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GLOBAL SURVEILLANCE FOR ANTITUBERCULOSIS-DRUG RESISTANCE, 1994–1997

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ABSTRACT

Background Drug-resistant tuberculosis threatens efforts to control the disease. This report describes the prevalence of resistance to four first-line drugs in 35 countries participating in the World Health Organization–International Union against Tuberculosis and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance between 1994 and 1997.

Methods The data are from cross-sectional surveys and surveillance reports. Participating countries followed guidelines to ensure the use of representative samples, accurate histories of treatment, standardized laboratory methods, and common definitions. A network of reference laboratories provided quality assurance. The median number of patients studied in each country or region was 555 (range, 59 to 14,344).

Results Among patients with no prior treatment, a median of 9.9 percent of *Mycobacterium tuberculosis* strains were resistant to at least one drug (range, 2 to 41 percent); resistance to isoniazid (7.3 percent) or streptomycin (6.5 percent) was more common than resistance to rifampin (1.8 percent) or ethambutol (1.0 percent). The prevalence of primary multidrug resistance was 1.4 percent (range, 0 to 14.4 percent). Among patients with histories of treatment for one month or less, the prevalence of resistance to any of the four drugs was 36.0 percent (range, 5.3 to 100 percent), and the prevalence of multidrug resistance was 13 percent (range, 0 to 54 percent). The overall prevalences were 12.6 percent for single-drug resistance (range, 2.3 to 42.4 percent) and 2.2 percent for multidrug resistance (range, 0 to 22.1 percent). Particularly high prevalences of multidrug resistance were found in the former Soviet Union, Asia, the Dominican Republic, and Argentina.

Conclusions Resistance to antituberculosis drugs was found in all 35 countries and regions surveyed, suggesting that it is a global problem. (N Engl J Med 1998;338:1641-9.)

IN the past 50 years, the proliferation of antimicrobial agents for use in humans and animals has placed an unprecedented selective pressure on microorganisms.[1] Drug resistance in patients with *Mycobacterium tuberculosis* infection became apparent soon after the introduction of effective antituberculosis agents.[2-5] It was not until the early 1990s, however, when outbreaks of multidrug-resistant tuberculosis were reported in patients with human immunodeficiency virus (HIV) infection in the United States and Europe,[6-16] that the problem received international attention.

Spontaneous mutations leading to drug resistance occur rarely in *M. tuberculosis,* and multidrug regimens can prevent the emergence of clinical drug resistance.[17] The problem of resistance results from treatment that is inadequate, often because of an irregular drug supply, inappropriate regimens, or poor compliance. Drug resistance is a potential threat to tuberculosis-control programs throughout the world.[18] Patients infected with strains resistant to multiple drugs are less likely to be cured,[19,20] particularly if they are infected with HIV or malnourished,[13,21-23] and their treatment is more toxic and more expensive than the treatment of patients with susceptible organisms.[24]

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The magnitude of the problem of resistance to antituberculosis drugs worldwide is not known. A review of the literature and unpublished reports from the past decade suggested high levels of resistance in some areas.[25] However, many of these studies were not based on representative samples or failed to distinguish between patients who had received previous treatment for tuberculosis and those who had not. Furthermore, there was no consensus on definitions, and laboratory results were not standardized. These limitations prevented an adequate assessment of the extent of the problem throughout the world and precluded meaningful comparisons among countries.

In 1994, the Global Tuberculosis Program of the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) initiated the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The purpose of the project, which is based on a network of reference laboratories, is to measure the prevalence of resistance to antituberculosis drugs in countries throughout the world with the use of standardized methods. This report summarizes the results of the first four years of the project.[26]

METHODS

Guidelines and Definitions

Common definitions and guidelines for the study were developed in 1994 and revised in 1996,[27] with three objectives: obtaining a sample of adequate size that is representative of patients with tuberculosis in the country, distinguishing between patients with no previous treatment and those with retreatment in order to separate primary from acquired drug resistance, and using standardized laboratory methods and quality assurance for drug-susceptibility testing.

Resistance to isoniazid, rifampin, ethambutol, and streptomycin was evaluated. Multidrug resistance was defined as resistance to at least isoniazid and rifampin.[28,29] A standardized algorithm was used to ascertain prior therapy with antituberculosis drugs[27]; in most cases, this information was obtained from the patients. Acquired drug resistance was defined as resistance in a patient who had previously received antituberculosis treatment for at least one month, including those with treatment failures and relapses. Primary drug resistance was defined as resistance to strains of *M. tuberculosis* in patients without histories or other evidence of previous treatment. Data on prior treatment were unavailable for less than 5 percent of patients, and these patients were excluded from the analysis.

Since Australia, India, and the Netherlands did not separate primary from acquired drug resistance, only the combined prevalence of drug resistance is presented for these countries. In countries conducting drug-resistance surveillance of all cases of tuberculosis, combined prevalence was estimated directly. For countries conducting surveys, which frequently oversampled cases with prior treatment, the contribution of acquired drug resistance to the combined prevalence of resistance was weighted according to the proportion of cases of retreatment among all registered cases.

