Standard Short-Course Chemotherapy for Drug-Resistant Tuberculosis

Treatment Outcomes in 6 Countries

Marcos A. Espinal, MD, DrPH
Sang Jae Kim, ScD
Pedro G. Suarez, MD
Kai Man Kam, MB
Alexander G. Khomenko, MD
Giovanni B. Migliori, MD
Janette Baéz, MD, MPH
Arata Kochi, MD, PhD
Christopher Dye, DPhil
Mario C. Raviglione, MD

Context No large-scale study has investigated the impact of multidrug-resistant tuberculosis (TB) on the outcome of standard short-course chemotherapy under routine countrywide TB control program conditions in the World Health Organization's (WHO) directly observed treatment short-course strategy for TB control.

Objective To assess the results of treatment with first-line drugs for patients enrolled in the WHO and the International Union Against Tuberculosis and Lung Disease's global project on drug-resistance surveillance.

Design and Setting Retrospective cohort study of patients with TB in the Dominican Republic, Hong Kong Special Administrative Region (People's Republic of China), Italy, Ivanovo Oblast (Russian Federation), the Republic of Korea, and Peru.

Patients New and retreatment TB cases who received short-course chemotherapy with isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin between 1994 and 1996.

Main Outcome Measure Treatment response according to WHO treatment outcome categories (cured; died; completed, defaulted, or failed treatment; or transferred).

Results Of the 6402 culture-positive TB cases evaluated, 5526 (86%) were new cases and 876 (14%) were retreatment cases. A total of 1148 (20.8%) new cases and 390 (44.5%) retreatment cases were drug resistant, including 184 and 169 cases of multidrug-resistant TB, respectively. Of the new cases 4585 (83%) were treated successfully, 138 (2%) died, and 151 (3%) experienced short-course chemotherapy failure. Overall, treatment failure (relative risk [RR], 15.4; 95% confidence interval [CI], 10.6-22.4; $P<.001$) and mortality (RR, 3.73; 95% CI, 2.13-6.53; $P<.001$) were higher among new multidrug-resistant TB cases than among new susceptible cases. Even in settings using 100% direct observation, cases with multidrug resistance had a significantly higher failure rate than those who were susceptible (9/94 [10%] vs 8/1410 [0.7%]; RR, 16.9; 95% CI, 6.6-42.7; $P<.001$). Treatment failure was also higher among patients with any rifampicin resistance (n=115) other than multidrug resistance (RR, 5.48; 95% CI, 3.04-9.87; $P<.001$), any isoniazid resistance (n=457) other than multidrug resistance (RR, 3.06; 95% CI, 1.85-5.05; $P<.001$), and among patients with TB resistant to rifampicin only (n=76) (RR, 5.47; 95% CI, 2.68-11.2; $P<.001$). Of the retreatment cases, 497 (57%) were treated successfully, 51 (6%) died, and 124 (14%) failed short-course chemotherapy treatment. Failure rates among retreatment cases were higher in those with multidrug-resistant TB, with any isoniazid resistance other than multidrug resistance, and in cases with TB resistant to isoniazid only.

Conclusions These data suggest that standard short-course chemotherapy, based on first-line drugs, is an inadequate treatment for some patients with drug-resistant TB. Although the directly observed treatment short-course strategy is the basis of good TB control, the strategy should be modified in some settings to identify drug-resistant cases sooner, and to make use of second-line drugs in appropriate treatment regimens.

