2 METHODS

Methods used in the Global Project have been extensively described. For this report, therefore, the methods are only summarized, while changes and new developments are described in detail. For more detailed information, the reader is encouraged to consult the following publications: Anti-tuberculosis Drug Resistance in the World: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance (WHO/TB/97.229);1 the New England Journal of Medicine 1998; 338:1641–1649;2 the WHO Guidelines for Surveillance of Drug Resistance in Tuberculosis (WHO/TB/96.216);28 the International Journal of Tuberculosis and Lung Disease 1998; 2:71–89;29 and the International Journal of Tuberculosis and Lung Disease 1997; 1:231–238.47

2.1 BACKGROUND OF THE GLOBAL PROJECT

WHO and the IUATLD developed a set of standardized methods of surveillance in 1994. They also established an international Working Group in the same year. The Working Group delineated a system to ascertain the global magnitude of the problem of anti-tuberculosis drug resistance. This system comprised two components: 1) standardized surveys/surveillance implemented on representative samples of TB patients at country or region-within-country level, i.e., state-wide, province-wide; and 2) proper bacteriological methodology in national laboratories through an international system of proficiency testing. Guidelines for the performance of anti-tuberculosis drug resistance surveillance were developed.28,29 These guidelines introduced standard definitions and the procedures to implement drug resistance surveillance. They are currently available in Chinese, English, French, Italian, Russian, and Spanish.

2.2 UPDATE ON THE SUPRANATIONAL REFERENCE LABORATORY (SRL) NETWORK

The WHO/IUATLD supranational reference laboratory (SRL) network was created in 1994, to ascertain the accuracy of the susceptibility test methods used in different laboratories across the world, and to allow comparability of the surveillance data gathered in countries participating in the Global Project. Today, the network has evolved and 23 SRLs actively participate. While in 1994–1998 the Canadian Laboratory Centre for Disease Control (LCDC) acted as the coordinating centre, a new network coordinating centre was appointed in 1999, namely The Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium. Two new SRLs have been incorporated while two others are no longer part of the network. Other laboratories are in the process of evaluation to become SRLs. As of September 1999, the network has SRLs located in the Americas (Argentina, Chile, and United States), Europe
(Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Portugal, Spain, Sweden, United Kingdom), Africa (Algeria, South Africa), Asia (India, Japan, and the Republic of Korea), and Oceania (Australia) (see Table 1).

Due to the success of the SRL network, requests from many laboratories around the globe to participate in the network became increasingly difficult to handle. As a result, WHO and IUATLD stimulated the creation of regional sub-networks of laboratories within this global network. For the purpose of proficiency testing one or various SRLs located in specific geographic regions coordinate the distribution of the strains received from the global coordinating centre (Belgium SRL) to other laboratories not directly linked with the global coordinating centre. As of 1999, sub-networks exist or are underway in Africa (coordinated by the SRL in South Africa), Asia (coordinated by the SRL in the Republic of Korea), Europe (coordinated by the SRLs in France, Germany, Sweden, and United Kingdom), and Oceania (coordinated by the SRL in Australia). This umbrella system has brought into the network more than 100 laboratories worldwide.

Inter-laboratory testing of the proficiency of drug susceptibility testing (DST) is conducted regularly on an annual basis within the network. Six rounds of strain exchange have been carried out between 1994 and 1999. Up to 1998, in each round, the then coordinating centre in Canada sent two identical sets of ten clinical isolates of *M. tuberculosis* (20 cultures) to all SRLs. In 1999 this exercise was conducted for the first time by the newly appointed coordinating centre (Belgium SRL). The SRLs are asked to test the susceptibility pattern of the reference strains with their usual methodology, and classify the cultures as resistant or susceptible. The susceptibility results of *M. tuberculosis* strains are compared to a ‘gold standard’ that is derived from the results obtained by the majority of the laboratories (judicial criterion). Sensitivity, specificity and reproducibility of susceptibility testing are calculated for each laboratory and for each of the four drugs tested, i.e., INH, RMP, streptomycin (SM), and ethambutol (EMB).47

### Quality assurance indicators for DST of *M. tuberculosis* in the WHO/IUATLD SRL network

- **Sensitivity**: Ability to detect true resistance
- **Specificity**: Ability to detect true susceptibility
- **Efficiency or Accuracy**: Ratio between the number of correct results and the total number of results
- **Predictive value for resistance**: The rate of true resistance to total resistance
- **Predictive value for susceptibility**: The rate of true susceptibility to total susceptibility
- **Reproducibility or Reliability**: Intra-laboratory agreement between duplicate cultures expressed as percent agreement

Issues on sample size, identification and transportation of cultures, and analysis (Bayesian analysis) of the results, are explained in detail in several publications.47-50 The number of SRLs which participated in all consecutive rounds of strain exchange is shown below.
2.3 METHODS OF LABORATORY DIAGNOSIS OF ANTI-TUBERCULOSIS DRUG RESISTANCE

Four DST methods have been standardized and are widely used throughout the world to measure drug resistance of *M. tuberculosis*. In general, participating laboratories used the DST method with which they were most familiar: this was to eliminate variability due to disruption of routine testing through changing to a new testing procedure. The Global Project focuses on resistance to four of the first-line anti-tuberculosis drugs, INH, RMP, EMB and SM.

2.4 REVISED TERMS TO IDENTIFY DRUG RESISTANCE

Since its initiation in 1994 the Global Project had used the terms “acquired drug resistance” and “primary drug resistance”. For the purpose of this report, and in the light of discussions in several international fora, these terms will not be used any longer. In fact, these terms suggest the exact causative nature of drug resistance, which is rarely possible to assess. For instance, for several reasons patients may not disclose prior TB treatment. If this occurs, the term “primary drug resistance” may be used inappropriately, as resistance may have been acquired during the previous concealed treatment. On the other hand, patients who fail treatment may do so because their strain was initially resistant and not because it acquired resistance during treatment. In view of this, the terms “drug resistance among new cases” as a proxy of primary resistance, and “drug resistance among previously treated cases” as a proxy of acquired resistance, will be used throughout this report. Countries are encouraged to double-check the patient history and thoroughly evaluate medical records and charts to prevent misclassification of previously treated cases as new cases. This will prevent an overestimation of the prevalence of drug resistance among new TB cases.
2.4.1 Drug resistance among new cases (formerly “primary drug resistance”)

Drug resistance among new cases is defined as the presence of resistant strains of *M. tuberculosis* in new TB cases who, in response to direct questioning, deny having had previous anti-tuberculosis treatment or having been treated for more than a month and, in countries where adequate documentation is available, no evidence of such treatment history exists.

