World Health Organization. Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis (MDR-TB). WHO/CDS/TB/2000.279. Geneva, Switzerland: WHO, 2000.

12 Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med 2003; 348: 119–128.

13 Weyer K. Standardized management of MDR-TB in South Africa. Session on Treatment of TB: new data from clinical trials and demonstration projects. Seattle, WA: American Thoracic Society 99th International Conference, 2003.

14 Zierski M. Treatment of patients with cultures resistant to the primary anti-tuberculosis drugs. Tubercle 1964; 45: 96–100.

15 Jancik E Z M, Tousek J, Makova M. Chemotherapy for patients with cultures resistant to streptomycin, isoniazid and PAS. Tubercle 1963; 44: 443–445.

16 Suarez P G, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet 2002; 359: 1980–1989.

17 Chavez Pachas A M, Hyson A, Lovera E, Bayona J. Importance of resistance among patients receiving standardized therapy for MDR-TB. Int J Tuberc Lung Dis 2002; 6 (Suppl 1): S133.

18 Espinal M A. The global situation of MDR-TB. Tuberculosis 2003; 83: 44–51.

19 Espinal M A, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. World Health Organization/International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001; 344: 1294–1303.

20 Ministerio de Salud. Actualizacion de la doctrina, normas y procedimientos para el control de la tuberculosis en el Peru. Lima, Peru: Ministerio de Salud, 2001.

21 Becerra M C, Freeman J, Bayona J, et al. Using treatment failure under effective directly observed short-course chemotherapy programs to identify patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2000; 4: 108–114.

22 Strong B, Kubica G. Isolation and identification of *Mycobacterium tuberculosis*: a guide for the level II laboratory. Atlanta, GA: DHHS, Centers for Disease Control, 1981.

23 Kent P, Kubica G. Public health mycobacteriology: a guide for the level III laboratory. Atlanta, GA: Centers for Disease Control, 1985.

24 Pfyffer G E, Bonato D A, Ebrahimzadeh A, et al. Multicenter laboratory validation of susceptibility testing of *Mycobacte-*

rium tuberculosis against classical second-line and newer anti-microbial drugs by using the radiometric BACTEC 460 technique and the proportion method with solid media. J Clin Microbiol 1999; 37: 3179–3186.

25 National Committee for Clinical Laboratory Standards. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes; approved standard. NCCLS document M24-A. Wayne, PA: NCCLS, 2003.

26 Furin J J, Becerra M C, Shin S S, Kim J Y, Bayona J, Farmer P E. Effect of administering short-course, standardized regimens in individuals infected with drug-resistant *Mycobacterium tuberculosis* strains. Eur J Clin Microbiol Infect Dis 2000; 19: 132–136.

27 Rigouts L, Portaels F. DNA fingerprints of *Mycobacterium tuberculosis* do not change during the development of resistance to various antituberculous drugs. Tubercle Lung Dis 1994; 75: 160.

28 Small P M, Shafer R W, Hopewell P C, et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N Engl J Med 1993; 328: 1137–1144.

29 Sonnenberg P, Murray J, Shearer S, Glynn J R, Kambashi B, Godfrey-Faussett P. Tuberculosis treatment failure and drug resistance—same strain or reinfection? Trans R Soc Trop Med Hyg 2000; 94: 603–607.

30 Quy H T, Lan N T, Borgdorff M W, et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? Int J Tuberc Lung Dis 2003; 7: 631–636.

31 Rastogi N, Ross B C, Dwyer B, et al. Emergence during unsuccessful chemotherapy of multiple drug resistance in a strain of *Mycobacterium tuberculosis*. Eur J Clin Microbiol Infect Dis 1992; 11: 901–917.

32 Vasquez L A L, Leo E, Quispe N, Salazar E, Bayona J, Becerra M C. Drug resistance trends among previously treated tuberculosis patients in a national registry in Peru, 1994–2001. Int J Tuberc Lung Dis 2004; 8: 465–472.

33 Espinal M A, Kim S J, Suarez P G, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA 2000; 283: 2537–2545.

34 McClatchy J K, Kanes W, Davidson P T, Moulding T S. Cross-resistance in *M. tuberculosis* to kanamycin, capreomycin and viomycin. Tubercle 1977; 58: 29–34.