Laboratory Standardization and Quality Assurance

Drug-susceptibility testing was conducted by national reference laboratories supported by a network of 20 supranational reference laboratories on five continents. In most of the industrialized countries, several local laboratories were involved in nationwide systems for ongoing surveillance of drug-resistant tuberculosis. Lowenstein–Jensen culture medium was used by the majority of laboratories. Procedures for drug-susceptibility testing conformed to one of several published methods[30-33]: the absolute-concentration method (in 1 country), the resistance-ratio method (in 4 countries or regions), or the proportion method with solid medium (in 23 countries) or radiometric Bactec 460 (in 7 countries or regions). In laboratories using the proportion method with solid medium, resistance was defined as at least 1 percent colony growth at critical concentrations of the drugs (i.e., 0.2 mg of isoniazid per liter, 2 mg of ethambutol per liter, 4 mg of dihydrostreptomycin sulfate per liter, and 40 mg of rifampin per liter).[27]

To ensure standardization among the laboratories, *M. tuberculosis* strains were sent periodically to the supranational reference laboratories for blind testing of drug susceptibility. The results of individual laboratories, as compared with those of the majority, improved from 1994 to 1996 and have been reported elsewhere.[34] Drug-susceptibility testing in national reference centers was standardized according to the assigned supranational laboratory. In 13 countries or regions, testing was performed by supranational laboratories, and the results were compared with those of the supranational network. A median of 20 strains were exchanged between laboratories for quality control. The median agreement between laboratories was 96 percent (range, 84 to 100 percent) for all four drugs.

Coordination of Surveys and Surveillance

A working group consisting of representatives of national tuberculosis programs and research institutions from more than 50 countries was established by WHO. Some participating countries had established surveillance programs, whereas others conducted ad hoc surveys on drug resistance. These surveys focused on sputum-smear–positive cases of tuberculosis in the public sector. Protocols were reviewed by WHO or IUATLD, and some countries were visited to ensure adequate implementation. A median of 6 percent of the specimens were contaminated or did not grow in the laboratory. Table 1 shows the sampling method used in each of the countries and regions surveyed; the WHO rating of tuberculosis control is also shown.[35]

Data Collection and Analysis

The principal investigators in each country or region reported the surveillance or survey results on standardized forms and submitted them to the coordinating center at WHO. SPSS software (SPSS, Chicago) was used for data management, tabulations, and statistical analysis.

RESULTS

During the first four years of the project, 35 countries or regions on five continents reported the results of drug-resistance surveys and surveillance programs. Twelve reports were from Europe, eight each from Africa and the Americas, four from the western Pacific regions, and three from Southeast Asia. The median number of patients with tuberculosis for whom drug-susceptibility data were available was 555, with a range of 59 to 14,344.

Tables 2 and 3 show the prevalence of primary drug resistance in 32 countries or regions within countries. The prevalence of acquired drug resistance was reported in 25 countries or regions (Table 4). Seven of the other 10 countries or regions excluded patients with previous antituberculosis treat-

TABLE 1. SURVEY METHODS USED BY 35 COUNTRIES AND REGIONS PARTICIPATING IN THE GLOBAL PROJECT.

COUNTRY OR REGION	CATEGORY OF TUBERCULOSIS CONTROL*	STUDY PERIOD	TYPE OF PROJECT	DURATION (MO)	TARGET AREA	TYPE OF SAMPLE
Argentina	1	1994	Survey	6	Countrywide	Cluster
Australia	5	1995	Surveillance	12	Countrywide	All cases
Benin	4	1995–1997	Survey	24	Countrywide	Proportionate clusters†
Bolivia	3	1996	Survey	11	Countrywide	Cluster
Botswana	4	1995–1996	Survey	22	Countrywide	Random sample
Brazil	1	1995–1996	Survey‡	14	Nearly countrywide	Proportionate clusters
Cuba	4	1995–1996	Surveillance	12	Countrywide	Proportionate clusters
Czech Republic	4	1995	Survey	6	Countrywide	All cases
Dominican Republic	1	1994–1995	Survey	21	Countrywide	Proportionate clusters
England and Wales	1	1995	Surveillance	12	Countrywide	All cases
Estonia	1	1994	Survey	12	Nearly countrywide	All cases
France	1	1995–1996	Surveillance	24	Sentinel sites	All cases
India (Delhi region)	2	1995	Survey	6	Province	All cases
Ivory Coast	4	1995–1996	Survey	12	Countrywide	Proportionate clusters
Kenya	3	1995	Survey	5	Nearly countrywide	Proportionate clusters
Latvia	1	1996	Survey	6	Countrywide	All cases
Lesotho	4	1994–1995	Survey	18	Countrywide	Proportionate clusters
Nepal	2	1996	Survey	6	Sentinel sites	All cases
Netherlands	4	1995	Surveillance	12	Countrywide	All cases
New Zealand	5	1995–1996	Surveillance	12	Countrywide	All cases
Northern Ireland	5	1995	Surveillance	12	Countrywide	All cases
Peru	4	1995–1996	Survey	4	Countrywide	Proportionate clusters
Portugal	4	1995	Survey	24	Countrywide	All cases
Puerto Rico	5	1994–1996	Surveillance	36	Islandwide	All cases
Republic of Korea	3	1994	Survey	3	Countrywide	All cases
Romania	1	1995	Survey	12	Countrywide	All cases
Russia (Ivanovo Oblast)	1	1995–1996	Survey‡	12	Province	All cases
Scotland	1	1995	Surveillance	12	Countrywide	All cases
Sierra Leone	3	1995–1996	Survey	24	Nearly countrywide	Random sample
Spain (Barcelona)	1	1995–1996	Survey	20	Citywide	Cluster
Swaziland	1	1994–1995	Survey	18	Countrywide	Proportionate clusters
Thailand	1	1996–1997	Survey‡	6	Countrywide	Proportionate clusters
United States	5	1995	Surveillance	12	Countrywide	All cases
Vietnam	3	1996–1997	Survey‡	10	Countrywide	Random clusters
Zimbabwe	4	1994–1995	Survey	30	Nearly countrywide	All cases

