Special Article

GLOBAL TRENDS IN RESISTANCE TO ANTITUBERCULOSIS DRUGS

MARCOS A. ESPINAL, M.D., DR.P.H., ADALBERT LASZLO, PH.D., LONE SIMONSEN, PH.D., FADILA BOULAHBAL, PH.D., SANG JAE KIM, SC.D., ANA RENIERO, PH.D., SVEN HOFFNER, PH.D., HANS L. RIEDER, M.D., M.P.H., NANCY BINKIN, M.D., M.P.H., CHRISTOPHER DYE, D.PHIL., ROSAMUND WILLIAMS, PH.D., AND MARIO C. RAVIGLIONE, M.D., FOR THE WORLD HEALTH ORGANIZATION–INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE WORKING GROUP ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE*

ABSTRACT

Background Data on global trends in resistance to antituberculosis drugs are lacking.

Methods We expanded the survey conducted by the World Health Organization and the International Union against Tuberculosis and Lung Disease to assess trends in resistance to antituberculosis drugs in countries on six continents. We obtained data using standard protocols from ongoing surveillance or from surveys of representative samples of all patients with tuberculosis. The standard sampling techniques distinguished between new and previously treated patients, and laboratory performance was checked by means of an international program of quality assurance.

Results Between 1996 and 1999, patients in 58 geographic sites were surveyed; 28 sites provided data for at least two years. For patients with newly diagnosed tuberculosis, the frequency of resistance to at least one antituberculosis drug ranged from 1.7 percent in Uruguay to 36.9 percent in Estonia (median, 10.7 percent). The prevalence increased in Estonia, from 28.2 percent in 1994 to 36.9 percent in 1998 ($P=0.01$), and in Denmark, from 9.9 percent in 1995 to 13.1 percent in 1998 ($P=0.04$). The median prevalence of multidrug resistance among new cases of tuberculosis was only 1.0 percent, but the prevalence was much higher in Estonia (14.1 percent), Henan Province in China (10.8 percent), Latvia (9.0 percent), the Russian oblasts of Ivanovo (9.0 percent) and Tomsk (6.5 percent), Iran (5.0 percent), and Zhejiang Province in China (4.5 percent). There were significant decreases in multidrug resistance in France and the United States. In Estonia, the prevalence in all cases increased from 11.7 percent in 1994 to 18.1 percent in 1998 ($P<0.001$).

Conclusions Multidrug-resistant tuberculosis continues to be a serious problem, particularly among some countries of eastern Europe. Our survey also identified areas with a high prevalence of multidrug-resistant tuberculosis in such countries as China and Iran. (N Engl J Med 2001;344:1294-303.)

A SURVEY conducted by the World Health Organization and the International Union against Tuberculosis and Lung Disease in 35 geographic sites revealed that drug-resistant tuberculosis was ubiquitous.[1,2] That survey did not include temporal changes in the prevalence of resistance to antituberculosis drugs, since data were available for only one year from each of the sites surveyed. In some countries with high burdens of tuberculosis, such as China, India, and Russia, surveys were conducted only in one administrative unit, if at all.[3] The global survey has now been expanded to assess trends and provide a more representative estimate of the global magnitude of the problem of drug-resistant tuberculosis.

METHODS

Methods previously described are summarized here,[1,2] and changes and new developments are described in detail. The new surveillance projects or surveys were conducted between 1996 and 1999. Data on temporal changes are from geographic sites that provided data for at least two time points between 1994 and 1999. Standard methods of surveillance were used.[4] Surveillance of drug resistance adhered to three principles: the samples of patients with tuberculosis in each country or region (e.g., state or province) were representative of that geographic site; recommended microbiologic methods were used by national laboratories that were monitored by an international system of proficiency testing; and in almost all countries, new cases were distinguished from previously treated cases.

New cases of tuberculosis were defined as incident cases in patients who, in response to direct questioning, denied having had previous antituberculosis treatment or having been treated for one month or more and, in countries where adequate documentation was available, for whom there was no evidence of a history of such treatment. Drug resistance among new cases was defined as the presence of resistant strains of *Mycobacterium tuberculosis* in new

From the Communicable Diseases Cluster, World Health Organization, Geneva (M.A.E., L.S., C.D., R.W., M.C.R.); the International Union against Tuberculosis and Lung Disease, Paris (A.L., H.L.R.); the Laboratory Centre for Disease Control, Ottawa, Ont., Canada (A.L.); the Institut Pasteur, Algiers, Algeria (F.B.); the Korean Institute of Tuberculosis, Seoul, Republic of Korea (S.J.K.); the Instituto Panamericano de Protección de Alimentos y Zoonosis, Buenos Aires, Argentina (A.R.); the Swedish Institute for Infectious Disease Control, Stockholm (S.H.); and the Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta (N.B.). Address reprint requests to Dr. Espinal at Communicable Diseases Control, Prevention, and Eradication, World Health Organization, 20 Ave. Appia, 1211 Geneva, Switzerland, or at espinalm@who.int.

*Other members of the group are listed in the Appendix.

cases of tuberculosis. Drug resistance among previously treated cases was defined as the absence of a response in patients with tuberculosis who had already received antituberculosis therapy for one month or more (as documented in the tuberculosis registry or in medical records or by the account of the patient) and who had begun a retreatment regimen. Previously treated patients included patients who had a relapse after having completed successful treatment in the past, patients in whom treatment failed, patients who returned to a health care provider after having discontinued treatment, and patients with chronic tuberculosis who had positive sputum smears after the completion of two fully supervised courses of treatment. These definitions are presented elsewhere.[5] Multidrug resistance was defined as resistance to at least isoniazid and rifampin.

Interlaboratory monitoring of the proficiency of testing for susceptibility to isoniazid, rifampin, streptomycin, and ethambutol has been conducted annually since 1994 within a network of 23 supranational reference laboratories. The methods used by the participating laboratories to test drug susceptibility include the absolute-concentration method, the resistance-ratio method, and the proportion method and its variants, including the BACTEC 460 radiometric culture method.[1,6,7] Descriptions of the methods and the early results of this program of proficiency testing have been published elsewhere.[7]

For each survey, the target population consisted of all registered patients in the survey area with sputum-smear–positive cases of tuberculosis. All newly registered patients with such cases were eligible for inclusion. In most countries, the survey area was the entire country. The calculation of the required sample size for surveys followed standard guidelines for the surveillance of drug resistance in tuberculosis.[4] The required sample size was calculated on the basis of the expected prevalence of resistance to rifampin among new cases of tuberculosis, which, in turn, was estimated on the basis of data from previous studies or from the national tuberculosis programs. In countries that were conducting surveillance of drug resistance, all registered patients with tuberculosis were enrolled for testing. Sites that provided data for two or more time points conducted their surveillance or surveys in similar populations of patients with new cases of tuberculosis and sampled them over time. Similar protocols, including similar sampling techniques and similar populations sampled between surveys, were used to ensure the comparability of populations.