2.4.2 Drug resistance among previously treated cases (formerly “acquired drug resistance”)

Patients diagnosed with TB and started on anti-tuberculosis treatment, whose disease is due to bacilli which have developed drug resistance to one or more of the medications used during treatment, are said to have developed “acquired (or secondary) drug resistance”. This can only be demonstrated if the baseline susceptibility of the infecting strain to a given drug was documented before treatment with the specified drug was given. Such an approach is only possible—and only to some extent—in countries with the resources to perform such determinations and document the results systematically. In most settings, however, documentation of drug susceptibility before the initial treatment is not feasible.

The term “drug resistance in previously treated cases” will thus be used to indicate resistance in TB cases who have already received at least one month of anti-tuberculosis therapy, as documented in the tuberculosis registry, medical records, or by the patient’s account, and who are started on a retreatment regimen. The following categories apply: patients who relapse after having successfully completed treatment in the past; patients who failed treatment; patients who return after treatment default; and chronic patients. These definitions and terms are in line with those described in the WHO Framework for Effective Tuberculosis Control.

2.4.3 Combined prevalence of drug resistance

Combined prevalence of drug resistance is that measured in all cases regardless of prior drug treatment, in a given year. To obtain estimates of the combined prevalence of drug resistance, for geographical settings reporting data from new and previously treated cases separately, we used the same approach as outlined in the first report. For geographical settings conducting surveillance in 100% of their TB patients, we added the data from new and previously treated cases. For geographical settings conducting surveys, regardless of the different sampling schemes for new and previously treated cases, we also combined their separate reports. However, the contribution of drug resistance in previously treated
cases was weighted by the proportion of previously treated cases among all cases registered for treatment in the NTP in the year of the survey, instead of using the proportions of the two subgroups as reported. These proportions were obtained directly from the geographical settings or from reports available to WHO through the NTPs.

2.5 SURVEY AREAS AND SAMPLING STRATEGIES

New surveillance/survey projects presented in this report were carried out between 1996 and 1999 (Table 1). Data on trends are based on geographical settings with at least two data points between 1994 and 1999. Specific details from some of the participant geographical settings follow. As in the first report, England & Wales, Scotland, and Northern Ireland are analysed separately, since they reported their data separately for the years of study. A new study is reported from Italy, a country that was excluded from the global analysis in the first report because only HIV-infected patients had been studied. The results from Henan Province (in China) for 1996 are included in this report, having been put on hold for verification in the first report. Final data from the Thailand survey are presented since the results presented in the first report were preliminary and limited to 131 cases. Final data from Colombia, Guangdong Province (China), Nepal, and Venezuela were not available at the time this report was written; thus, the results included in this report should be considered preliminary.

2.5.1 Target survey areas

For each survey, the target population was made up of all registered smear-positive TB cases in the survey area. In most countries, the survey area was the entire country (Table 2). In Sierra Leone, the survey area excluded some centres a priori because of problems primarily related to access (i.e. remote regions, war zones, etc.). Surveys in some large countries, such as China, India, Mexico, the Russian Federation, and South Africa, were restricted to one or more large administrative units (e.g., province, state, oblast). Also, in the Central African Republic, Morocco and Spain, the surveys were limited to the cities of Bangui, Casablanca and Barcelona, respectively. In France, the surveyed area was again composed of selected sentinel sites. Denmark data did not include Greenland and Faroe Islands. In Uganda, the survey only included three of the nine regions of the country. These were the regions assisted by the German Leprosy Relief Association (GLRA).