*WHO classifies tuberculosis-control programs as follows: 1, an incidence of more than 10 cases per 100,000 persons and no implementation of the WHO control strategy; 2, implementation of the strategy in less than 10 percent of the population; 3, implementation of the strategy in 10 to 90 percent of the population; 4, implementation of the strategy in more than 90 percent of the population; and 5, an incidence of less than 10 per 100,000 and no implementation of the strategy.

†Proportionate clusters refers to a weighted sampling technique based on clusters of patients who are representative of the patient population in the country.[27]

‡The survey is ongoing.

ment from the survey, and Australia, India (Delhi region), and the Netherlands reported combined prevalence only.

The prevalence of primary resistance to any of the four drugs tested ranged from 2.0 percent (in the Czech Republic) to 40.6 percent (in the Dominican Republic), with a median value of 9.9 percent. The median prevalence of resistance was higher for isoniazid (7.3 percent) and streptomycin (6.5 percent) than for rifampin (1.8 percent) or ethambutol (1.0 percent); the prevalence of resistance to rifampin alone was very low (Table 2). Resistance to all four drugs tested was found in a median of 0.2 percent of the cases (range, 0 to 4.6 percent). Primary multidrug resistance was found in every country surveyed except Kenya; the median prevalence was 1.4 percent (range, 0 to 14.4 percent) (Table 3).

Drug resistance was much more frequent in cases of retreatment than in cases of new treatment. The prevalence of acquired resistance to any of the four drugs ranged from 5.3 percent (in New Zealand) to 100 percent (in Ivanovo Oblast, Russia), with a me-

TABLE 2. PREVALENCE OF PRIMARY DRUG RESISTANCE IN 32 COUNTRIES AND REGIONS.

COUNTRY OR REGION	NO. OF PATIENTS	DRUG RESISTANCE*							
		ISONIAZID		RIFAMPIN		ETHAMBUTOL		STREPTOMYCIN	
		Single	*Any*	*Single*	*Any*	*Single*	*Any*	*Single*	*Any*
		percentage of patients							
Argentina	606	2.0	7.8	0.3	5.1	0.2	3.1	4.1	7.6
Benin	333	3.3	5.4	0	0.3	0	0.6	2.7	4.8
Bolivia	498	6.8	10.2	2.8	6.0	3.6	5.0	6.8	9.8
Botswana	407	1.2	1.5	0.7	1.0	0	0	1.5	1.5
Brazil	2,095	3.8	5.9	0.2	1.1	0.1	0.1	2.4	3.6
Cuba	763	1.0	2.0	0.1	0.9	0	0	6.0	6.9
Czech Republic	199	1.0	2.0	0	1.0	0	1.0	0	1.0
Dominican Republic	303	8.6	19.8	6.9	16.2	0.3	3.6	9.9	21.1
England and Wales	2,742	3.3	5.5	0.2	1.2	0	0.3	1.1	2.5
Estonia	266	4.1	21.1	0	10.2	0.8	7.1	6.4	21.1
France	1,491	0.8	3.4	0.2	0.7	0.1	0.3	4.5	7.0
Ivory Coast	320	3.1	11.3	0	5.3	0	0.3	2.2	6.9
Kenya	445	5.4	6.3	0	0	0	0	0	0.9
Latvia	347	5.5	31.7	0	14.7	0	4.9	2.0	28.0
Lesotho	330	5.2	7.9	0	0.9	0	0	0.9	3.0
Nepal	787	1.7	5.6	0.4	1.7	0	1.1	3.7	7.4
New Zealand	418	3.1	4.3	0	0.7	0	0.5	0.5	1.0
Northern Ireland	59	0	1.7	0	1.7	0	0	1.7	1.7
Peru	1,500	3.1	7.5	1.5	4.6	0.4	1.6	5.1	8.7
Portugal	815	1.8	7.1	0	1.8	0	0.2	6.5	11.7
Puerto Rico	369	4.1	6.8	0.5	2.7	1.4	3.0	1.1	2.4
Republic of Korea	2,486	4.5	7.7	0.3	2.2	0.5	2.6	1.5	2.7
Romania	1,636	3.2	7.4	0.5	3.4	1.7	1.7	0	3.3
Russia (Ivanovo Oblast)	248	1.2	12.9	0.4	5.2	0	6.5	13.7	26.6
Scotland	290	2.4	2.8	0	0.3	0	0.3	0	0.3
Sierra Leone	463	2.6	13.4	0.2	1.3	0.6	2.4	13.2	24.0
Spain (Barcelona)	218	2.3	3.2	0.5	0.9	1.8	1.8	4.1	4.6
Swaziland	334	3.9	9.0	0	0.9	0.3	0.9	2.4	7.2
Thailand	131	4.6	11.5	6.9	16.8	2.3	9.9	7.6	18.3
United States	13,511	4.0	7.8	0.6	2.4	0.5	2.0	3.0	6.2
Vietnam	640	6.7	20.0	1.1	3.6	0.2	1.1	11.1	24.1
Zimbabwe	676	1.3	3.3	0	1.9	0	0.6	0	0.7
Median	431.5	3.2	7.3	0.2	1.8	0.3	1.0	2.5	6.5
Minimum	59	0	1.5	0	0	0	0	0	0.3
Maximum	13,511	8.6	31.7	6.9	16.8	3.6	9.9	13.7	28.0