Testing of drug susceptibility was performed by the national reference laboratory, which was linked to one supranational reference laboratory for the validation of data. The results for a subsample of all strains tested were validated and confirmed by the supranational laboratory.

Statistical Analysis

The software packages Epi Info (version 6.04, Centers for Disease Control and Prevention, Atlanta) and SPSS for Windows (version 7.5.2, SPSS, Chicago) were used for the analyses. Median values were calculated for the prevalence of drug resistance among new cases, among previously treated cases, for individual drugs, and for pertinent combinations. Data on prevalence are from the latest year of surveillance or survey in each participating site. The analysis of trends focused on drug resistance found in new cases and previously treated cases. The standard chi-square test and Fisher's exact test were used for the comparison of two data points (proportions), and the chi-square test for trends was used for the comparison of three or more data points. The coverage of the global project was estimated with the use of data on tuberculosis notification that were reported to the World Health Organization,[8-12] and the population figures used for 1997 were those estimated by the United Nations Population Division.[13] In the case of geographic sites for which data on the prevalence in two or more years were reported, only the latest one was used in the calculation of coverage. When surveys were conducted in administrative units of large countries (states, provinces, or oblasts), only the tuberculosis cases and populations of these administrative units were used in the calculation of coverage.

RESULTS

Prevalence

Between 1996 and 1999, patients were surveyed in 58 geographic sites, in 54 of which there was drug-resistant tuberculosis among new cases and in 48 of which there was drug-resistant tuberculosis among previously treated cases. Australia, Belgium, Canada, and Israel reported drug resistance but did not distinguish between new and previously treated cases. The surveillance and surveys conducted in this phase of the global project tested a total of 61,415 patients with tuberculosis (median per geographic site, 661; range, 41 [Northern Ireland] to 12,675 [United States]). These geographic sites accounted for approximately 610,000 of the 3.3 million cases of tuberculosis reported to the World Health Organization in 1997 (18 percent) and 1.5 billion of the world's 5.8 billion inhabitants (26 percent). Proficiency testing in 1998 by the supranational reference laboratories of susceptibility to the four drugs for which the national laboratories tested showed an overall sensitivity of 98 percent and an overall specificity of 95 percent.

Among new cases of tuberculosis, the prevalence of resistance to at least one drug ranged from 1.7 percent in Uruguay to 36.9 percent in Estonia (median, 10.7 percent) (Table 1). The prevalence of multidrug-resistant tuberculosis ranged from 0 percent in eight sites to 14.1 percent in Estonia (median, 1.0 percent). The prevalence of multidrug-resistant tuberculosis was also high in Henan Province, China (10.8 percent), Latvia (9.0 percent), the Russian oblasts of Ivanovo (9.0 percent) and Tomsk (6.5 percent), Iran (5.0 percent), and Zhejiang Province, China (4.5 percent). The prevalence of resistance to a single drug ranged from 1.3 percent in the Czech Republic to 17.9 percent in Sierra Leone (data not shown). Resistance to all four drugs for which testing was conducted ranged from 0 percent in 24 sites to 8.5 percent in Estonia (data not shown).

Among previously treated cases of tuberculosis, the prevalence of resistance to at least one drug ranged from 0 percent in Finland to 93.8 percent in Uruguay (median, 23.3 percent) (Table 2). The prevalence of multidrug-resistant tuberculosis among previously treated cases ranged from 0 percent in four sites to 48.2 percent in Iran (median, 9.3 percent). The median prevalence of resistance to a single drug was 11.3 percent, and the median prevalence of resistance to all four drugs was 1.8 percent (data not shown).

Temporal Changes

Data from two or more years were available from 28 of the 58 geographic sites. Of these sites, 24 provided data on new cases of tuberculosis, 20 provided data on previously treated cases, and 4 did not distinguish between the two types of cases. Table 3 shows trends among new and previously treated cases.