2.5.2 Sample size and sampling strategies

Table 2 presents sampling methods used by the geographical settings participating in this phase of the Global Project. Sample size calculation for surveys followed the principles outlined in the WHO/IUATLD Guidelines for Surveillance of Drug Resistance in Tuberculosis. Sample size was calculated from the expected prevalence of RMP resistance in new TB cases, or the drug with the lowest prevalence of resistance, estimated from previous studies or based on data available from the NTP. In the absence of previous data, the educated guess of investigators was used. Annex 1 provides additional details and examples of sampling methodology. Previously treated cases were sampled but no calculation of sample size was made, because of the small proportion of this population in the total pool of TB cases. Thus, sampling of previously treated cases was in most instances limited to the period needed to complete the sample size of new TB cases.
<table>
<thead>
<tr>
<th>Supranational Reference Laboratory</th>
<th>Country or territory</th>
<th>Status</th>
<th>National Reference Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queensland Diagnostic and Reference Laboratory for</td>
<td>Australia</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Mycobacterial Diseases, Brisbane, Australia</td>
<td>New Zealand</td>
<td>Ongoing surveillance</td>
<td>TB Reference Laboratory, Green Lane Hospital, Auckland</td>
</tr>
<tr>
<td></td>
<td>Tamil Nadu, India</td>
<td>Completed survey</td>
<td>Tuberculosis Research Centre, Madras</td>
</tr>
<tr>
<td>INPPAZ - Instituto Panamericano de Proteccion de Alimentos</td>
<td>Argentina</td>
<td>Ongoing</td>
<td>Administracion Nacional de Laboratorios e Institutos de</td>
</tr>
<tr>
<td>y Zoonosis, Buenos Aires, Argentina</td>
<td>Chile</td>
<td>Completed survey</td>
<td>Salud (ANLIS), Buenos Aires</td>
</tr>
<tr>
<td></td>
<td>Cuba</td>
<td>Ongoing surveillance</td>
<td>Instituto de Salud Pública de Chile, Santiago de Chile</td>
</tr>
<tr>
<td></td>
<td>Nicaragua</td>
<td>Completed survey</td>
<td>Instituto de Medicina Tropical “Pedro Kouri”, Havana</td>
</tr>
<tr>
<td></td>
<td>Peru</td>
<td>Completed survey</td>
<td>Ministerio de Salud, Managua</td>
</tr>
<tr>
<td></td>
<td>Uruguay</td>
<td>Completed survey</td>
<td>Instituto Nacional de Salud, Lima</td>
</tr>
<tr>
<td></td>
<td>Venezuela</td>
<td>Ongoing survey</td>
<td>Comision Honoraria para la Lucha Antituberculosa y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enfermedades Prevalentes, Montevideo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Laboratorio Nacional de Referencia El Algodonal</td>
</tr>
<tr>
<td>Laboratory Centre for Disease Control, Ottawa, Canada</td>
<td>Canada</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Instituto de Salud Pública de Chile, Chile</td>
<td>Colombia</td>
<td>Ongoing survey</td>
<td>Instituto Nacional de Salud, Bogota</td>
</tr>
<tr>
<td>National Institute of Public Health, Czech Republic</td>
<td>Czech Republic</td>
<td>Ongoing survey</td>
<td>National Institut of TB and Respiratory Diseases, Bratislava</td>
</tr>
<tr>
<td></td>
<td>Slovakia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institut Pasteur, Paris, France</td>
<td>Bangui, Central African</td>
<td>Completed survey</td>
<td>Institut Pasteur de Bangui</td>
</tr>
<tr>
<td></td>
<td>Republic</td>
<td></td>
<td>National Reference Centre for the Surveillance of TB, Paris</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td></td>
<td>Laboratoire de Reference des Mycobacteries, Conakry</td>
</tr>
<tr>
<td></td>
<td>Guinea</td>
<td></td>
<td>Institut Pasteur de Maroc, Casablanca</td>
</tr>
<tr>
<td></td>
<td>Morocco</td>
<td></td>
<td>Laboratoire de bacteriologie, institut Pasteur de Nouvelle Caledonie</td>
</tr>
<tr>
<td></td>
<td>New Caledonia</td>
<td></td>
<td>National Reference TB Laboratory, Darsait</td>
</tr>
<tr>
<td></td>
<td>Oman</td>
<td></td>
<td>Nigerian Institute of Medical Research, Lagos</td>
</tr>
<tr>
<td></td>
<td>Nigeria</td>
<td></td>
<td>Central Tuberculosis Research Institute, Moscow</td>
</tr>
<tr>
<td></td>
<td>Ivanovo Oblast, Russian Fed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Reference Center for</td>
<td>Germany</td>
<td>Completed survey</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Mycobacteria, Borstel, Germany</td>
<td>Slovenia</td>
<td>Ongoing surveillance</td>
<td>University Clinic Respiratory Diseases and Allergy, Laboratory for Mycobacteria, Golnik</td>
</tr>
<tr>
<td>Kuratorium Tuberkulose in der Welt E. V., Gauting, Germany</td>
<td>Nepal</td>
<td>Ongoing survey</td>
<td>GENETUP National Tuberculosis Centre and Laboratory, Kathmandu</td>
</tr>
<tr>
<td>Armauer-Hansen Institute, Wurtzburg, Germany</td>
<td>Sierra Leone</td>
<td>Completed survey</td>
<td>The SRL itself</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td></td>
<td>Central Tuberculosis Laboratory, Kampala</td>
</tr>
<tr>
<td>Istituto Superiore di Sanità, Rome, Italy</td>
<td>Italy</td>
<td>Completed survey</td>
<td>Istituto Villa Marelli, Milan</td>
</tr>
<tr>
<td></td>
<td>Albania</td>
<td>Planning stage</td>
<td>Institute of TB and Lung Diseases</td>
</tr>
<tr>
<td>Research Institute of Tuberculosis, Japan</td>
<td>Cambodia</td>
<td>Planning stage</td>
<td>To be determined</td>
</tr>
<tr>
<td></td>
<td>Islamic Republic of Iran</td>
<td></td>
<td>National Research Institute of Tuberculosis and Lung</td>
</tr>
<tr>
<td></td>
<td>Malaysia</td>
<td></td>
<td>Disease, Tehran</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Institute of Respiratory Medicine, Kuala Lumpur</td>
</tr>
<tr>
<td>Country/Region</td>
<td>Survey Status</td>
<td>Survey Details</td>
<td>Laboratory/Institute</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Mongolia</td>
<td>Ongoing</td>
<td>National Centre for Tuberculosis, Ulaanbaatar</td>
<td>National Centre for Tuberculosis, Ulaanbaatar</td>
</tr>
<tr>
<td>Philippines</td>
<td>Planning stage</td>
<td>Central Tuberculosis Laboratory, Department of Respiratory Medicine, Ten Tock Seng Hospital, Singapore</td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td>Completed</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>Completed</td>
<td>To be determined</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Shandong Province, China</td>
<td>Completed</td>
<td>Provincial Reference Laboratory, Shandong Tuberculosis Reference Laboratory, Yung Fung Shee Memorial Centre, Hong Kong SAR</td>
<td></td>
</tr>
<tr>
<td>Henan Province, China</td>
<td>Completed</td>
<td>Henan Anti-tuberculosis Institute, Henan</td>
<td>Henan Anti-tuberculosis Institute, Henan</td>
</tr>
<tr>
<td>Guangdong Province, China</td>
<td>Completed</td>
<td>Provincial Reference Laboratory, Guangdong</td>
<td>Provincial Reference Laboratory, Guangdong</td>
</tr>
<tr>
<td>Zhejiang Province, China</td>
<td>Completed</td>
<td>Provincial Reference Laboratory, Zhejiang</td>
<td>Provincial Reference Laboratory, Zhejiang</td>
</tr>
<tr>
<td>Thailand</td>
<td>Completed</td>
<td>Laboratory of Tuberculosis Division (DCDC), Ministry of Health, Bangkok</td>
<td>Laboratory of Tuberculosis Division (DCDC), Ministry of Health, Bangkok</td>
</tr>
<tr>
<td>Netherlands Poland</td>
<td>Ongoing surveillance</td>
<td>Various laboratories under coordination by SRL itself</td>
<td>Various laboratories under coordination by SRL itself</td>
</tr>
<tr>
<td>National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, Netherlands</td>
<td>Completed survey</td>
<td>Microbiology Department, National TB and Research Institute, Warsaw</td>
<td>Microbiology Department, National TB and Research Institute, Warsaw</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Completed</td>
<td>National Reference Laboratory of Mozambique, Maputo</td>
<td>National Reference Laboratory of Mozambique, Maputo</td>
</tr>
<tr>
<td>Barcelona</td>
<td>Completed</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Medical Research Council National TB Research Programme, South Africa</td>
<td>Completed survey</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Mpumalanga Province, South Africa</td>
<td>Completed survey</td>
<td>Lusaka Chest Disease Laborator, Lusaka</td>
<td>Lusaka Chest Disease Laborator, Lusaka</td>
</tr>
<tr>
<td>Denmark</td>
<td>Ongoing surveillance</td>
<td>Statens Serum Institute, Copenhagen</td>
<td>Statens Serum Institute, Copenhagen</td>
</tr>
<tr>
<td>Estonia</td>
<td>Ongoing surveillance</td>
<td>Tuberculosis Reference Laboratory, Tartu</td>
<td>Tuberculosis Reference Laboratory, Tartu</td>
</tr>
<tr>
<td>Finland</td>
<td>Ongoing surveillance</td>
<td>Mycobacterial Reference Laboratory, National Public Health Institute, Turku</td>
<td>Mycobacterial Reference Laboratory, National Public Health Institute, Turku</td>
</tr>
<tr>
<td>Latvia</td>
<td>Ongoing surveillance</td>
<td>State Centre of Tuberculosis and Lung Diseases, Riga</td>
<td>State Centre of Tuberculosis and Lung Diseases, Riga</td>
</tr>
<tr>
<td>Norway</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Sweden</td>
<td>Ongoing surveillance</td>
<td>Lusaka Chest Disease Laborator, Lusaka</td>
<td>Lusaka Chest Disease Laborator, Lusaka</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Scotland</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Belgium</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Gambia</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Israel</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Ongoing surveillance</td>
<td>The SRL itself</td>
<td>The SRL itself</td>
</tr>
<tr>
<td>United States of America</td>
<td>Completed survey</td>
<td>Multiple laboratories following national standards</td>
<td>Multiple laboratories following national standards</td>
</tr>
<tr>
<td>Botswana</td>
<td>Ongoing surveillance</td>
<td>National Health Laboratory, Gaborone</td>
<td>National Health Laboratory, Gaborone</td>
</tr>
<tr>
<td>Mexico</td>
<td>Ongoing surveillance</td>
<td>Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (INDRE), Mexico City</td>
<td>Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (INDRE), Mexico City</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>Ongoing surveillance</td>
<td>Laboratorio Central de Tuberculosis, San Juan</td>
<td>Laboratorio Central de Tuberculosis, San Juan</td>
</tr>
<tr>
<td>Tomsk Oblast, Russian Fed</td>
<td>Completed survey</td>
<td>Central Tuberculosis Research Institute, Moscow</td>
<td>Central Tuberculosis Research Institute, Moscow</td>
</tr>
</tbody>
</table>
Table 2. Sampling methodology in the Global Project