*Single denotes resistance only to the drug in question; any denotes resistance to the drug in question with or without resistance to other drugs.

dian value of 36.0 percent. Among previously treated patients, the median prevalence of resistance to all four drugs was 4.4 percent (range, 0 to 17 percent). The median prevalence of acquired multidrug resistance was 13.0 percent, with a range of 0 percent (in Kenya) to 54.4 percent (in Latvia) (Table 4).

The combined prevalence of resistance to any of the four drugs tested ranged from 2.3 percent (in the Czech Republic) to 42.4 percent (in the Dominican Republic), with a median value of 12.6 percent (Table 5). The prevalence of monoresistance was 7.5 percent (range, 1.2 to 25.2 percent). The prevalence of combined resistance to all four drugs was 0.6 percent (range, 0 to 7 percent). The median combined prevalence of multidrug resistance was 2.2 percent, with a range of 0 percent (in Kenya) to 22.1 percent (in Latvia).

DISCUSSION

The Global Project on Anti-Tuberculosis Drug Resistance Surveillance provides a standardized overview of the prevalence of drug resistance in many countries around the world. Drug-resistant strains were found in all countries surveyed, and resistance to isoniazid or streptomycin was most common. Although the overall prevalence of multidrug-resistant

TABLE 3. PREVALENCE OF VARIOUS PATTERNS OF PRIMARY DRUG RESISTANCE.

COUNTRY OR REGION	NO. OF PATIENTS	DRUG SUSCEPTIBILITY	DRUG RESISTANCE						MULTIDRUG RESISTANCE (95% CI)*
			ANY DRUG	ONE DRUG	TWO DRUGS	THREE DRUGS	FOUR DRUGS	>1 DRUG	
			percentage of patients						
Argentina	606	87.5	12.5	6.6	2.5	1.8	1.7	5.9	4.6 (3.1–6.7)
Benin	333	91.6	8.4	6.0	2.1	0.3	0	2.4	0.3 (0–1.9)
Bolivia	498	74.5	25.5	20.1	5.2	0.2	0	5.4	1.2 (0.5–2.7)
Botswana	407	96.3	3.7	3.4	0.2	0	0	0.2	0.2 (0–1.6)
Brazil	2,095	91.4	8.6	6.4	2.1	0	0	2.1	0.9 (0.6–1.4)
Cuba	763	91.7	8.3	7.2	0.5	0.5	0	1.0	0.7 (0.2–1.6)
Czech Republic	199	98.0	2.0	1.0	0	0	1.0	1.0	1.0 (0.2–4.0)
Dominican Republic	303	59.4	40.6	25.7	10.9	2.6	1.3	14.9	6.6 (4.2–10.2)
England and Wales	2,742	93.1	6.9	4.6	1.9	0.4	0	2.3	1.1 (0.7–1.5)
Estonia	266	71.8	28.2	11.3	7.1	5.3	4.5	16.9	10.2 (6.9–14.6)
France	1,491	91.8	8.2	5.6	2.1	0.5	0.1	2.6	0.5 (0.2–1.1)
Ivory Coast	320	86.6	13.4	5.3	6.3	1.6	0.3	8.1	5.3 (3.2–8.5)
Kenya	445	93.7	6.3	5.4	0.9	0	0	0.9	0 (0–1.1)
Latvia	347	66.0	34.0	7.5	12.4	9.5	4.6	26.5	14.4 (11.0–18.7)
Lesotho	330	91.2	8.8	6.1	2.4	0.3	0	2.7	0.9 (0.2–2.9)
Nepal	787	90.2	9.8	5.7	2.8	0.6	0.6	4.1	1.1 (0.6–2.2)
New Zealand	418	95.2	4.8	3.6	0.7	0.5	0	1.2	0.7 (0.2–2.3)
Northern Ireland	59	96.6	3.4	1.7	1.7	0	0	1.7	1.7 (0.1–10.3)
Peru	1,500	84.6	15.4	10.1	3.9	1.0	0.4	5.3	2.5 (1.8–3.4)
Portugal	815	86.3	13.7	8.3	3.9	1.2	0.2	5.4	1.7 (1.0–2.9)
Puerto Rico	369	90.0	10.0	7.0	1.4	1.4	0.3	3.0	1.9 (0.8–4.0)
Republic of Korea	2,486	89.6	10.4	6.9	2.3	1.0	0.2	3.5	1.6 (1.1–2.2)
Romania	1,636	90.3	9.7	5.3	2.6	1.7	0	4.3	2.8 (2.0–3.7)
Russia (Ivanovo Oblast)	248	71.8	28.2	15.3	6.5	2.8	3.6	12.9	4.0 (2.1–7.5)
Scotland	290	97.2	2.8	2.4	0	0	0.3	0.3	0.3 (0–2.2)
Sierra Leone	463	71.9	28.1	16.6	10.2	1.1	0.2	11.4	1.1 (0.4–2.7)
Spain (Barcelona)	218	90.4	9.6	8.7	0.9	0	0	0.9	0.5 (0–2.9)
Swaziland	334	88.3	11.7	6.6	3.9	1.2	0	5.1	0.9 (0.2–2.8)
Thailand	131	63.4	36.6	21.4	11.5	3.1	0.8	15.3	3.8 (1.4–9.1)
United States	13,511	87.7	12.3	8.2	2.8	0.7	0.6	4.1	1.6 (1.4–1.9)
Vietnam	640	67.5	32.5	19.1	11.6	0.9	0.9	13.4	2.3 (1.4–3.9)
Zimbabwe	676	96.7	3.3	1.3	1.2	0.1	0.6	1.9	1.9 (1.1–3.4)
Median	431.5	90.1	9.9	6.6	2.5	0.6	0.2	3.8	1.4 (0.5–3.0)
Minimum	59	59.4	2.0	1.0	0	0	0	0.2	0 (0–1.1)
Maximum	13,511	98.0	40.6	25.7	12.4	9.5	4.6	26.5	14.4 (11.0–18.7)