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THE WORLD HEALTH ORGANIZATION (WHO) tuberculosis (TB) control strategy, directly observed treatment short-course (DOTS), consists of 5 components, including the administration of standardized short-course chemotherapy (SCC) regimens with first-line drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol or both) under direct observation, at least in the intensive treatment phase, regardless of patient drug-susceptibility pattern.[1] This strategy, which is considered by the World Bank as one of the most cost-effective interventions in human health,[2] has now been adopted by 119 countries worldwide.[3]

A recent study revealed that TB cases with multidrug-resistance to isoniazid and rifampicin are a major problem in some countries.[4] Patients carrying multidrug-resistant strains of *Mycobacterium tuberculosis* might be at greater risk of experiencing SCC failure and of dis-

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Author Affiliations are listed at the end of this article. **Corresponding Author and Reprints:** Marcos A. Espinal, MD, DrPH, World Health Organization, Communicable Diseases Programme, Ave Appia #20, 1211 Geneva 27, Switzerland (e-mail: espinalm@who.ch).

seminating multidrug-resistant strains in the community. Thus, the current recommended treatment strategy might need to be adapted to manage multidrug-resistant TB at the program level in middle- and low-income countries, in which 95% of the TB burden exists. No data are available on the response of patients with TB who have multidrug resistance to SCC with first-line drugs under routine countrywide control program conditions. Currently, the only available data are from patients treated in limited or special settings[5,6] or in clinical trials.[7] In these trials, higher efficacy of SCC rifampicin-containing regimens was shown in patients with resistance to isoniazid or streptomycin or both compared with the conventional 12-month regimens based on *p*-aminosalicylic acid and isoniazid.[7]

In several of the countries that participated in the WHO and the International Union Against Tuberculosis and Lung Disease's (WHO/IUATLD's) project of drug-resistance surveillance (DRS), the techniques used for culture of *M tuberculosis* and drug susceptibility testing (DST) (Löwenstein-Jensen and proportion methods) required up to 3 to 4 months to produce results.[8] Furthermore, in many of these countries, second-line drugs to manage multidrug-resistant TB are not widely available because of high costs.[9,10] In addition, most of the surveys, done for epidemiological reasons, were unlinked to clinical management of individual patients. Patients enrolled in these projects who failed treatment were therefore unlikely to be switched from the standard treatment regimens to second-line drugs. As a result, the WHO/IUATLD DRS project offers a unique opportunity to assess outcomes in patients with drug-resistant strains who were treated with first-line drugs throughout the entire duration of treatment under routine program conditions.

METHODS

Design and Patients

This is a retrospective cohort study of patients enrolled in the WHO/IUATLD global project on DRS in the Dominican Republic, Hong Kong Special Administrative Region (People's Republic of China), Italy, Ivanovo Oblast (Russian Federation), the Republic of Korea, and Peru. These countries were selected by 2 main criteria: the existence of a large number of cases of multidrug-resistant TB detected by DRS studies and the availability of treatment results that could be linked with DRS results. The methods of the WHO/IUATLD global project on DRS have been previously published.[4] Briefly, surveys of drug-resistant TB in each of the above settings took place between 1994 and 1996.

The investigations strictly followed 3 methodological principles to gather comparable data: (1) surveys and surveillance were representative of the TB population of the country or area surveyed; (2) differentiation between new and retreatment TB cases based on history of prior treatment by interviews and review of medical records or both was ensured; and (3) DST followed recommended techniques. The DST was performed at each country's national reference laboratory and a network of international reference laboratories validated results. Since 1994, these laboratories have participated in a quality assurance exercise to maintain high levels of proficiency testing.[11] The Republic of Korea, Hong Kong, and Ivanovo Oblast surveyed all TB cases; the Dominican Republic and Peru used proportionate cluster sampling. In Italy, 50% of all eligible health institutions were sampled.