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>REPORT YEAR</th>
<th>PROJECT STATUS</th>
<th>TOTAL DURATION (MONTHS)</th>
<th>TARGET AREA</th>
<th>SAMPLING METHOD</th>
<th>FRACTION SAMPLED (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1996</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Belgium</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Botswana</td>
<td>1999</td>
<td>Completed survey</td>
<td>22</td>
<td>Country-wide</td>
<td>Random</td>
<td>10</td>
</tr>
<tr>
<td>Canada</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Central African Republic (Bangui)</td>
<td>1998</td>
<td>Completed survey</td>
<td>3</td>
<td>City-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Chile</td>
<td>1997</td>
<td>Completed survey</td>
<td>6</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>50</td>
</tr>
<tr>
<td>China (Henan Province)</td>
<td>1996</td>
<td>Completed survey</td>
<td>9</td>
<td>Province</td>
<td>Proportionate cluster</td>
<td>11</td>
</tr>
<tr>
<td>China (Guangdong Province)</td>
<td>1998–99</td>
<td>Completed survey</td>
<td>12</td>
<td>Province</td>
<td>Proportionate cluster</td>
<td>5</td>
</tr>
<tr>
<td>China (Hong Kong SAR **)</td>
<td>1996</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Province</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>China (Shandong Province)</td>
<td>1997</td>
<td>Completed survey</td>
<td>12</td>
<td>Province</td>
<td>Proportionate cluster</td>
<td>5</td>
</tr>
<tr>
<td>China (Zhejiang Province)</td>
<td>1998–99</td>
<td>Ongoing survey</td>
<td>12</td>
<td>Province</td>
<td>Proportionate cluster</td>
<td>4</td>
</tr>
<tr>
<td>Colombia</td>
<td>1999</td>
<td>Ongoing survey</td>
<td>12</td>
<td>Country-wide</td>
<td>Cluster</td>
<td>10</td>
</tr>
<tr>
<td>Cuba</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>33</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1999</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Denmark</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Estonia</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Finland</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>France</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Sentinel sites</td>
<td>Random</td>
<td>66</td>
</tr>
<tr>
<td>Germany</td>
<td>1998</td>
<td>Completed survey</td>
<td>12</td>
<td>Sentinel sites</td>
<td>Random</td>
<td>15</td>
</tr>
<tr>
<td>Guinea</td>
<td>1998</td>
<td>Completed survey</td>
<td>10</td>
<td>State</td>
<td>Proportionate cluster</td>
<td>100</td>
</tr>
<tr>
<td>India (Tamil Nadu State)</td>
<td>1997</td>
<td>Completed survey</td>
<td>3</td>
<td>Country-wide</td>
<td>Random</td>
<td>10</td>
</tr>
<tr>
<td>Islamic Republic of Iran</td>
<td>1997–98</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Israel</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Half of the country</td>
<td>Cluster</td>
<td>23</td>
</tr>
<tr>
<td>Italy</td>
<td>1998–99</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Latvia</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>3</td>
<td>Peninsular Malaysia</td>
<td>Cluster</td>
<td>9</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1996–97</td>
<td>Completed survey</td>
<td>17</td>
<td>3 of 31 States</td>
<td>All cases</td>
<td>50</td>
</tr>
<tr>
<td>Mexico (Baja California, Oaxaca and Sinaloa)</td>
<td>1997</td>
<td>Completed survey</td>
<td>7</td>
<td>City-wide</td>
<td>Cluster</td>
<td>25</td>
</tr>
<tr>
<td>Morocco (Casablanca)</td>
<td>1997–98</td>
<td>Completed survey</td>
<td>6</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>7</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1998–99</td>
<td>Completed survey</td>
<td>9</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Nepal</td>
<td>1999</td>
<td>Ongoing survey</td>
<td>6</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1996</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>1995–96</td>
<td>Completed survey</td>
<td>21</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>1997–98</td>
<td>Completed survey</td>
<td>20</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>20</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>COUNTRY</td>
<td>REPORT YEAR</td>
<td>PROJECT STATUS</td>
<td>TOTAL DURATION (MONTHS)</td>
<td>TARGET AREA</td>
<td>SAMPLING METHOD</td>
<td>FRACTION SAMPLED (%)*</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
<td>----------------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Norway</td>
<td>1996</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Oman</td>
<td>1998–99</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Peru</td>
<td>1999</td>
<td>Completed survey</td>
<td>8</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>7</td>
</tr>
<tr>
<td>Poland</td>
<td>1996–97</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>1998–99</td>
<td>Completed survey</td>
<td>4</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Russian Fed. (Tomsk Oblast)</td>
<td>1998–99</td>
<td>Complete survey</td>
<td>12</td>
<td>Province</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Russian Fed. (Ivanovo Oblast)</td>
<td>1998</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Province</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Scotland</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>1997</td>
<td>Completed survey</td>
<td>6</td>
<td>Nearly country-wide</td>
<td>Random</td>
<td>15</td>
</tr>
<tr>
<td>Singapore</td>
<td>1996</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Slovakia</td>
<td>1998</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>South Africa (Mpumalanga Prov.)</td>
<td>1997</td>
<td>Completed survey</td>
<td>6</td>
<td>Province</td>
<td>Proportionate cluster</td>
<td>43</td>
</tr>
<tr>
<td>Spain (Barcelona)</td>
<td>1997–98</td>
<td>Completed survey</td>
<td>24</td>
<td>City-wide</td>
<td>Cluster</td>
<td>59</td>
</tr>
<tr>
<td>Sweden</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1997</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Uganda (GLRA supported zones)</td>
<td>1996–97</td>
<td>Completed survey</td>
<td>18</td>
<td>3 Zones</td>
<td>Cluster</td>
<td>3</td>
</tr>
<tr>
<td>United States of America</td>
<td>1997</td>
<td>Ongoing surveillance</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Uruguay</td>
<td>1997</td>
<td>Completed survey</td>
<td>12</td>
<td>Country-wide</td>
<td>All cases</td>
<td>100</td>
</tr>
<tr>
<td>Venezuela</td>
<td>1998</td>
<td>Ongoing survey</td>
<td>6</td>
<td>Country-wide</td>
<td>Proportionate cluster</td>
<td>100</td>
</tr>
</tbody>
</table>