*Multidrug resistance was defined as resistance to at least isoniazid and rifampin. CI denotes confidence interval.

tuberculosis was low, the high prevalence in several countries warrants international attention.

In the Americas, one of the countries with a high prevalence of multidrug resistance was the Dominican Republic. The problem is probably the result of weaknesses in the tuberculosis-control program, although another possible explanation is migration between the Dominican Republic and New York City — where the prevalence of multidrug resistance was high in the early 1990s.[12] The high prevalence of primary multidrug resistance in Argentina may be related to outbreaks among HIV-infected patients in metropolitan hospitals.[36] Elsewhere in the Americas, including Brazil and the United States, there was relatively little multidrug-resistant tuberculosis.

Among the African countries surveyed, the prevalence of drug resistance was generally low, despite high rates of HIV coinfection[37] and political turmoil in some regions. The low level of multidrug resistance in particular may be due to the relatively late introduction of rifampin and the unavailability of antituberculosis drugs outside national programs. However, resistance to isoniazid was found in almost 10 percent of cases, rifampin is now available on the open market, and multidrug resistance was present in 5.3 percent of new cases in the Ivory Coast.

TABLE 4. PREVALENCE OF ACQUIRED DRUG RESISTANCE IN 25 COUNTRIES AND REGIONS.

COUNTRY OR REGION	NO. OF PATIENTS	DRUG SUSCEPTIBILITY	DRUG RESISTANCE						MULTIDRUG RESISTANCE (95% CI)*
			ANY DRUG	ONE DRUG	TWO DRUGS	THREE DRUGS	FOUR DRUGS	>1 DRUG	
			percentage of patients						
Argentina	288	58.7	41.3	12.2	9.7	11.1	8.3	29.2	22.2 (17.6–27.6)
Bolivia	107	58.9	41.1	32.7	7.5	0	0.9	8.4	4.7 (1.7–11.1)
Botswana	114	85.1	14.9	7.0	2.6	0.9	4.4	7.9	6.1 (2.7–12.7)
Brazil	793	85.6	14.4	7.3	5.5	1.5	0	7.1	5.4 (4.0–7.3)
Cuba	23	8.7	91.3	65.2	13.0	13.0	0	26.1	13.0 (3.4–34.7)
Czech Republic	16	87.5	12.5	6.3	0	0	6.3	6.3	6.3 (0.3–32.3)
Dominican Republic	117	47.9	52.1	22.2	11.1	12.8	6.0	29.9	19.7 (13.1–28.2)
England and Wales	148	67.6	32.4	12.2	13.5	5.4	1.4	20.3	16.9 (11.4–24.1)
Estonia	26	53.8	46.2	7.7	11.5	15.4	11.5	38.5	19.2 (7.3–40.0)
France	195	78.5	21.5	12.3	7.2	0.5	1.5	9.2	4.1 (1.9–8.2)
Kenya	46	63.0	37.0	30.4	6.5	0	0	6.5	0 (0–7.7)
Latvia	228	26.3	73.7	4.8	18.0	33.8	17.1	68.9	54.4 (47.7–60.9)
Lesotho	53	66.0	34.0	20.8	5.7	5.7	1.9	13.2	5.7 (1.5–16.6)
New Zealand	19	94.7	5.3	5.3	0	0	0	0	0 (0–17.6)
Peru	458	64.0	36.0	16.2	10.9	6.3	2.6	19.9	15.7 (12.6–19.5)
Portugal	117	62.4	37.6	12.0	11.1	9.4	5.1	25.6	18.8 (12.4–27.3)
Puerto Rico	22	72.7	27.3	4.5	13.6	4.5	4.5	22.7	13.6 (3.6–36.0)
Republic of Korea	189	47.1	52.9	14.3	14.8	16.9	6.9	38.6	27.5 (21.4–34.6)