TABLE 1. PREVALENCE OF DRUG RESISTANCE AMONG NEW CASES OF TUBERCULOSIS, ACCORDING TO GEOGRAPHIC SITE, 1996–1999.*

COUNTRY OR REGION	YEAR	TARGET AREA	FRACTION SAMPLED (%)†	NO. OF PATIENTS	DRUG SUSCEPTIBILITY‡	DRUG RESISTANCE§									MULTIDRUG RESISTANCE (95% CI)¶
						ANY DRUG	ISONIAZID		RIFAMPIN		ETHAMBUTOL		STREPTOMYCIN		
							Single	*Any*	*Single*	*Any*	*Single*	*Any*	*Single*	*Any*	
					% of patients	% of patients									% of patients
America															
Canada‖	1997	All	100	1,593	89.5	10.5	4.1	7.9	0.1	1.1	0.3	1.3	2.3	5.1	1.1 (0.6–1.1)
Chile	1997	All	50	732	90.7	9.0	1.2	3.8	0.1	0.7	0.0	0.0	4.9	7.4	0.4 (0.1–1.2)
Colombia	1999	All	10	201	86.6	13.4	3.0	8.5	0.0	0.5	0.0	0.5	5.0	10.0	0.5 (0.0–2.7)
Cuba	1998	All	33	284	95.4	4.6	0.7	0.7	0.0	0.0	0.0	0.4	3.5	3.9	0.0 (0.0–1.3)
Mexico (Baja California, Oaxaca, Sinaloa)	1997	3 States	50	334	85.9	14.1	4.2	7.2	0.6	3.6	0.3	3.0	5.4	7.2	2.4 (1.0–4.7)
Nicaragua	1998	All	20	564	84.4	15.6	5.9	9.4	0.5	1.8	0.2	0.7	5.5	8.7	1.2 (0.6–3.0)
Peru	1999	All	7	1,879	82.0	18.0	3.6	9.0	0.7	4.0	0.8	2.6	6.8	11.7	3.0 (2.3–3.9)
Puerto Rico	1997	All	100	160	88.8	11.3	3.1	6.9	0.6	3.1	0.6	3.1	2.5	5.6	2.5 (0.7–6.3)
United States	1997	All	100	12,063	88.0	12.0	4.4	8.0	0.4	1.7	0.5	1.6	3.0	5.9	1.2 (1.0–1.4)
Uruguay	1997	All	100	484	98.3	1.7	0.4	0.4	0.4	0.4	0.0	0.0	0.8	0.8	0.0 (0.0–0.8)
Venezuela	1998	All	26	221	95.9	4.1	1.4	1.8	0.0	0.5	0.0	0.5	1.4	2.7	0.0 (0.0–1.6)
Europe															
Belgium‖**	1997	All	100	791	—	—	8.6	10.6	0.4	2.4	—	—	—	—	2.0 (1.2–3.3)
Czech Republic	1999	All	100	311	96.5	3.5	1.0	3.2	0.3	1.9	0.0	1.3	0.0	2.3	1.6 (0.5–3.7)
Denmark	1998	All	100	412	86.9	13.1	1.7	6.1	0.0	0.5	0.0	0.0	7.0	11.4	0.5 (0.0–1.7)
England and Wales	1997	All	100	3,053	92.8	7.2	2.9	5.0	0.1	0.9	0.0	0.3	3.6	6.6	0.8 (0.5–1.2)
Estonia	1998	All	100	377	63.1	36.9	2.7	26.0	0.3	14.3	0.3	11.1	10.3	32.4	14.1 (10.7–17.9)
Finland	1997	All	100	410	95.6	4.9	4.1	4.6	0.0	0.5	0.0	0.0	0.2	0.7	0.0 (0.0–0.9)
France	1997	Sentinel sites	14	787	90.7	9.3	2.3	3.6	0.3	0.3	0.1	0.1	5.3	6.6	0.0 (0.0–0.5)
Germany	1998	Sentinel sites	66	1,455	91.1	8.9	3.2	5.7	0.3	1.4	0.2	1.2	2.4	4.7	0.9 (0.5–1.5)
Italy	1999	Half the country	23	683	87.7	12.3	2.9	5.6	0.9	2.2	0.4	0.9	5.3	7.0	1.2 (0.5–2.3)
Latvia	1998	All	100	789	70.1	29.9	7.2	28.1	0.0	9.0	0.0	4.6	1.8	21.9	9.0 (7.1–11.2)
Netherlands	1996	All	100	1,042	89.7	10.3	3.5	6.3	0.3	1.1	0.4	0.5	2.1	4.8	0.6 (0.2–1.2)
Northern Ireland	1997	All	100	41	95.1	4.9	2.4	2.4	0.0	0.0	0.0	0.0	2.4	2.4	0.0 (0.0–8.6)
Norway	1996	All	100	138	89.1	10.9	4.3	8.0	0.0	2.2	0.0	0.7	2.9	4.3	2.2 (0.4–6.2)
Poland	1997	All	100	2,976	96.4	3.6	1.5	2.7	0.1	0.7	0.0	0.1	0.8	1.8	0.6 (0.4–1.0)
Russia															
Tomsk Oblast	1999	Province	100	417	71.0	29.0	2.4	19.4	0.5	7.9	0.2	7.0	7.4	24.9	6.5 (4.3–9.3)
Ivanovo Oblast	1998	Province	100	222	67.6	32.4	7.2	22.1	0.0	15.8	2.7	9.9	6.3	18.0	9.0 (5.6–13.6)
Scotland	1997	All	100	299	96.3	3.7	3.0	3.7	0.0	0.3	0.0	0.0	0.0	0.3	0.3 (0.0–1.8)
Slovakia	1998	All	100	589	97.3	2.7	1.4	2.0	0.0	0.3	0.0	0.2	0.7	1.0	0.3 (0.0–1.2)
Slovenia	1997	All	100	290	97.6	2.4	0.3	1.0	0.0	0.7	0.0	0.7	1.4	2.1	0.7 (0.1–2.5)
Spain (Barcelona)	1998	City	59	315	96.5	3.5	1.9	2.2	0.0	0.3	0.0	0.3	1.3	1.6	0.3 (0.0–1.8)
Sweden	1997	All	100	356	92.1	7.9	3.1	5.6	0.0	0.6	0.0	0.0	2.2	4.8	0.6 (0.1–2.0)
Switzerland	1997	All	100	322	96.9	3.1	2.8	2.8	0.0	0.0	0.0	0.0	0.3	0.3	0.0 (0.0–1.1)

TABLE 1. CONTINUED.

COUNTRY OR REGION	YEAR	TARGET AREA	FRACTION SAMPLED (%)†	NO. OF PATIENTS	DRUG SUSCEPTIBILITY‡	DRUG RESISTANCE§									MULTIDRUG RESISTANCE (95% CI)¶
						ANY DRUG	ISONIAZID		RIFAMPIN		ETHAMBUTOL		STREPTOMYCIN		
							Single	*Any*	*Single*	*Any*	*Single*	*Any*	*Single*	*Any*	
					% of patients	% of patients									% of patients
Africa															
Botswana	1998	All	10	638	93.7	6.3	3.6	4.4	0.2	0.6	0.0	0.2	1.6	2.2	0.5 (0.1–1.4)
Central African Republic (Bangui)	1998	City	100	464	83.6	16.4	4.1	9.5	0.2	1.3	0.0	2.4	6.5	11.0	1.1 (0.4–2.5)
Guinea	1998	Sentinel sites	15	539	85.3	14.7	4.5	9.3	0.2	0.7	0.0	0.6	5.2	9.5	0.6 (0.1–1.6)
Morocco (Casablanca)	1998	Province	25	510	91.4	8.6	2.7	7.8	0.2	2.4	0.0	0.2	0.6	4.5	2.2 (1.1–3.8)
Mozambique	1999	All	7	1,028	79.3	20.8	7.9	16.5	1.8	5.3	0.0	0.5	2.5	10.5	3.5 (2.5–4.8)
Sierra Leone	1997	Nearly all	15	117	75.2	24.8	3.4	10.3	0.0	0.9	0.0	0.0	14.5	21.4	0.9 (0.0–4.7)
South Africa (Mpumalanga Province)	1997	Province	43	661	92.0	8.0	3.5	5.6	0.2	1.7	0.0	0.5	2.3	3.8	1.5 (0.7–2.8)
Uganda (GLRA zones)	1997	3 Zones	3	374	80.2	19.8	3.2	6.7	0.3	0.8	2.4	6.1	7.0	13.4	0.5 (0.1–1.9)
Asia															
China															
Henan Province	1996	Province	11	646	65.0	35.0	5.1	24.0	1.4	14.6	0.5	7.7	6.3	26.0	10.8 (8.5–13.5)
Guangdong Province	1999	Province	5	461	87.0	13.0	4.8	9.3	0.4	3.5	0.0	2.4	2.8	6.1	2.8 (1.5–4.8)
Shandong Province	1997	Province	5	1,009	82.4	17.6	3.8	11.3	0.6	3.8	0.1	1.7	5.4	12.2	2.9 (1.9–4.1)
Zhejiang Province	1999	Province	4	802	85.2	14.8	2.7	8.9	1.6	6.5	0.2	1.5	3.7	9.0	4.5 (3.2–6.2)
Hong Kong SAR	1996	Province	100	4,424	87.8	12.2	2.6	6.1	0.0	1.6	0.5	1.6	5.3	8.2	1.4 (1.1–1.8)
India (Tamil Nadu State)	1997	State	2	384	81.3	18.8	7.6	15.4	0.5	4.4	0.5	7.0	1.8	6.8	3.4 (1.8–5.7)
Iran	1998	All	10	666	84.1	15.9	2.7	9.8	0.9	6.2	0.3	4.7	4.2	9.8	5.0 (3.4–6.9)
Israel‖	1998	All	100	307	80.8	19.2	1.6	15.6	0.3	8.5	0.0	6.2	3.3	16.0	8.1 (5.3–11.7)
Malaysia	1997	Peninsular Malaysia	9	1,001	95.2	4.8	1.0	1.6	0.4	0.5	0.4	0.5	2.4	3.0	0.1 (0.0–0.6)
Nepal	1999	All	100	104	94.2	5.8	1.0	1.9	0.0	1.0	0.0	0.0	3.8	4.8	1.0 (0.0–5.2)
Oman	1999	All	100	133	95.5	4.5	1.5	3.0	0.8	1.5	0.0	1.5	0.8	2.3	0.8 (0.0–4.1)
Republic of Korea	1999	All	100	2,370	89.4	10.6	4.9	8.6	0.7	3.0	0.0	1.1	1.2	3.1	2.2 (1.6–2.9)
Singapore	1996	All	100	980	95.2	4.8	2.6	3.4	0.1	0.4	0.0	0.3	1.3	1.9	0.3 (0.1–0.9)
Thailand	1997	All	13	1,137	74.5	25.5	6.2	12.5	2.0	5.8	3.0	8.0	5.6	11.2	2.1 (1.4–3.1)
Oceania															
Australia‖	1996	All	100	750	89.5	10.5	7.2	9.7	0.1	2.1	0.1	0.3	2.4	7.3	2.0 (1.1–3.3)
New Caledonia	1996	All	100	93	97.8	2.2	0.0	0.0	0.0	0.0	0.0	0.0	2.2	2.2	0.0 (0.0–3.9)
New Zealand	1997	All	100	179	88.8	11.2	6.7	9.5	0.0	1.1	0.6	0.6	1.1	2.8	1.1 (0.1–4.0)
Median for all countries				474	89.3	10.7	3.0	6.2	0.2	1.2	0.0	0.6	2.5	5.2	1.0 (0.3–2.4)