* Sampled fraction of all eligible tuberculosis patients in the target area
** Special administrative region
*** German Leprosy Relief Association
METHODS

2.6 BACTERIOLOGICAL METHODS USED IN SURVEYS/SURVEILLANCE

The majority of laboratories used Löwenstein-Jensen (L-J) culture medium. A few others used the Ogawa culture medium. Identification of the strains was based on the niacin production test, the nitrate reduction test, the aminobenzoic acid (500 mg/l) and the thiophene carboxylic acid (2 mg/l) resistance test. Some countries use also hybridization probes. Species other than the pathogenic species of the *M. tuberculosis* complex were excluded from analysis.

Drug resistance tests were performed using the economic variant of the proportion method on L-J medium, the absolute concentration method, the resistance ratio method, or the radiometric Bactec 460 method (Table 3). The proportion method was the most frequently used (62% of the participating settings) in this phase of the Global Project. Resistance was expressed as the percentage of colonies that grew on critical concentrations of the drugs (i.e. 0.2 mg/l for INH, 2 mg/l for EMB, 4 mg/l for dihydrostreptomycin sulphate and 40 mg/l for RMP when L-J medium was used). The criterion for resistance to a particular drug was growth of 1% of the population on medium containing the critical concentration. The results of the tests were then recorded on standardized laboratory forms (see Annex 1), copies of which were collected by each national coordinator and reported to WHO.

Proficiency testing was conducted between participant settings and the corresponding SRLs, as in the first phase of the Global Project.1,2 Table 3 lists the number of specimens exchanged and the overall agreement (i.e. concordance of results) between national reference laboratories (NRLs) of participant geographical settings and SRLs for the four drugs evaluated. In most cases, significant discrepancies were clarified before implementing the survey.

2.7 COLLECTION OF DATA

All newly registered patients with smear-positive TB were eligible for inclusion, including children, foreign-born persons, hospitalized patients, and those with known HIV co-infection. As in the previous phase of the Global Project, HIV testing was not a systematic component of these surveys. Geographical settings that performed HIV testing as part of the survey were advised to follow international guidelines on counselling and confidentiality. Reports from Australia, Belgium, Canada, and Israel did not distinguish between resistance in new and previously treated cases, and only the combined prevalence of drug resistance is presented and analysed. Belgium reported resistance data for INH and RMP, since testing for EMB and SM was not systematically performed.