Romania	1521	63.7	36.3	16.7	10.5	9.1	0	19.6	14.4 (12.7–16.3)
Russia (Ivanovo Oblast)	33	0	100	45.5	30.3	18.2	6.1	54.5	27.3 (13.9–45.8)
Sierra Leone	172	47.1	52.9	16.3	24.4	5.2	7.0	36.6	12.8 (8.4–18.9)
Spain (Barcelona)	44	70.5	29.5	9.1	4.5	9.1	6.8	20.5	20.5 (10.3–35.8)
Swaziland	44	79.5	20.5	9.1	4.5	2.3	4.5	11.4	9.1 (3.0–22.6)
United States	833	76.4	23.6	12.5	5.9	3.2	2.0	11.2	7.1 (5.5–9.1)
Zimbabwe	36	86.1	13.9	5.6	5.6	2.8	0	8.3	8.3 (2.2–23.6)
Median	114	64.0	36.0	12.2	9.7	5.4	4.4	19.9	13.0 (7.0–19.4)
Minimum	16	0	5.3	4.5	0	0	0	0	0 (0–7.7)
Maximum	1521	94.7	100	65.2	30.3	33.8	17.1	68.9	54.4 (47.7–60.9)

*Multidrug resistance was defined as resistance to at least isoniazid and rifampin. CI denotes confidence interval.

In Europe, the prevalence of drug resistance parallels the overall situation with tuberculosis in the region. In Western European countries, where tuberculosis-notification rates are low,[38] the median prevalence of primary multidrug resistance was less than 1 percent. Even in Barcelona, Spain, where 28 percent of patients with tuberculosis were coinfected with HIV, the prevalence was only 0.5 percent. These figures are well below the average worldwide prevalence, and in some countries, the problem seems to be confined to subgroups of recent immigrants.[39]

Eastern Europe, and particularly the former Soviet Union, has witnessed a recent reversal of previously declining rates of tuberculosis,[40] probably because of an irregular supply of drugs and nonstandardized regimens; nosocomial infections and outbreaks in prisons may be contributing factors.[23] The prevalence of multidrug-resistant tuberculosis was higher in the Baltic states than in any of the other countries surveyed. Unless sound control policies are implemented rapidly, the prevalence of multidrug-resistant tuberculosis is likely to increase in this region.

Tuberculosis remains endemic in many parts of Asia.[37,41,42] There was little primary drug resistance in Korea,[43] a finding consistent with previous periodic surveys.[44] The situation is different, however, in neighboring countries. Cases in India alone account for almost a third of the worldwide burden of tuberculosis,[37] and the combined prevalence of multidrug resistance in Delhi (13.3 percent) approaches that of the Baltic countries. The results of the ongoing surveys in Vietnam and Thailand also reflect the regional threat of multidrug-resistant tuberculosis.

These results suggest a link between the quality of tuberculosis-control programs and levels of drug resistance. Of the 13 countries in WHO category 1 (countries that have a high incidence of tuberculosis and have not implemented the WHO control strat-

TABLE 5. COMBINED PREVALENCE OF DRUG RESISTANCE IN 28 COUNTRIES AND REGIONS.