Following the national policy of these countries or areas, patients received routine treatment with SCC regimens. New cases received an initial phase of treatment with 4 drugs (isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin) for 2 months, followed by a continuation phase with rifampicin and isoniazid for 4 months (standard regimen among new cases). Retreatment cases (relapses, failures, and defaulters [patients who did not collect drugs for at least 2 months] returning for treatment) received an initial phase of treatment with 5 drugs (isoniazid, rifampicin, streptomycin, ethambutol, and pyrazinamide; streptomycin for first 2 months only) for 3 months, followed by a continuation phase with rifampicin, isoniazid, and ethambutol for 5 months (standard retreatment regimen). These regimens are administered daily in all participating countries; however, the continuation phase is given twice a week in Peru and 3 times a week in Ivanovo Oblast and in the Dominican Republic. Health care workers administered treatment ensuring direct observation when applicable. At the time of the surveys, the DOTS strategy was used for 100% of the patient population in Peru, 50% in the Republic of Korea, and 21% in Italy.[12] Ivanovo Oblast started DOTS about the same time DRS was launched. Hong Kong and the Dominican Republic were not using DOTS because 1 or more components of the strategy were not in place. In particular, the Dominican Republic did not use direct observation and Hong Kong did not use the recommended recording and reporting system. However, in Hong Kong, treatment was administered using direct observation to all TB patients.

Monitoring of treatment outcome and the change from treatment to retreatment regimens in participating countries were based on the results of sputum smear microscopy.[1] In Italy and Hong Kong, where sputum culture and DST are available, change of regimens also follow the drug susceptibility pattern. Six standard and mutually exclusive categories were used to define treatment outcomes.[13] These are cure, treatment completed, death, failure, default, and transfer-out. Documented treatment success is obtained by adding the percentage of cured cases (negative sputum smear microscopy at the end of treatment) and the percentage of cases who completed treatment (no sputum smear microscopy at the end of treatment with no or only 1 negative sputum smear result at the end of the intensive phase). Treatment failures were patients who maintained smear-positive status at 5 months after the start of treatment. Defaulters were patients

who did not collect drugs for 2 months or more at any time after registration. Transferred out was used for patients transferred to another reporting unit and for whom results were not known. Under routine circumstances, change from a standard 4-drug treatment regimen to a standard 5-drug regimen, including the same 4 drugs used previously, takes place when the patient is declared a treatment failure, or when he/she returns after defaulting or relapsing. Report of smear microscopy results follows WHO/IUATLD recommendations. Smear microscopy quality assurance programs are in place in the participating countries.

Data on previous human immunodeficiency virus (HIV) testing were collected. Patients enrolled in the global project of DRS were asked if they were tested for HIV in the past. The provision of such information was entirely voluntary and patients may have chosen not to disclose it.

Data Management and Statistical Analysis

Treatment outcomes were recorded on standardized registry forms supplied to each treatment unit by the national TB program or corresponding entities of the participating countries. These forms, which are part of the routine recording and reporting system recommended by the WHO, were returned to a national TB program central unit in which the data were checked and entered. Study coordinators linked treatment outcome information with the DRS database. In each country, data were checked twice for completeness and consistency and all errors or discrepancies corrected.

Epi Info (version 6.04b, Centers for Disease Control and Prevention, Atlanta, Ga) and SPSS (version 7.5.2, SPSS Inc, Chicago, Ill) statistical software were used for analysis. Univariate analyses included χ^2 with continuity correction factor and Fisher exact test for the comparison of categorical variables. To assess the association of the different patterns of drug resistance with treatment outcomes and to account for the effect of each country, we performed stratified analysis considering participating countries as strata. The Mantel-Haenszel weighted relative risk (RR) and the Greenland-Robins 95% confidence intervals (CIs) for stratified analysis are reported accordingly.

RESULTS

Information on treatment outcomes for the 6 participating countries was available for 6402 (54%) of 11 764 patients enrolled for DST in the DRS. Of the 5362 patients enrolled for DST without available treatment outcomes, 4411 (82%) were from Hong Kong. The lowest coverage was in Hong Kong (15% [796/5207 patients]), followed by Italy (67% [545/807 patients]). Hong Kong did not implement the reporting system recommended by the WHO and the Italian survey did not cover the entire country. The Dominican Republic (89% [373/420 patients]), Peru (88% [1732/1959 patients]), Ivanovo Oblast in Russia (91% [637/697 patients]), and the Republic of Korea (87% [2319/2675 patients]) had high coverage. Of the 6402 patients with information available, 5526 (86%) were new cases and 876 (14%) were retreatment cases. The mean (SD) age of the patients was 37 (14) years and 4107 were men (64%).