In several surveys (Benin, Henan and Shandong Provinces in China, Morocco, New Caledonia, Oman, Peru, and Uganda), re-interview and double-checking of the patients’ his-
tories was undertaken to reduce the possibility of misclassification of previously treated cases as new cases. In this phase of the Global Project, version 2 of the WHO software “Surveillance of Drug Resistance in Tuberculosis” (SDRTB 2.0) was used for data entry, management and analysis at the local level. Most industrialized countries use their own software for surveillance. Aggregated (all geographical settings) and individual (selected geographical settings) data were provided to WHO for global analysis. Demographics, including sex and age, prior history of TB therapy and HIV test results, were the variables recommended for collection.

2.7.1 Data collection by place of origin

For the first time, data according to the place of origin of patients were requested in this phase of the Global Project. A simple data collection form was designed (Annex 1) for projects to provide information on the magnitude of any drug resistance and MDR-TB according to indigenous and foreign-born populations. Responses to this request were mainly from low TB incidence countries.

2.7.2 Statistical analysis

Descriptive statistics of the study population and bivariate analyses were calculated in Epi-Info 6 and SPSS/Windows 7.5.2. Median values were calculated for the prevalence of drug resistance in new cases, previously treated cases, or combined, for individual drugs and pertinent combinations. In addition to median values, mean values were weighted by the estimated number of smear-positive cases in each geographical setting using the SPSS weighting procedure. This procedure weights cases for analysis based on the value of the weight variable. The distribution of the prevalence of the different patterns of drug resistance was illustrated using box-plots, which display the median, quartiles and outliers. The latest data point available for each geographical setting was used in box-plots, maps, and figures.

Estimation of coverage of the Global Project was done using TB cases reported to WHO, and population figures for year 1997 as estimated by the United Nations Population Division “World Population Prospects; 1998 Revision”. For geographical settings reporting more than two data points, only the latest one was used for these calculations. Also, for surveys carried out in administrative units of large countries (states, provinces, oblasts) only notified TB cases and population of these administrative units were used. It is important to acknowledge that estimates regarding coverage are approximations. They should be interpreted with caution because of the changes in population and in the incidence of TB over time. Nevertheless, while there is a certain degree of uncertainty about these estimates, TB incidence and population figures do not change grossly between years.

Standard chi-square and Fisher’s exact two-tailed test were used to compare differences between indigenous and foreign-born cases with TB (new and previously treated) for any drug resistance and MDR-TB.

2.8 TRENDS IN DRUG RESISTANCE SURVEILLANCE

In order to assess current trends in anti-tuberculosis drug resistance prevalence, geographical settings surveyed in the first phase of the Global Project were encouraged to repeat the surveys or to provide new data if a surveillance system was in place.
Table 3. Laboratory and performance at each of the NRLs in the Global Project