*CI denotes confidence interval, GLRA German Leprosy Relief Association, and SAR special administrative region.

†Numbers represent the proportion of all patients in the target area with new cases of smear- or culture-positive tuberculosis.

‡Drug susceptibility indicates strains of *M. tuberculosis* that are susceptible to all four drugs tested.

§"Single" indicates resistance to only one drug; "any" indicates resistance to a specific drug with or without resistance to the other drugs tested.

¶Multidrug resistance was defined as resistance to at least isoniazid and rifampin.

‖Data are for all patients (with no distinction made between new and previously treated cases).

**In Belgium, only resistance to isoniazid and rifampin was tested.

TABLE 2. PREVALENCE OF DRUG RESISTANCE AMONG PREVIOUSLY TREATED CASES OF TUBERCULOSIS, ACCORDING TO GEOGRAPHIC SITE, 1996–1999.*

COUNTRY OR REGION	YEAR	TARGET AREA	NO. OF PATIENTS	DRUG SUSCEPTIBILITY†	DRUG RESISTANCE‡									MULTIDRUG RESISTANCE (95% CI)§
					ANY DRUG	ISONIAZID		RIFAMPIN		ETHAMBUTOL		STREPTOMYCIN		
						Single	*Any*	*Single*	*Any*	*Single*	*Any*	*Single*	*Any*	
				% of patients	% of patients									% of patients
America														
Chile	1997	All	149	81.9	18.1	2.0	10.7	0.7	6.0	0.0	0.7	6.0	12.8	4.7 (1.9–9.4)
Cuba	1998	Province	43	67.4	32.6	9.3	18.6	0.0	7.0	0.0	0.0	14.0	20.9	7.0 (1.5–19.1)
Mexico (Baja California, Oaxaca, Sinaloa)	1997	3 States	107	58.9	41.1	10.3	32.7	1.9	28.0	0.0	14.0	2.8	18.7	22.4 (14.9–31.5)
Peru	1999	All	260	76.5	23.5	3.1	16.2	1.9	14.6	0.0	5.4	5.0	12.7	12.3 (8.6–16.9)
Puerto Rico	1997	All	12	41.7	58.3	16.7	50.0	8.3	25.0	0.0	8.3	0.0	25.0	16.7 (2.1–48.1)
United States	1997	All	612	79.1	20.9	6.4	15.4	2.3	8.0	0.7	4.1	2.5	8.3	5.6 (3.9–7.7)
Uruguay	1997	All	16	6.3	93.8	68.8	81.3	12.5	18.8	0.0	0.0	0.0	6.3	6.3 (0.2–30.2)
Venezuela	1998	All	24	83.3	16.7	4.2	12.5	0.0	12.5	0.0	4.2	0.0	4.2	8.3 (1.0–26.9)
Europe														
Czech Republic	1999	Province	52	78.8	21.2	7.7	21.2	0.0	11.5	0.0	11.5	0.0	9.6	11.5 (4.4–23.4)
Denmark	1998	All	32	87.5	12.5	0.0	12.5	0.0	3.1	0.0	3.1	0.0	12.5	3.1 (0.1–16.2)
England and Wales	1997	All	189	77.8	22.2	5.8	20.6	0.0	13.2	0.0	7.9	2.6	16.5	13.2 (8.7–18.9)
Estonia	1998	All	82	40.2	59.8	4.9	54.9	1.2	39.0	0.0	18.3	3.7	50.0	37.8 (27.3–49.1)
Finland	1997	All	2	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0–84.1)
France	1997	All	65	80.0	20.0	3.1	7.7	1.5	6.2	0.0	3.1	9.2	12.3	3.1 (0.4–10.7)
Germany	1998	All	256	82.0	18.0	7.4	16.0	0.4	6.6	0.4	3.9	1.2	7.0	6.3 (3.6–10.0)
Italy	1999	Half the country	127	39.4	60.6	4.7	43.3	4.7	44.9	0.8	26.8	6.3	29.9	33.9 (25.7–42.7)
Latvia	1998	All	224	69.2	30.8	3.1	29.0	1.3	25.0	0.0	10.3	0.4	24.6	23.7 (18.2–29.7)
Netherlands	1996	All	172	84.3	15.7	5.8	9.3	0.0	1.2	0.0	0.0	4.7	7.6	0.6 (0.0–31.9)
Norway	1996	All	6	83.3	16.7	0.0	16.7	0.0	16.7	0.0	0.0	0.0	0.0	16.7 (0.4–64.1)
Poland	1997	All	994	83.0	17.0	5.0	14.1	0.6	7.8	0.0	2.5	2.1	9.3	7.0 (5.5–8.8)
Russia														
Tomsk Oblast	1999	Province	232	42.2	57.8	1.7	42.7	0.4	31.0	0.9	21.1	9.9	53.4	26.7 (21.1–32.9)
Ivanovo Oblast	1998	Province	54	31.5	68.5	1.9	33.3	7.4	42.6	7.4	29.6	9.3	46.3	25.9 (14.9–39.6)
Scotland	1997	All	8	75.0	25.0	12.5	25.0	0.0	12.5	0.0	12.5	0.0	12.5	12.5 (0.3–52.6)
Slovakia	1998	All	157	84.1	15.9	3.2	10.8	1.3	10.2	0.0	5.1	0.0	4.5	8.3 (4.5–13.7)
Slovenia	1997	All	36	91.7	8.3	2.8	5.6	0.0	2.8	0.0	0.0	2.8	2.8	2.8 (0.1–14.5)
Spain (Barcelona)	1998	City	69	76.8	23.2	8.7	21.7	0.0	11.6	0.0	5.8	1.4	2.9	11.6 (5.1–21.5)
Sweden	1997	All	24	83.3	16.7	8.3	16.7	0.0	8.3	0.0	0.0	0.0	4.2	8.3 (1.0–26.9)
Switzerland	1997	All	40	72.5	27.5	10.0	25.0	2.5	15.0	0.0	10.0	0.0	10.0	12.5 (4.2–26.8)

TABLE 2. CONTINUED.