New Cases

Of the 5526 new cases, 4585 (83%) were successfully treated, 138 (2%) died, and 151 (3%) experienced SCC failure

Table 1. Treatment Outcome of New Tuberculosis (TB) Cases According to the *Mycobacterium tuberculosis* Drug Susceptibility

Region	Treatment Outcome, No. (%)						Total	Treatment Success
	Cured	Treatment Completed	Died	Failure	Default	Transfer		
TB Cases Due to Pan-Susceptible Strains								
Republic of Korea	1660 (85)	8 (0.4)	23 (1)	40 (2)	66 (3)	163 (8)	**1960**	1668 (85)
Peru	995 (85)	52 (4)	21 (2)	8 (1)	69 (6)	26 (2)	**1171**	1047 (89)
Hong Kong*	213 (89)	2 (0.8)	3 (1)	0	7 (3)	14 (6)	**239**	215 (90)
Ivanovo Oblast†	168 (37)	168 (37)	35 (8)	19 (4)	46 (10)	15 (3)	**451**	336 (75)
Dominican Republic	48 (28)	58 (34)	3 (2)	7 (4)	36 (21)	17 (10)	**169**	106 (63)
Italy	245 (63)	87 (22)	16 (4)	2 (0.5)	19 (5)	19 (5)	**388**	332 (86)
Total	**3329** (76)	**375** (9)	**101** (2)	**76** (2)	**243** (5)	**254** (6)	**4378**	**3704** (85)
TB Cases Due to Resistant Strains (≥1 Drug)								
Republic of Korea	144 (75)	0	3 (1)	21 (11)	8 (4)	16 (8)	**192**	144 (75)
Peru	136 (79)	7 (4)	10 (5)	11 (6)	8 (5)	1 (1)	**173**	143 (83)
Hong Kong*	370 (80)	11 (2)	13 (3)	4 (1)	11 (2)	52 (11)	**461**	381 (83)
Ivanovo Oblast†	19 (24)	17 (21)	9 (11)	20 (25)	10 (13)	5 (6)	**80**	36 (45)
Dominican Republic	26 (23)	48 (42)	1 (1)	11 (10)	22 (19)	5 (4)	**113**	74 (65)
Italy	56 (43)	47 (36)	1 (1)	8 (6)	9 (7)	8 (6)	**129**	103 (80)
Total	**751** (65)	**130** (12)	**37** (3)	**75** (6)	**68** (6)	**87** (8)	**1148**	**881** (77)
Grand Total	**4080** (74)	**505** (9)	**138** (2)	**151** (3)	**311** (6)	**341** (6)	**5526**	**4585** (83)

*Part of the People's Republic of China.
†Part of the Russian Federation.

(TABLE 1). Results regarding different patterns of resistance are shown in TABLE 2. Mantel-Haenszel weighted RRs for drug-resistant cases vs drug-susceptible cases for 3 categories of treatment outcome are presented in TABLE 3. According to the susceptibility pattern, treatment failure was significantly more likely among resistant cases than among susceptible cases (RR, 5.35; 95% CI, 3.87-7.40; $P<.001$). Patients with multidrug-resistant TB were more likely to experience treatment failure (RR, 15.4; 95% CI, 10.6-22.4; $P<.001$) and to die (RR, 3.73; 95% CI, 2.13-6.53; $P<.001$) than were patients with TB strains considered susceptible. This relationship was statistically significant in all countries with strains studied. Analysis of settings with 100% direct observation (Peru and Hong Kong) showed a significantly higher fail-

Table 2. Treatment Outcome of New Tuberculosis Cases According to the *Mycobacterium tuberculosis* Resistance