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>CULTURE METHOD</th>
<th>DST METHOD</th>
<th>PT* STRAINS</th>
<th>NRL/SRL AGREEMENT (%)</th>
<th>Specificity for RMP DST</th>
<th>PATIENTS TESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Bactec</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>750</td>
</tr>
<tr>
<td>Belgium</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion</td>
<td>20</td>
<td>90</td>
<td>100</td>
<td>791</td>
</tr>
<tr>
<td>Botswana</td>
<td>Löwenstein-Jensen</td>
<td>Resistance ratio</td>
<td>18</td>
<td>94</td>
<td>100</td>
<td>783</td>
</tr>
<tr>
<td>Canada</td>
<td>Various</td>
<td>Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>1593</td>
</tr>
<tr>
<td>Central African Republic (Bangui)</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>97</td>
<td>100</td>
<td>497</td>
</tr>
<tr>
<td>Chile</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>881</td>
</tr>
<tr>
<td>China (Henan Province)</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>292</td>
<td>91</td>
<td>92</td>
<td>1372</td>
</tr>
<tr>
<td>China (Guangdong Province)</td>
<td>Löwenstein-Jensen</td>
<td>Resistance ratio</td>
<td>30</td>
<td>96</td>
<td>97</td>
<td>524</td>
</tr>
<tr>
<td>China (Shandong Province)</td>
<td>Löwenstein-Jensen</td>
<td>Absolute concentration</td>
<td>30</td>
<td>94</td>
<td>100</td>
<td>5207</td>
</tr>
<tr>
<td>China (Zhejiang Province)</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>30</td>
<td>96</td>
<td>100</td>
<td>1229</td>
</tr>
<tr>
<td>Colombia</td>
<td>Ogawa</td>
<td>Proportion</td>
<td>20</td>
<td>97</td>
<td>100</td>
<td>201</td>
</tr>
<tr>
<td>Cuba</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>60</td>
<td>98</td>
<td>100</td>
<td>327</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Löwenstein-Jensen &amp; others</td>
<td>Proportion</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>363</td>
</tr>
<tr>
<td>Denmark</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>444</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Resistance ratio</td>
<td>20</td>
<td>96</td>
<td>100</td>
<td>3242</td>
</tr>
<tr>
<td>Estonia</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion + Bactec</td>
<td>65</td>
<td>90</td>
<td>100</td>
<td>499</td>
</tr>
<tr>
<td>Finland</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>95</td>
<td>100</td>
<td>412</td>
</tr>
<tr>
<td>France</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>852</td>
</tr>
<tr>
<td>Germany</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion + Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>1711</td>
</tr>
<tr>
<td>Guinea</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>26</td>
<td>95</td>
<td>100</td>
<td>571</td>
</tr>
<tr>
<td>India (Tamil Nadu State)</td>
<td>Löwenstein-Jensen</td>
<td>Resistance ratio</td>
<td>20</td>
<td>99</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td>Islamic Republic of Iran</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>260</td>
<td>94</td>
<td>100</td>
<td>722</td>
</tr>
<tr>
<td>Israel</td>
<td>Löwenstein-Jensen</td>
<td>Resistance ratio</td>
<td>20</td>
<td>95</td>
<td>100</td>
<td>307</td>
</tr>
<tr>
<td>Italy</td>
<td>Löwenstein-Jensen</td>
<td>Proportion + Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>810</td>
</tr>
<tr>
<td>Latvia</td>
<td>Löwenstein-Jensen</td>
<td>Absolute concentration</td>
<td>35</td>
<td>95</td>
<td>100</td>
<td>1013</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Ogawa</td>
<td>Absolute concentration</td>
<td>84</td>
<td>98</td>
<td>100</td>
<td>1017</td>
</tr>
<tr>
<td>Mexico (Baja California, Oaxaca and Sinaloa)</td>
<td>Löwenstein-Jensen</td>
<td>Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>441</td>
</tr>
<tr>
<td>Morocco (Casablanca)***</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>510</td>
<td>100</td>
<td>100</td>
<td>510</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>70</td>
<td>90</td>
<td>100</td>
<td>1150</td>
</tr>
<tr>
<td>Nepal</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>77</td>
<td>92</td>
<td>97</td>
<td>131</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Various</td>
<td>Absolute concentration</td>
<td>20</td>
<td>91</td>
<td>100</td>
<td>1214</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>8</td>
<td>95</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>9</td>
<td>100</td>
<td>100</td>
<td>564</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Resistance ratio</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>41</td>
</tr>
<tr>
<td>COUNTRY</td>
<td>CULTURE METHOD</td>
<td>DST METHOD</td>
<td>PT* STRAINS</td>
<td>NRL/SRL AGREEMENT (%)</td>
<td>Specificity for RMP DST</td>
<td>PATIENTS TESTED</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Norway</td>
<td>Löwenstein-Jensen</td>
<td>Bactec</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>282</td>
</tr>
<tr>
<td>Oman</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>9</td>
<td>91</td>
<td>100</td>
<td>133</td>
</tr>
<tr>
<td>Peru</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>16</td>
<td>100</td>
<td>100</td>
<td>2139</td>
</tr>
<tr>
<td>Poland</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion</td>
<td>40</td>
<td>96</td>
<td>100</td>
<td>3970</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>Bactec</td>
<td>Proportion &amp; Bactec</td>
<td>20</td>
<td>92</td>
<td>100</td>
<td>172</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>97</td>
<td>100</td>
<td>2653</td>
</tr>
<tr>
<td>Russian Fed. (Tomsk Oblast)</td>
<td>Löwenstein-Jensen</td>
<td>Absolute concentration</td>
<td>121</td>
<td>82</td>
<td>96</td>
<td>649</td>
</tr>
<tr>
<td>Russian Fed. (Ivanovo Oblast)</td>
<td>Löwenstein-Jensen</td>
<td>Absolute concentration</td>
<td>39</td>
<td>95</td>
<td>97</td>
<td>276</td>
</tr>
<tr>
<td>Scotland</td>
<td>Bactec</td>
<td>Proportion</td>
<td>17</td>
<td>100</td>
<td>100</td>
<td>307</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>130</td>
<td>95</td>
<td>100</td>
<td>130</td>
</tr>
<tr>
<td>Singapore</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Bactec</td>
<td>20</td>
<td>99</td>
<td>100</td>
<td>1131</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>94</td>
<td>90</td>
<td>746</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>10</td>
<td>100</td>
<td>100</td>
<td>326</td>
</tr>
<tr>
<td>South Africa (Mpumalanga Prov.)</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>89</td>
<td>91</td>
<td>761</td>
</tr>
<tr>
<td>Spain (Barcelona)</td>
<td>Löwenstein-Jensen &amp; Bactec</td>
<td>Proportion</td>
<td>20</td>
<td>95</td>
<td>100</td>
<td>384</td>
</tr>
<tr>
<td>Sweden</td>
<td>Löwenstein-Jensen</td>
<td>Bactec</td>
<td>20</td>
<td>94</td>
<td>100</td>
<td>380</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Various</td>
<td>Various</td>
<td>20</td>
<td>99</td>
<td>100</td>
<td>362</td>
</tr>
<tr>
<td>Thailand</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>30</td>
<td>91</td>
<td>97</td>
<td>1137</td>
</tr>
<tr>
<td>Uganda (GLRA supported zones ****)</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>121</td>
<td>98</td>
<td>100</td>
<td>419</td>
</tr>
<tr>
<td>United States of America</td>
<td>Various</td>
<td>Various</td>
<td>20</td>
<td>92</td>
<td>100</td>
<td>12675</td>
</tr>
<tr>
<td>Uruguay</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>20</td>
<td>98</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Löwenstein-Jensen</td>
<td>Proportion</td>
<td>13</td>
<td>90</td>
<td>100</td>
<td>245</td>
</tr>
</tbody>
</table>

* Number of strains exchanged between NRL and SRL for proficiency testing (PT)
** Special administrative region
*** All strains collected in Morocco were re-tested at the SRL due to the high discordant results on the quality control exercise. Values for agreement and specificity are those of SRL
**** German Leprosy Relief Association
28.1 Statistical analysis of trends
Analysis focused on drug resistance found in new cases, previously treated cases and in the combined prevalence of drug resistance. The following patterns of drug resistance were highlighted: any drug resistance, MDR-TB, any INH resistance, and any RMP resistance. Chi-square standard test was used for the comparison of two data points (proportions), and chi-square for trends was used for the comparison of three or more data points.

2.9 ECOLOGICAL ANALYSIS OF DRUG RESISTANCE AND NATIONAL TUBERCULOSIS PROGRAMME CHARACTERISTICS
In the first phase of the Global Report the prevalence of drug resistance in each geographical setting was correlated with characteristics of the NTP. One of the limitations of this analysis was the lack of sufficient statistical power to perform sub-analyses. The greater number of geographical settings available in the two phases of the Global Project combined (n = 72) increased substantially the statistical power to detect differences. Therefore, a new ecological analysis was done to compare aggregated data on drug resistance at group level (by geographical setting) with indicators of TB control and development. For geographical settings with more than two data points, the data collected in the most recent year of surveillance were used for this analysis.