COUNTRY OR REGION	YEAR	TARGET AREA	NO. OF PATIENTS	DRUG SUSCEPTIBILITY†	DRUG RESISTANCE‡								MULTIDRUG RESISTANCE (95% CI)§
					ANY DRUG	ISONIAZID		RIFAMPIN		ETHAMBUTOL		STREPTOMYCIN	
						Single	*Any*	*Single*	*Any*	*Single*	*Any*	*Single*	*Any*
				% of patients	% of patients								% of patients
Africa													
Botswana	1998	All	145	77.2	22.8	6.2	16.6	4.1	13.1	0.0	2.8	2.1	4.8	9.0 (4.9–14.8)
Central African Republic (Bangui)	1998	City	33	63.6	36.4	9.1	30.3	0.0	21.2	0.0	18.2	3.0	12.1	18.2 (7.0–35.4)
Guinea	1998	Sentinel sites	32	50.0	50.0	9.4	50.0	0.0	28.1	0.0	18.8	0.0	34.4	28.1 (13.7–46.7)
Mozambique	1999	All	122	54.9	45.1	18.0	41.0	0.8	4.1	0.0	0.8	3.3	24.6	3.3 (0.9–8.2)
Sierra Leone	1997	Nearly all	13	38.5	61.5	30.8	61.5	0.0	23.1	0.0	7.7	0.0	23.1	23.1 (5.0–53.8)
South Africa (Mpumalanga Province)	1997	Province	100	78.0	22.0	5.0	16.0	1.0	9.0	0.0	1.0	5.0	7.0	8.0 (3.5–15.1)
Uganda (GLRA zones)	1997	3 Zones	45	48.9	51.1	17.8	37.8	0.0	4.4	6.7	11.1	4.4	22.2	4.4 (0.5–15.1)
Asia														
China														
Henan Province	1996	Province	726	34.0	66.0	4.8	48.8	2.6	43.5	0.6	18.9	7.4	50.7	34.4 (30.9–38.0)
Guangdong Province	1999	Province	63	61.9	38.1	3.2	23.8	1.6	22.2	0.0	14.3	9.5	20.6	17.5 (9.0–29.1)
Shandong Province	1997	Province	220	50.0	50.0	9.5	40.5	0.5	23.2	0.0	10.5	5.9	34.5	19.5 (14.5–25.4)
Zhejiang Province	1999	Province	140	40.7	59.3	7.1	44.3	6.4	45.0	0.7	17.9	4.3	27.9	35.0 (27.1–43.5)
Hong Kong SAR	1996	Province	783	73.1	26.9	3.8	17.4	1.3	11.6	0.6	6.0	6.8	16.3	9.6 (7.6–11.8)
India (Tamil Nadu State)	1997	State	16	50.0	50.0	12.5	50.0	0.0	25.0	0.0	31.3	0.0	12.5	25.0 (7.3–52.3)
Iran	1998	All	56	42.9	57.1	1.8	50.0	0.0	50.0	0.0	32.1	5.4	39.3	48.2 (34.6–61.9)
Malaysia	1997	Peninsular Malaysia	16	81.2	18.8	0.0	0.0	6.3	6.3	0.0	0.0	12.5	12.5	0.0 (0.0–20.5)
Nepal	1999	All	27	85.2	14.8	3.7	11.1	0.0	7.4	0.0	7.4	3.7	11.1	7.4 (0.9–24.8)
Republic of Korea	1999	All	283	78.1	21.9	6.7	17.3	1.8	10.2	0.0	3.5	1.4	6.7	7.1 (4.4–10.7)
Singapore	1996	All	151	86.8	13.2	5.3	11.9	0.7	5.3	0.0	2.0	0.0	2.0	4.0 (1.5–8.4)
Oceania														
New Caledonia	1996	All	12	91.7	8.3	0.0	8.3	0.0	0.0	0.0	0.0	0.0	8.3	0.0 (0.0–26.4)
New Zealand	1997	All	21	81.0	19.0	4.8	9.5	0.0	9.5	0.0	9.5	0.0	9.5	0.0 (0.0–16.1)
Median for all countries			64	76.7	23.3	5.1	19.6	0.5	12.0	0.0	5.9	2.3	12.4	9.3 (3.5–19.2)

*CI denotes confidence interval, GLRA German Leprosy Relief Association, and SAR special administrative region.

†Drug susceptibility indicates strains of *M. tuberculosis* that are susceptible to all four drugs tested.

‡"Single" indicates resistance to only one drug; "any" indicates resistance to a specific drug with or without resistance to the other drugs tested.

§Multidrug resistance was defined as resistance to at least isoniazid and rifampin.