COUNTRY OR REGION	NO. OF PATIENTS	DRUG SUSCEPTIBILITY	DRUG RESISTANCE*							MULTIDRUG RESISTANCE (95% CI)†
			ANY DRUG	ISONIAZID	RIFAMPIN	ETHAMBUTOL	STREPTOMYCIN	ALL FOUR DRUGS	>1 DRUG	
			percentage of patients							
Argentina	894	82.0	18.0	12.5	9.2	5.2	10.9	2.9	10.4	8.0 (6.3–10.0)
Australia	705	90.5	9.5	7.5	1.1	0.3	7.5	0.1	6.0	0.7 (0.3–1.7)
Bolivia	605	70.6	29.4	10.3	9.2	5.6	11.1	0.2	6.2	2.1 (1.1–3.6)
Botswana	521	95.2	4.8	2.4	1.7	0.5	2.2	0.4	1.0	0.8 (0.3–2.2)
Brazil	2,888	91.0	9.0	6.3	1.5	0.2	3.8	0	2.5	1.3 (0.9–1.8)
Cuba	786	89.3	10.7	2.8	1.4	0	9.2	0	1.8	1.0 (0.5–2.1)
Czech Republic	215	97.7	2.3	2.3	1.2	1.2	1.2	1.2	1.2	1.2 (0.3–4.0)
Dominican Republic	420	57.6	42.4	22.4	18.6	5.1	21.8	2.0	17.2	8.6 (6.2–11.8)
England and Wales	2,890	91.8	8.2	6.8	2.1	0.4	2.9	0.1	3.2	1.9 (1.4–2.4)
Estonia	292	68.8	31.2	25.3	11.7	9.2	24.0	5.7	20.5	11.7 (8.3–16.1)
France	1,686	90.4	9.6	4.5	1.3	0.5	7.5	0.2	3.3	0.9 (0.5–1.5)
India (Delhi region)	2,240	67.6	32.4	28.8	14.0	7.0	18.1	3.5	21.5	13.3 (11.9–14.8)
Kenya	491	87.6	12.4	12.4	0	0	2.0	0	2.0	0 (0–1.0)
Latvia	575	58.4	41.6	39.0	23.0	7.4	35.1	7.0	34.7	22.1 (18.8–25.8)
Lesotho	383	89.6	10.4	9.3	1.2	0.2	3.9	0.1	3.4	1.2 (0.4–3.1)
Netherlands	1,104	85.9	14.1	8.6	1.2	0.4	8.7	0.1	4.2	1.1 (0.6–1.9)
New Zealand	437	95.2	4.8	4.3	0.7	0.5	0.9	0	1.1	0.7 (0.2–2.2)
Peru	1,958	81.5	18.5	10.0	7.0	2.3	10.0	0.7	7.5	4.5 (3.6–5.5)
Portugal	932	83.5	16.5	9.8	3.8	1.0	13.5	0.8	7.8	3.7 (2.6–5.2)
Puerto Rico	391	89.0	11.0	7.7	3.6	3.6	2.8	0.5	4.1	2.6 (1.3–4.8)
Republic of Korea	2,675	87.1	12.9	10.0	4.0	4.2	3.5	0.6	5.6	3.1 (2.5–3.9)
Romania	3,157	88.3	11.7	9.2	4.3	1.7	4.1	0	5.5	3.6 (3.0–4.3)
Russia (Ivanovo Oblast)	281	61.7	38.3	18.7	12.1	9.4	29.7	4.0	18.7	7.3 (4.6–11.1)
Sierra Leone	635	65.2	34.8	21.4	4.9	4.1	28.9	2.0	18.2	4.2 (2.9–6.2)
Spain (Barcelona)	262	88.6	11.4	5.4	2.7	2.3	5.8	0.6	2.7	2.3 (0.9–5.1)
Swaziland	378	87.2	12.8	9.6	1.9	1.4	8.3	0.6	5.9	1.9 (0.9–4.0)
United States	14,344	87.1	12.9	8.4	2.7	2.1	6.4	0.7	4.5	2.0 (1.7–2.2)
Zimbabwe	712	96.0	4.0	4.0	2.4	0.5	0.9	0.5	2.4	2.4 (1.4–3.9)
Median	552	87.4	12.6	9.2	2.7	1.5	7.5	0.6	5.0	2.2 (1.1–3.8)
Minimum	199	57.6	2.3	2.3	0	0	0.9	0	1.0	0 (0–1.0)
Maximum	14,344	97.7	42.4	39.0	23.0	9.4	35.1	7.0	34.7	22.1 (17.9–26.9)

*Resistance to isoniazid, rifampin, ethambutol, or streptomycin was defined as resistance to the drug with or without resistance to other drugs.

†Multidrug resistance was defined as resistance to at least isoniazid and rifampin. CI denotes confidence interval.

egy[35]), 7 (54 percent) had a prevalence of primary multidrug resistance that was higher than 2 percent, as compared with only 3 (20 percent) of the 15 countries in category 2, 3, or 4 (countries that have implemented the WHO control strategy) and none of those in category 5 (countries with a low incidence of tuberculosis). Studies in Kolin, Czechoslovakia,[45] Algeria,[46] Korea,[43,44] Baltimore,[47] New York,[48,49] and Texas[50] have shown that sound control policies are associated with decreases in drug-resistance levels. However, the relation between drug resistance and the quality of a control program is complex.[51] Areas not using rifampin would not have multidrug resistance. Immigration is an important contributor to drug-resistance rates in some countries.[39,52-54] A final consideration in using the prevalence of drug resistance to evaluate the performance of tuberculosis programs is the delayed effect of control interventions.

The Global Project on Anti-Tuberculosis Drug Resistance Surveillance, which represents a coordinated international effort, has several major achievements. One of the most important has been the establishment of an expanding, multinational system for the surveillance of drug resistance. Laboratory standardization and quality assurance provided the basis for reliable results.[34] This global system, one of the first in microbiology, could be a model for research on and surveillance of drug resistance in other diseases.

A working consensus on definitions and terminology was another achievement of this project. The WHO–IUATLD guidelines[27] effectively provided a common framework for determining the prevalence of drug resistance in regions that vary with respect to the burden of tuberculosis, the health care infrastructure, and laboratory procedures. However, distinguishing accurately between primary and acquired resistance is not always possible. In the absence of tuberculosis registries, this distinction depends on a patient's report of prior treatment and on the training of clinicians in obtaining reliable histories. Patients may be unaware of or choose to conceal information about previous treatment. Misclassification of patients with new and previously treated disease may have artificially increased the prevalence of primary drug resistance. Among previously treated patients, on the other hand, drug resistance may have been present in the original episode and perhaps contributed to the failure of treatment. Thus, not all cases of presumably acquired drug resistance can be ascribed to inadequate regimens or noncompliance.