	Treatment Outcome, No. (%)							
Region	Cured	Treatment Completed	Died	Failure	Default	Transfer	Total	Treatment Success
Any Resistance*								
Republic of Korea	124 (87)	0	2 (1)	10 (6)	8 (5)	12 (8)	**156**	124 (80)
Peru	123 (83)	6 (4)	6 (4)	5 (3)	8 (5)	1 (1)	**149**	129 (87)
Hong Kong†	329 (84)	10 (3)	7 (2)	1 (0.2)	6 (1)	38 (10)	**391**	339 (87)
Ivanovo Oblast‡	18 (29)	16 (26)	5 (8)	12 (19)	7 (11)	4 (7)	**62**	34 (54)
Dominican Republic	21 (22)	43 (47)	0	8 (8)	18 (19)	4 (4)	**94**	64 (68)
Italy	46 (41)	50 (45)	1 (1)	0	7 (6)	8 (7)	**112**	96 (86)
Total	**661** (68)	**125** (13)	**21** (2)	**36** (4)	**54** (6)	**67** (7)	**964**	**786** (81)
Multidrug Resistance								
Republic of Korea	20 (56)	0	1 (3)	11 (31)	0	4 (11)	**36**	20 (56)
Peru	13 (54)	1 (4)	4 (17)	6 (25)	0	0	**24**	14 (58)
Hong Kong†	41 (59)	1 (1)	6 (9)	3 (4)	5 (7)	14 (20)	**70**	42 (60)
Ivanovo Oblast‡	1 (6)	1 (6)	4 (22)	8 (44)	3 (17)	1 (6)	**18**	2 (11)
Dominican Republic	5 (26)	5 (26)	1 (5)	3 (16)	4 (21)	1 (5)	**19**	10 (53)
Italy	6 (35)	1 (6)	0	8 (47)	2 (12)	0	**17**	7 (41)
Total	**86** (47)	**9** (5)	**16** (9)	**39** (21)	**14** (7)	**20** (11)	**184**	**95** (52)
Any Rifampicin Resistance*								
Republic of Korea	10 (71)	0	0	2 (14)	1 (7)	1 (7)	**14**	10 (71)
Peru	15 (75)	1 (5)	0	3 (15)	1 (5)	0	**20**	16 (80)
Hong Kong†	10 (66)	2 (13)	0	1 (7)	0	2 (13)	**15**	12 (80)
Ivanovo Oblast‡	5 (31)	4 (25)	2 (12)	3 (19)	2 (13)	0	**16**	9 (56)
Dominican Republic	8 (27)	14 (47)	0	4 (13)	3 (10)	1 (3)	**30**	22 (73)
Italy	10 (50)	5 (25)	0	0	4 (20)	1 (5)	**20**	15 (75)
Total	**58** (50)	**26** (23)	**2** (2)	**13** (11)	**11** (9)	**5** (4)	**115**	**84** (73)
Any Isoniazid Resistance*								
Republic of Korea	103 (80)	0	2 (2)	8 (6)	7 (5)	9 (7)	**129**	103 (80)
Peru	45 (76)	2 (3)	4 (6)	2 (3)	5 (8)	1 (2)	**59**	47 (80)
Hong Kong†	153 (87)	4 (2)	2 (1)	0	4 (2)	12 (7)	**175**	157 (90)
Ivanovo Oblast‡	8 (35)	3 (13)	1 (4)	5 (22)	4 (17)	2 (9)	**23**	11 (48)
Dominican Republic	9 (25)	18 (50)	0	2 (5)	6 (17)	1 (3)	**36**	27 (75)
Italy	16 (46)	14 (40)	0	0	2 (6)	3 (9)	**35**	30 (86)
Total	**334** (73)	**41** (9)	**9** (2)	**17** (4)	**28** (6)	**28** (6)	**457**	**375** (82)
Any Resistance Excluding Multidrug, Rifampicin, and Isoniazid								
Republic of Korea	11 (85)	0	0	0	0	2 (15)	**13**	11 (85)
Peru	63 (90)	3 (4)	2 (3)	0	2 (3)	0	**70**	66 (94)
Hong Kong†	166 (83)	4 (2)	5 (2)	0	2 (2)	24 (12)	**201**	170 (85)
Ivanovo Oblast‡	5 (22)	9 (39)	2 (9)	4 (17)	1 (4)	2 (9)	**23**	14 (61)
Dominican Republic	4 (14)	11 (39)	0	2 (7)	9 (32)	2 (7)	**28**	15 (54)
Italy	23 (40)	28 (49)	1 (2)	0	1 (2)	4 (7)	**57**	51 (90)
Total	**272** (69)	**55** (14)	**10** (3)	**6** (1)	**15** (4)	**34** (9)	**392**	**327** (83)