TABLE 3. TRENDS IN DRUG RESISTANCE AMONG NEW AND PREVIOUSLY TREATED CASES OF TUBERCULOSIS.*

COUNTRY	PATIENTS WITH DRUG RESISTANCE																		P VALUE FOR DR	P VALUE FOR MR
	1994			1995			1996			1997			1998			1999				
	no.	% DR	% MR	no.	% DR	% MR	no.	% DR	% MR	no.	% DR	% MR	no.	% DR	% MR	no.	% DR	% MR		
New cases																				
Australia†				705	9.5	0.7	750	10.5	2.0											0.03
Belgium†‡				763		1.2	750		1.7	791		2.0								
Botswana							407	3.7	0.2				638	6.3	0.5					
Canada†							1,407	10.4	0.6	1,599	10.2	1.1								
Chile				920	10.8	0.0				732	9.3	0.4								
Cuba							700	8.3	0.7	241	8.7	0.0	284	4.6	0.0					
Czech Republic				393	3.3	0.8										311	3.5	1.6		
Denmark				382	9.9	0.3	383	8.6	0.0	405	13.8	0.2	412	13.1	0.5				0.04	
England and Wales				2742	6.9	1.1				3,053	7.2	0.8								
Estonia	266	28.2	10.2							332	29.5	11.1	377	36.9	14.1				0.01	
Finland	405	3.7	0.0	450	3.5	0.0	427	3.1	0.0	410	5.2	0.0								
France				1491	8.2	0.5				787	9.3	0.0								0.03
Germany										1,765	5.9	0.7	1455	8.9	0.9				0.001	
Latvia										587	29.3	9.0	789	29.9	9.0					
Nepal							787	9.8	1.1							104	5.8	1.0		
Netherlands†				1104	14.1	1.1	1,214	11.0	0.6										0.02	
New Zealand							418	4.8	0.7	179	11.2	1.1							0.004	
Northern Ireland				59	3.4	1.7				41	4.9	0.0								
Peru							1,500	15.4	2.5							1879	18.7	3.0	0.01	
Puerto Rico				369	10.0	1.9				160	11.3	2.5								
Republic of Korea	2486	10.4	1.6										2370	10.6	2.2					
Russia (Ivanovo Oblast)				33	24.2	6.1	259	26.3	4.6	201	21.4	5.0	222	32.4	9.0					
Scotland				290	3.4	0.3				299	3.7	0.3								
Sierra Leone							463	28.1	1.1	117	24.8	0.9								
Spain (Barcelona)							218	9.6	0.5				315	3.5	0.3				<0.001	
Sweden	402	5.0	0.5	436	8.9	0.2	391	7.2	1.3	356	7.9	0.6								
Switzerland							320	6.6	0.6	322	3.1	0.0							0.04	
United States							13,511	12.3	1.6	12,063	12.0	1.2								0.004
Previously treated cases																				
Botswana							114	14.9	6.1				145	22.8	9.0					
Cuba							11	100.0	9.1	25	36.0	24.0	43	32.6	7.0				<0.001	
Czech Republic				23	17.4	8.7										52	21.2	11.5		
Denmark				29	13.8	3.4	36	11.1	5.6	44	9.1	2.3	32	12.5	3.1					
England and Wales				148	32.4	16.9				189	22.2	13.2							0.03	
Estonia	26	46.2	19.2							48	41.7	25.0	82	59.8	37.8					0.04
Finland	11	27.3	27.3	7	42.8	14.3	7	42.8	0.0	2	0.0	0.0								
France				195	21.5	4.1				65	20.0	3.1								
Germany										310	18.1	6.8	256	18.4	6.3					
Latvia										197	33.0	17.8	224	30.8	23.7					
New Zealand							19	5.3	0.0	21	19.0	0.0								
Peru							458	36.0	15.7							260	23.5	12.3	<0.001	
Puerto Rico				22	27.3	13.6				12	58.3	16.7								
Republic of Korea	189	52.9	27.5										283	21.9	7.1				<0.001	<0.001
Russia (Ivanovo Oblast)							33	100.0	27.3	95	38.9	9.5	54	68.5	25.9					
Sierra Leone							172	52.9	12.8	13	61.5	23.1								
Spain (Barcelona)							44	29.5	20.5				69	23.2	11.6					
Sweden	37	8.1	2.7	24	12.5	0.0	26	11.5	3.8	24	16.7	8.3								
Switzerland							46	23.9	8.7	40	27.5	12.5								
United States							833	23.6	7.1	612	20.9	5.6								

*DR denotes resistance to any drug, and MR multidrug resistance. P values were calculated by the standard chi-square test, Fisher's exact test, or the chi-square test for trend. P values are shown only for significant differences.

†Data are for all patients (with no distinction made between new and previously treated cases). In the Netherlands, no distinction was made during the first year of the study.

‡In Belgium, only resistance to isoniazid and rifampin was tested.

Among countries with data available for three or more years, there was a statistically significant upward trend in the prevalence of resistance to any drug among new cases in Estonia, from 28.2 percent in 1994 to 36.9 percent in 1998 ($P=0.01$ for the trend across three data points), and in Denmark, from 9.9 percent in 1995 to 13.1 percent in 1998 ($P=0.04$ for the trend across four data points). Of the sites with data available for two years, Peru, New Zealand, and Germany had significant increases in the proportions of drug-resistant tuberculosis among new cases, whereas Barcelona (Spain) and Switzerland had significant decreases. Although no significant increases occurred in Latvia, Estonia, and the Russian oblast of Ivanovo, a high prevalence of multidrug-resistant tuberculosis (9.0 percent or higher in all sites) was still found among new cases in the most recent year of surveillance. France and the United States reported significant decreases.

Among previously treated cases, there was no evidence of an increase in the prevalence of resistance to at least one drug. There were, in fact, statistically significant decreases in Cuba, England and Wales, Peru, and the Republic of Korea. In Estonia, the prevalence of multidrug-resistant tuberculosis among previously treated cases increased from 19.2 percent in 1994 to 37.8 percent in 1998 ($P=0.04$). The prevalence of multidrug-resistant tuberculosis among all cases increased in Estonia from 11.1 percent in 1994 to 18.1 percent in 1998 ($P<0.001$, data not shown).

DISCUSSION

We attempted to quantify global trends in resistance to antituberculosis drugs by means of standard epidemiologic and microbiologic methods. Our findings indicate that multidrug-resistant tuberculosis continues to be a serious problem in countries of eastern Europe — especially Estonia, Latvia, and Russia. Such findings suggest the continued creation and increased circulation of drug-resistant strains due to poor tuberculosis control, which poses a threat to other countries. Trends in the Russian oblast of Ivanovo confirm that the situation is critical, and the high prevalence of drug resistance found in the newly surveyed oblast of Tomsk, in Siberia, shows that the problem exists in other parts of the country and may be widespread throughout Russia. There are newly identified areas with a high prevalence of multidrug-resistant tuberculosis in heavily populated countries such as China and Iran, which indicates that the creation of highly resistant strains of *M. tuberculosis* is not limited to one part of the world.

Since multidrug-resistant tuberculosis is associated with higher rates of failure and death than is drug-susceptible tuberculosis[14] and is more difficult and expensive to treat,[15] great pressure is being put on the health care systems of these countries. They should immediately adopt or expand programs of tuberculosis control by making use of proven and cost-effective interventions such as the directly-observed-treatment, short-course strategy of the World Health Organization.[16] The use of second-line drugs to cure multidrug-resistant tuberculosis and to reduce further transmission should be considered, but only as part of well-structured programs of tuberculosis control. Trials to assess the feasibility and cost effectiveness of the use of second-line drugs in settings with limited resources are currently being conducted as part of a new international initiative to manage multidrug-resistant tuberculosis.[17]

There is, however, reassuring news from this phase of the global project. There were no significant increases in the prevalence of multidrug-resistant tuberculosis among new cases in Botswana, Chile, Cuba, Czech Republic, Denmark, England and Wales, Finland, France, Germany, Nepal, the Netherlands, New Zealand, Northern Ireland, the Republic of Korea, Peru, Scotland, Sierra Leone, Spain (Barcelona), Sweden, Switzerland, and the United States. Many of these areas have been able to maintain high cure rates for tuberculosis.[18-22]

In the Americas, all the countries that were surveyed for the first time in this phase of the project — including Canada, Chile, Colombia, Mexico, Nicaragua, Uruguay, and Venezuela — showed no signs of a serious problem. Most African countries surveyed — even those with a high incidence of human immunodeficiency virus–related tuberculosis — were not seriously affected by multidrug-resistant tuberculosis.[23,24] This low prevalence could be the result of various factors, including the recent introduction of rifampin in these countries, the use of rifampin-free treatment regimens in the continuation phase of therapy, and the growing use of direct observation of treatment.[25,26] Lack of access to treatment may also contribute to the low prevalence of multidrug-resistant tuberculosis. Several countries in Africa with a very high incidence of tuberculosis — including the Democratic Republic of Congo, Ethiopia, and Nigeria — have not yet been surveyed.[27] Thus, more data are needed to produce a balanced picture of drug resistance in Africa.