35 Farmer P E, Kim J Y, Mitnick C D, Timperi R. Responding to outbreaks of multi-drug resistant tuberculosis: introducing DOTS-Plus. In: Reichman L B, Hershfield E S, eds. Tuberculosis: a comprehensive approach. New York, NY: Marcel Dekker, 2000: 447–470.

36 Safonova S G, Blinova L N, Golyshevskaya V I, et al. Evaluation of the Griess method for *M. tuberculosis* DST in the penitentiary system in Russia. Int J Tuberc Lung Dis 2001; 5 (Suppl 1): S156.

RÉSUMÉ

CONTEXTE : Lima, Pérou.

OBJECTIF : Décrire les profils de résistance aux médicaments des isolats de TB provenant de patients à risque de tuberculose multirésistante (TB-MR) et envisager les implications de ces observations pour le traitement.

SCHÉMA : Etude descriptive des résultats des tests de sensibilité aux médicaments (DST) sur les isolats de TB provenant de 1.680 patients qui avaient été référés pour suspicion de TB-MR entre 1996 et 2001.

RÉSULTATS : Sur 1.680 isolats testés, 1.144 (68%) étaient résistants à l'égard d'au moins un médicament antituberculeux et 926 (55%) étaient des souches TB-MR. Sur les 926 isolats MDR, 50 (5%) étaient résistants uniquement à l'INH et à la RMP, alors que 367 (40%) étaient résistants à l'égard d'au moins cinq médicaments de première ligne. Nous avons identifié 146 profils particuliers de résistance aux médicaments dont le plus courant rendait compte d'environ 11% des isolats résistants. La prévalence annuelle des isolats montrant une résistance à l'égard d'au moins cinq médicaments de première ligne a augmenté de façon significative pendant la période d'étude, passant de 29% à 37% ($P = 0,00086$).

CONCLUSIONS : Il s'agit ici d'un groupe très hétérogène de patients dont la maladie TB était causée par un spectre très large de souches souvent hautement résistantes aux médicaments. Un régime unique standardisé de retraitement pourrait s'avérer inadéquat pour traiter la plupart de ces patients. Pour développer de multiples régimes standardisés de retraitement ou des régimes individualisés de traitement et pour planifier la surveillance épidémiologique, il faut être capable d'exécuter des tests de sensibilité aux médicaments.

RESUMEN

LUGAR : Lima, Perú.

OBJETIVO : Describir los patrones de drogo resistencia de los aislamientos de TB de pacientes con riesgo de tuberculosis multidrogo resistente (TB-MDR), y considerar las implicancias de estos hallazgos para el tratamiento.

DISEÑO : Estudio descriptivo de los resultados de la prueba de resistencia a fármacos (PRF) para los aislamientos de TB de 1680 pacientes que fueron transferidos por sospecha de TB-MDR entre 1996 y 2001.

RESULTADOS : De 1680 aislamientos examinados, 1144 (68%) fueron resistentes al menos a un fármaco antituberculoso y 926 (55%) fueron cepas TB-MDR. De 926 aislamientos MDR, 50 (5%) fueron resistentes sólo a INH y RMP, mientras 367 (40%) fueron resistentes a por lo menos cinco fármacos de primera línea. Identificamos 146 patrones de drogo resistencia único, el más común de ellos representa el 11% de los aislamientos resistentes. La prevalencia anual de aislamientos con resistencia a por lo menos cinco fármacos de primera línea se incrementó significativamente durante el periodo de estudio, de 29% a 37% ($P = 0,00086$).

CONCLUSIONES : En este grupo de pacientes con cepas elevadamente resistentes, parece estar incrementando con el tiempo la prevalencia de resistencia a un alto número de fármacos. Un solo esquema estandarizado de retratamiento podría resultar inapropiado para curar a la mayoría de estos pacientes. Se requiere capacidad de hacer pruebas de sensibilidad para elaborar varios esquemas estandarizados o individualizados de retratamiento y para la vigilancia y la planificación.