*Excludes multidrug resistance.
†Part of the People's Republic of China.
‡Part of the Russian Federation.

ure rate in cases with multidrug resistance compared with susceptible cases (10% [9/94] vs 0.7% [8/1410]; RR, 16.9; 95% CI, 6.6-42.7; $P<.001$). Similar results were obtained in settings with limited or no direct observation (33% [30/90] vs 2% [68/2968]; RR, 14.5; 95% CI, 10-21.2; $P<.001$).

When multidrug-resistant TB cases were excluded from analysis, drug-resistant cases (all types combined) were still more likely to fail (RR, 3.27; 95% CI, 2.20-4.87; $P<.001$) and less likely to respond to SCC than were susceptible cases (RR, 0.95; 95% CI, 0.92-0.99; $P=.009$). The risk of treatment failure was greater among cases with any rifampicin resistance (RR, 5.48; 95% CI, 3.04-9.87; $P<.001$) or any isoniazid resistance (RR, 3.06; 95% CI, 1.85-5.05; $P<.001$) other than multidrug-resistant TB. These associations held when Ivanovo Oblast and the Dominican Republic were excluded from analysis. No differences, however, were observed for any streptomycin and ethambutol resistance combined in the absence of multidrug resistance ($P=.67$).

Among all single drug-resistant cases together, the likelihood of failing was greater among resistant cases (13% [17/135]) than among susceptible cases (2% [76/4378]; RR, 2.66; 95% CI, 1.63-4.35; $P<.001$). Single rifampicin resistance was significantly associated with treatment failure (RR, 5.47; 95% CI, 2.68-11.2; $P<.001$). While the association was of borderline statistical significance with regard to single isoniazid resistance ($P=.05$), no differences were observed for single ethambutol ($P=.93$) or streptomycin ($P=.13$) resistance. Mortality and treatment success rates among cases with single-drug resistance were not different from those of susceptible cases. On the other hand, an approximately linear increase in the likelihood of treatment failures was observed as the number of drugs to which the strains were resistant increased (χ^2 for trend, 87.4; $P<.001$).

Information on previous HIV testing was available for 816 patients, of whom 46 were HIV-positive (9 in Peru, 6 in the Dominican Republic, 30 in Italy, and 1 in Hong Kong). Of these patients, 29 had susceptible strains (26 treatment successes, 2 failures, and 1 default) and 17 had resistant strains, of whom 5 had multidrug-resistant TB (4 failures and 1 default), 10 had single resistance to isoniazid (7 treatment successes, 1 failed, 1 died, and 1 transferred), 1 had single resistance to rifampicin (treatment success), and 1 had single resistance to ethambutol (defaulted).

Retreatment Cases

Of the retreatment patients (Table 3, TABLE 4, and TABLE 5), 497 (57%) successfully responded to SCC, 51 (6%) died, and 124 (14%) failed. Mortality (RR, 2.49; 95% CI, 1.44-4.49; $P=.003$) and treatment failure (RR, 3.26; 95% CI, 2.26-4.69; $P<.001$) were higher among resistant retreatment cases than among susceptible ones.