In western Europe, multidrug-resistant tuberculosis is not a major public health problem. Among new cases in Denmark and Germany, there were increases in the prevalence of resistance to at least one drug. An increase in the transmission of strains resistant to streptomycin and isoniazid has been reported among persons in Denmark who are 25 to 54 years of age.[28] A higher prevalence of drug resistance among immigrants has also increased the overall prevalence in these countries.[28,29] The increase in the prevalence of multidrug-resistant tuberculosis in Australia could be due to a large influx of immigrants from neighboring countries where the prevalence is high.[30]

The two most populous countries, China and India,

account for an estimated 3.1 million of the world's estimated 8.0 million incident cases of tuberculosis (39 percent).[31] It has been estimated that 75 percent of the cases worldwide occur in five countries in Asia. The spread of multidrug-resistant tuberculosis in Asia could seriously hamper global efforts to control tuberculosis. The high prevalence of drug-resistant tuberculosis in this region emphasizes the need for a rapid expansion of the directly-observed-treatment, short-course strategy, which is being used for only 44 percent of the population of this region.[27] Management of multidrug resistance will require the wise use of second-line drugs.

Our data have some limitations. First, more information on the magnitude of drug-resistant tuberculosis is needed from countries with the highest rates of incidence of the disease.[31] Of the 22 countries with the highest incidence rates (which account for an estimated 80 percent of all new cases annually), only 11 have relevant data available. It is therefore necessary to continue expanding surveillance efforts in these countries. Second, selection bias and misclassification of previously treated cases as new cases cannot be completely ruled out in some of the participating sites. Third, for some sites, apparent decreases in the prevalence of multidrug-resistant tuberculosis among previously treated cases could be related to sampling bias between surveys. For surveys of drug resistance, the required sample size is normally calculated only for new cases, because the proportion of patients with previously treated cases is usually a small fraction of the total number of patients registered for treatment in the geographic site.

A paradox was observed in countries that have had good tuberculosis-control programs for many years. In countries such as Uruguay and Cuba, almost all previously treated patients had drug-resistant tuberculosis, but there were only small numbers of such patients. Therefore, a very small number of drug-resistant, previously treated cases should not be regarded as a sign of the failure of a control program.[32] Finally, several sites provided data for only two time points, which can only suggest a trend.

Despite such limitations, we attempt to present follow-up data on the magnitude of drug resistance around the world. The 58 new sites recruited to the study represent a 65 percent increase in the number of countries that have been surveyed.[1] The follow-up data confirm that the prevalence of multidrug-resistant tuberculosis is still alarmingly high in some countries in eastern Europe. Newly surveyed areas with a high prevalence have also been identified, suggesting that drug resistance is not limited to eastern Europe.

Measures to manage multidrug-resistant tuberculosis are urgently needed, but these will be successful only if the management of drug-susceptible tuberculosis, which accounts for the large majority of cases, is also successful.[33] Thus, if proper case management of drug-susceptible tuberculosis with first-line treatment regimens cannot be guaranteed,[34-36] the use of second-line drugs should be discouraged. The undisciplined use of both first- and second-line drugs will lead to the further spread of untreatable disease.

Supported by a grant from the United States Agency for International Development.

We are indebted to the national authorities in the participating countries and the institutions that hosted the national and international laboratories; to Dr. Eduardo Netto for his help with the analysis; and to Corazon Dolores and Zahra Ali-Piazza for secretarial assistance.

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: *Australia* — D. Dawson, W. Chew, F. Haverkort, R. Lumb, A. Sievers; *Belgium* — M. Fauville Dufaux, M. Wanlin, M. Uydebrouck, F. Portaels; *Botswana* — M. Mwasekaga, T. Kenyon, E. Talbot; *Canada* — H. Njoo, P. Nault; *Central African Republic (Bangui)* — E. Kassa-Kelembho; *Chile* — P. Valenzuela, S. Piffardi; *China (Beijing)* — D. Hong-jin, W. Sumin, Z. Ben; *China (Guangdong Province)* — Z. Qiu, Q. Ming, L. Hong-qiao; *China (Henan Province)* — W. Guobin, P. Vili, Z. Guolong, Z. Li; *China (Shandong Province)* — Z. Sheng, G. Xiang, Z. Guo; *China (Zhejiang Province)* — L.. Qun, W. Xiaomeng, H. Haibo; *Colombia* — C. Leon Franco, M. Irinirida, C. Sierra, N. Naranjo, M. Garzon; *Cuba* — J. Valdivia, E. Montoro, A. Marrero Figueroa; *Czech Republic* — M. Havelková, O. OšŤádal; *Denmark* — V. Thomsen, S. Glisman; *Estonia* — A. Krüüner, K. Vink, M. Danilovich; *Finland* — M. Viljanen, M. Kokki, P. Ruutu; *France* — J. Grosset, V. Vincent, B. Carbonnelle, J. Robert; *Germany* — M. Forßohm, S. Ruesch-Gerdes, K. Feldmann, G. Bretzel; *Guinea* — B. Mamadou Dian, O. Younoussa Sow, D. Aliomou; *Hong Kong Special Administrative Region of China* — M. Kai, M. Cheuk; *India (Tamil Nadu State)* — C. Paramasivan, K. Bhaskaran, P. Venkataraman, T. Frieden; *Iran* — M.-R. Masjedi, A.-A. Velayati, M. Bahadori, S. Javad Tabatabaii; *Israel* — D. Chemtob, O. Dreazen; *Italy* — G. Migliori, G. Besozzi, A. Cassone, G. Orefici, L. Fattorini, E. Iona; *Japan* — C. Abe; *Latvia* — J. Leimans, V. Leimane, D. Mihalovska; *Malaysia* — I. Kuppusamy, D. Padmini, S. Ramayah; *Mexico* — A. Santaella-Solis, S. Balandrano Campos, A. Flisser Steinbruch, R. Granich; *Morocco* — S.-E. Ottmani, J. Mahjour, P. Chaulet; *Mozambique* — A. MacArthur, P. Perdigao, S. Gloyd; *Nepal* — D. Singh Bam, P. Malla, I. Smith; *the Netherlands* — B. van Klingeren, C. Lambregts-van Weezenbeek, N. Kalisvaart; *New Caledonia* — P. Duval; *New Zealand* — M. Brett, R. Vaughan, M. Carr, C. Tocker; *Nicaragua* — L. Chacon, J. Cruz; *Norway* — E. Heldal, N. Brattås, P. Sandven; *Oman* — A. Ahmed Ba Omar, S. Al-Awan, S. Al-Busaidy, J. George; *Peru* — L. Vàsquez Campos, J. Portocarrero Céliz, P. Suarez; *Poland* — Z. Zwolska, K. Roszkowski; *Puerto Rico* — O. Joglar; *Republic of Korea* — G.-H. Bai; *Russia (Ivanovo Oblast)* — A. Khomenko (deceased), M. Stoyunin, N. Katulina, I. Danilova, V. Golyshevskaya; *Russia (Tomsk Oblast)* — A. Sloutsky, A. Goldfarb, T. Healing, M. Kimerling; *Sierra Leone* — L. Westman, A. George; *Singapore* — J. Yap, I. Snodgrass; *Slovakia* — M. Svejnochová, E. Rajecová, L. Chovan; *Slovenia* — M. Žolnir-Dovč, J. Sorli, D. Eržen; *South Africa* — K. Weyer; *Spain (Barcelona)* — N. Martin-Casabona; *Sweden* — G. Källenius, V. Romanus; *Switzerland* — P. Helbling, G. Pfyffer, J.-P. Zellweger; *Thailand* — V. Payanandana, D. Rienthong, S. Rienthong, L. Ratanavichit, H. Sawert; *Uganda* — F. Adatu, M. Aziz, H.-U. Wendl-Richter, T. Aisu; *United Kingdom* — J. Watson, F. Drobniewski, J. Herbert, P. Christie, B. Watt, B. Smyth, M. Crowe; *United States* — E. McCray, I. Onorato, B. Metchock, K. Laserson, A. Pablos-Méndez, D. Cohn, E. Brenner; *Uruguay* — V. Cuesta Aramburu, C. Rivas; *Venezuela* — R. Armengol, A. Guilarte, L. Albina Vázquez de Salas; *World Health Organization* — P. Nunn, R. Rodriguez, A. Seita, L. Blanc, D. Il Ahn.