The 35 countries included in this report do not constitute a complete atlas of the prevalence of drug resistance. Participating countries are located on five continents and represent various categories of tuberculosis control, but they were selected to some extent according to convenience rather than a strict, balanced sampling design. The prevalence of disease may be higher in some regions not included in the study, notably much of India and the People's Republic of China, since countries with better tuberculosis control and laboratory facilities were more likely to participate in the project.

Despite these limitations, our study provides comprehensive data on the prevalence of drug resistance in countries around the globe. Although the validity of the individual surveys varied,[26] the major weaknesses of earlier studies — namely, nonrepresentative sampling, nonstandardized laboratory results, and the failure to distinguish between primary and acquired resistance — were largely overcome in our study.

Several recommendations can be derived from the results of this project. First, the network of supranational reference laboratories should be maintained as a model and a global resource. Second, surveys need to be repeated in the same countries around the year 2000 to determine trends in multidrug resistance over time and in relation to programmatic interventions. Third, an adequate assessment of the level of multidrug-resistant tuberculosis in large countries (China, India, and Russia) requires an expansion of surveillance activities. Areas not adequately covered during the first phase of the global project, particularly in Africa and the Middle East, should be targeted in future surveys. However, surveillance may be difficult in some settings and can be justified only if the results are followed by appropriate interventions.[55] Therefore, continued international collaboration is essential.

Our study did not directly address the issue of treatment regimens. On the basis of previous experience,[43,44,46,56] no alterations of the standardized regimens recommended by WHO and IUATLD seem to be indicated at present.[57] However, individual patients with multidrug-resistant tuberculosis should, if possible, be referred for expert treatment at specialized centers.[58] Cost-effectiveness analyses are needed to determine the best allocation of resources to control multidrug-resistant tuberculosis.

Finally, additional research will be necessary to assess the transmissibility and clinical virulence of multidrug-resistant tuberculosis as compared with disease caused by drug-susceptible organisms. The effect of multidrug resistance on treatment outcomes in developing countries is another important issue, as is the risk of engendering additional resistance by using standard four-drug regimens in settings where primary multidrug resistance is common and routine drug-susceptibility testing is unavailable. Progress in understanding the genesis and consequences of resistance to antituberculosis drugs depends on continued surveillance and research.

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APPENDIX

The following members of the World Health Organization–International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance also participated in the study: Algeria — F. Boulahbal; Argentina — I. de Kantor, L. Barrera, and O. Latini; Australia — D. Dawson; Belgium — F. Portaëls; Benin — M. Gninafon, S. Anagonou, and A. Trébucq; Bolivia — M. Ferrel Urquidi and M. Camacho; Botswana — M. Mwasekaga and T. Kenyon; Brazil — A. Werneck Barreto, J.U. Braga, and M. Aiub Hijjar; China (Henan Province) — W. Guobin and C. Shao Ji; Cuba — J.A. Valdivia, E. Montoro, and A. Marrero Figueroa; Czech Republic — M. Havelková, M. Kubin, and O. Ostádal; Dominican Republic — M. Espinal; Estonia — A. Kruuner; France — V. Vincent, J. Grosset, V. Schwoebel, and B. Carbonnelle; Germany — G. Bretzel, K. Feldmann, S. Rüsch-Gerdes, V. Sticht-Groh, and R. Urbanczik; India — N.K. Jain; Italy — G. Angarano and S. Carbonara; Ivory Coast — M.I. Coulibaly, M. Dosso, and A. Trébucq; Japan — C. Abe and M. Aoki; Kenya — W.A. Githui; Latvia — R. Zalesky, C. Wells, A. Karklina, and R. Smithwick; Lesotho — B. Corcoran; Nepal — D.S. Bam, I. Smith, and P. Malla; the Netherlands — B. van Klingeren; New Zealand — M. Brett; Peru — J. Portocarrero Céliz, P.G. Suarez, and L. Vázquez Campos; Portugal — M.L. Antunes, M.F. Rodrigues, and M.F. Pereira; Puerto Rico — O. Joglar; Romania — E. Corlan; Russia (Ivanovo Oblast) — A.G. Khomenko and V.I. Golyshevskaya; Sierra Leone — L. Weitman and A.G. George; South Africa — K. Weyer; Spain — N. Martin-Casabona; Swaziland — R. Lemmer; Sweden — S. Hoffner and G. Källenius; Thailand — V. Payanandana and D. Rienthong; United Kingdom — J. Watson, F. Drobniewski, E. Mitchell, and P. Christie; United States — J. Crawford, R. Smithwick, E. McCray, and I. Onorato; Vietnam — Le Ngoc Van, N.D. Huong, N. Thi Ngoe Lan, and N. Viet Co; and Zimbabwe — J. van der Have.

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