2.9.1 Variables included in the ecological analysis
Outcome (dependent) variables examined in this report included:
- proportion of any drug resistance among new cases
- proportion of MDR-TB among new cases.
Potential explanatory (independent) variables examined in this report included:
- notified TB incidence rate
- proportion of all cases presenting to treatment that were previously treated [i.e. failures, patients returning after default, relapses and chronic cases];
- treatment success;

Geographical settings for which two or more data points in drug-resistant TB were analysed

- **AFRICA** Sierra Leone, Botswana
- **AMERICAS** Canada, Chile, Cuba, Peru, Puerto Rico, United States of America
- **EUROPE** Barcelona (Spain), Belgium, Czech Republic, Denmark, England & Wales, Estonia, Finland, France, Germany, Ivanovo Oblast (Russian Federation), Latvia, Netherlands, Northern Ireland, Scotland, Sweden, Switzerland
- **ASIA** Nepal, Republic of Korea
- **OCEANIA** Australia, New Zealand
• proportion of TB patients under treatment with SCC;
• proportion of TB patients under DOT;
• proportion of TB patients treated with fixed-dose combination (FDC) tablets;
• gross national product (GNP) per capita income;
• estimated proportion of TB patients infected with HIV.

Median values of any drug resistance and MDR-TB among new cases were estimated according to WHO geographical regions* and to WHO/DOTS control category.**

These data were obtained from the participating countries through a standardized questionnaire (see Annex 1) and from the publications *Global Tuberculosis Control* 1997, 1998, and 1999.58–60

Data reported to WHO in 1994, 1995, and 1996 were used to derive a three-year average treatment success in each participant setting. Patients registered in DOTS and non-DOTS areas were added to obtain the total number of patients registered in a given setting/area. Then, patients who were not evaluated (unknown outcome) were excluded. If the total number of patients evaluated was less than 10% of all smear-positive cases registered for the setting, the data were excluded since they were judged not to be representative.

2.9.2 Statistical analysis of ecological data

Initially, associations between continuous predictors and drug resistance values were evaluated by the Spearman’s correlation coefficient ($r_s$). Scatterplots were generated to illustrate selected correlations. Weighted logistic regression modelling was used to explore the contribution of different variables to the prevalence of any drug resistance and of MDR-TB (separate modelling for both response variables) in new TB cases. Since the prevalence of any drug resistance and of MDR-TB take the form of proportions in each geographical setting, these variables are strictly bounded (i.e., no percentage > 100% or < 0%) and thus follow a binomial distribution (i.e. number of TB cases with any drug resistance out of the total number of cases tested). Therefore, to ensure linearity we used the logit link function to regress the explanatory or independent variables on the response or dependent variable. Modelling was weighted using the individual sample sizes (of each geographical setting) as weights in order not to lose information of the size of the sample from which such proportions were estimated. If only the percentages of any drug resistance or MDR-TB are used as dependent variables, sample sizes are not taken into account.66

Each variable was modelled by univariate logistic regression and plotted against the response variable in order to explore its individual contribution as well as departures from normality and variance instability. As a result, three variables were transformed: GNP per capita income and TB incidence into the logarithmic scale; and the proportion of patients under SCC into the arcsine or angular transformation.

Multivariate weighted logistic regression modelling was used to obtain adjusted estimates. Several models were explored using the backward elimination method in order to find the model that best fitted the data. To assess the goodness of fit of the models and account for over-dispersion (i.e., random variation), we divided the Pearson $\chi^2$ value by the

* AFR for sub-Saharan Africa, AMR for the Americas, EMR for the Eastern Mediterranean region, EUR for Europe, SEAR for South-East Asia, and WPR for the Western Pacific Region
** Category 0 for countries not reporting to WHO, category 1 for countries not implementing DOTS and TB notification rate $>10/100 000$, category 2 for countries implementing DOTS in $<10\%$ of the population, category 3 for countries implementing DOTS in $10\%$–$90\%$ of the population, category 4 for countries implementing DOTS in $>90\%$ of the population, and category 5 for countries not using DOTS and TB notification rates $<10/100\ 000$
degrees of freedom and compared the resulting scaled deviances for terms in the model using an $F$-Test instead of $\chi^2$ (as in conventional ANOVA).

2.10 EFFECT OF DEMOGRAPHICS AND OTHER INDIVIDUAL PATIENT’S DATA ON DRUG RESISTANCE

2.10.1 Participant countries and procedures
Population-based patient data from 11 geographical settings, surveyed within the WHO/IUATLD Global Project between 1994 and 1998, were used to assess the effects of demographic characteristics (age, sex), prior history of anti-TB treatment, and HIV on the dynamics of drug-resistant TB. Data were available from Bolivia, Dominican Republic, Republic of Korea, Lesotho, Nepal, Peru, Portugal, Sierra Leone, Swaziland, Barcelona (Spain), and Shandong Province (China). These geographical settings provided (before a pre-established deadline) detailed individual-level data on the patients enrolled in their drug resistance studies. Some other geographical settings also provided individual data. However, since these data arrived late, they could not be included in this analysis.

Patients also reported the number of past episodes of treatment and number of months of treatment during each episode. This information allowed the calculation of the total time a patient was on prior TB treatment. In addition, clinical and laboratory records were reviewed and abstracted to detect previous treatment for TB.

At each site, data were entered into the WHO software for drug resistance, SDRTB-2. Data were then sent to WHO for review and merging into a global database. Inconsistencies and apparent data entry errors were discussed and clarified with the survey coordinators of each geographical setting when necessary. Since SDRTB-2 allowed the investigators to adapt the original entries to the local conditions, including translation to languages other than English, for the purpose of this analysis electronic data provided in other languages were not used.

2.10.2 Statistical analysis of determinants of anti-tuberculosis drug resistance
Statistical analysis was performed using STATA (Stata statistical software. Release 5.0. College Station, Texas: Stata Corporation, 1997). Simple proportions and 95% confidence intervals (95% CI) were calculated; differences between proportions were assessed by standard chi-square; differences between means of continuous variables were assessed by Student’s t-test. Separate univariate and multivariate logistic regression analyses were performed to determine variables associated with resistance to one or more drugs and with MDR-TB. These analyses were performed for all available individuals ($n = 9615$), as well as for a subset of individuals for whom information was available on prior HIV test results ($n = 463$), in order to assess the association between HIV and drug resistance. Odds ratios (OR) and 95% CI were calculated to measure the association between variables at the univariate and multivariate level.