REFERENCES

1. Anti-tuberculosis drug resistance in the world: The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994–1997. WHO/TB/97.229. Geneva: World Health Organization, 1997.

2. Pablos-Méndez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. N Engl J Med 1998;338:1641-9. [Erratum, N Engl J Med 1998;339:139.]

3. Chan-Tack KM. Antituberculosis-drug resistance. N Engl J Med 1998; 339:1079.
4. WHO/IUATLD. Guidelines for surveillance of drug resistance in tuberculosis. Int J Tuberc Lung Dis 1998;2:71-89.
5. WHO tuberculosis programme: framework for effective tuberculosis control. WHO/TB/94.179. Geneva: World Health Organization, 1994.
6. Canetti G, Fox W, Khomenko A, et al. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organ 1969;41:21-43.
7. Laszlo A, Rahman M, Raviglione M, Bustreo F. Quality assurance programme for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Laboratory Network: first round of proficiency testing. Int J Tuberc Lung Dis 1997;1:231-8.
8. Global Tuberculosis Programme. Global tuberculosis control: WHO report 1997. WHO/TB/97.225. Geneva: World Health Organization, 1997.
9. *Idem*. Global tuberculosis control: WHO report 1998. WHO/TB/98.237. Geneva: World Health Organization, 1998.
10. *Idem*. Global tuberculosis control: WHO report 1999. WHO/CDS/CPC/TB/99.259. Geneva: World Health Organization, 1999.
11. Raviglione MC, Dye C, Schmidt S, Kochi A. Assessment of worldwide tuberculosis control. Lancet 1997;350:624-9.
12. Netto EM, Dye C, Raviglione MC. Progress in global tuberculosis control 1995-1996, with emphasis on 22 high-incidence countries. Int J Tuberc Lung Dis 1999;3:310-20.
13. World population prospects: the 1998 revision. New York: United Nations, 1999.
14. Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA 2000;283:2537-45.
15. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. JAMA 1993;270:65-8.
16. The World Bank. World development report 1993: investing in health. New York: Oxford University Press, 1993.
17. Espinal MA, Dye C, Raviglione M, Kochi A. Rational 'DOTS plus' for the control of MDR-TB. Int J Tuberc Lung Dis 1999;3:561-3.
18. Kenyon TA, Mwasekaga MJ, Huebner R, Rumisha D, Binkin N, Maganu E. Low levels of drug resistance amidst rapidly increasing tuberculosis and human immunodeficiency virus co-epidemics in Botswana. Int J Tuberc Lung Dis 1999;3:4-11.
19. Marrero A, Caminero JA, Rodríguez R, Billo NE. Towards elimination of tuberculosis in a low income country: the experience of Cuba, 1962-97. Thorax 2000;55:39-45.
20. Farga V, Valenzuela P, Valenzuela MT, Yáñez A, García P, Scheel G. Una década de quimioterapia antituberculosa abreviada en Chile. Rev Chil Enf Respir 1991;7:94-106.
21. Hong YP, Kim SJ, Lew WJ, Lee SH, Lee EK. Cohort analyses of the treatment of smear-positive pulmonary tuberculosis patients under programme conditions in Korea, 1983-1994. Int J Tuberc Lung Dis 1998;2: 365-71.
22. Bloch AB, Cauthen GM, Simone PM, Kelly GD, Dansbury KG, Castro KG. Completion of tuberculosis therapy for patients reported in the United States in 1993. Int J Tuberc Lung Dis 1999;3:273-80.
23. De Cock KM, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. Int J Tuberc Lung Dis 1999;3:457-65.
24. Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS 1997;11:Suppl B:S115-S123.
25. Trébucq A, Anagonou S, Gninafon M, Lambregts K, Boulahbal F. Prevalence of primary and acquired resistance of *Mycobacterium tuberculosis* to antituberculosis drugs in Benin after 12 years of short-course chemotherapy. Int J Tuberc Lung Dis 1999;3:466-70.
26. Chaisson RE, Coberly JS, De Cock KM. DOTS and drug resistance: a silver lining to a darkening cloud. Int J Tuberc Lung Dis 1999;3:1-3.
27. Global tuberculosis control: WHO report 2000. WHO/CDS/TB/2000.275. Geneva: World Health Organization, 2000.
28. Thomsen VØ, Bauer J, Lillebaek T, Glisman S. Results from 8 years of susceptibility testing of clinical *Mycobacterium tuberculosis* isolates in Denmark. Eur Respir J 2000;16:203-8.
29. Borchardt J, Kirsten D, Jorres R, Kroeger C, Magnussen H. Drug-resistant tuberculosis in northern Germany: a retrospective hospital-based study of 1,055 patients from 1984 until 1993. Eur Respir J 1995;8:1076-83.
30. Dawson DJ, Cheah DF, Chew WK, Haverkort FC, Lumb R, Sievers AS. Tuberculosis in Australia, 1989-1992: bacteriologically confirmed cases and drug resistance. Med J Aust 1995;162:287-90.
31. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement: global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA 1999;282:677-86.
32. Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? Proc R Soc Lond [B] 2001;268:45-52.
33. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City — turning the tide. N Engl J Med 1995;333:229-33.
34. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986;133:423-30.
35. Tanzanian/British Medical Research Council. Controlled clinical trial of two 6-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1985;131:727-31.
36. Controlled trial of 6-month and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong: the results up to 30 months. Am Rev Respir Dis 1977;115:727-35.