Table 3. Mantel-Haenszel Weighted Relative Risks for Treatment Outcome of New and Retreatment Tuberculosis (TB) Cases With Drug Resistance*

	Weighted Relative Risk (95% Confidence Interval)		
	Treatment Success	Mortality	Failure
New Cases			
All resistant cases	0.90 (0.86-0.93)†	1.45 (0.97-2.16)	5.35 (3.87-7.40)†
Any resistance excluding multidrug-resistant TB	0.95 (0.92-0.99)‡	1.01 (0.62-1.66)	3.27 (2.20-4.87)†
Multidrug-resistant TB	0.61 (0.53-0.70)†	3.73 (2.13-6.53)†	15.4 (10.6-22.4)†
Any rifampicin resistance excluding multidrug-resistant TB	0.92 (0.82-1.03)	0.68 (0.16-2.39)	5.48 (3.04-9.87)†
Any isoniazid resistance excluding multidrug-resistant TB	0.97 (0.91-1.00)§	1.08 (0.54-2.14)	3.06 (1.85-5.05)†
Any resistance excluding multidrug, rifampicin, and isoniazid	0.98 (0.93-1.02)	1.07 (0.52-2.23)	1.33 (0.59-2.97)
Single-drug resistance	0.96 (0.93-1.00)	1.20 (0.70-2.07)	2.66 (1.63-4.35)†
Rifampicin	0.92 (0.80-1.06)	0.51 (0.08-3.41)	5.47 (2.68-11.2)†
Isoniazid	0.96 (0.90-1.02)	1.51 (0.68-3.34)	2.21 (1.00-4.51)
Streptomycin	0.96 (0.91-1.01)	1.27 (0.59-2.73)	2.33 (0.95-5.71)
Ethambutol	1.08 (0.99-1.17)	2.13 (0.47-9.75)	0.00 (0.00-0.00)
Resistance to 2 drugs	0.85 (0.78-0.92)†	1.38 (0.71-2.66)	8.62 (5.78-12.7)†
Resistance to 3 drugs	0.69 (0.58-0.82)†	2.95 (1.35-6.47)†	10.4 (6.10-17.9)†
Resistance to 4 drugs	0.62 (0.46-0.83)†	2.62 (0.78-8.85)	10.8 (5.35-21.7)†
Retreatment Cases			
All resistant cases	0.70 (0.61-0.79)†	2.49 (1.44-4.49)†	3.26 (2.26-4.69)†
Any resistance excluding multidrug-resistant TB	0.87 (0.77-0.99)§	2.11 (1.09-4.08)‡	1.96 (1.28-3.01)‡
Multidrug-resistant TB	0.45 (0.35-0.58)†	3.19 (1.67-6.09)†	5.05 (3.36-7.60)†
Any rifampicin resistance excluding multidrug-resistant TB	0.85 (0.64-1.14)	3.83 (1.42-10.4)§	1.97 (1.00-3.92)
Any isoniazid resistance excluding multidrug-resistant TB	0.86 (0.73-1.02)	1.72 (0.73-4.03)	2.08 (1.30-3.35)‡
Any resistance excluding multidrug, rifampicin, and isoniazid	0.88 (0.71-1.09)	2.25 (0.67-5.39)	1.48 (0.55-4.01)
Single-drug resistance	0.93 (0.80-1.07)	1.98 (0.86-4.52)	1.85 (1.13-3.04)§
Rifampicin	0.88 (0.60-1.28)	4.95 (1.16-21.2)§	1.49 (0.52-4.25)
Isoniazid	1.01 (0.84-1.22)	0.66 (0.11-4.04)	2.24 (1.29-3.89)§
Streptomycin	0.82 (0.63-1.06)	1.96 (0.67-5.70)	1.28 (0.42-3.84)
Ethambutol	0.72 (0.32-1.61)	4.06 (0.48-34.5)	7.38 (1.00-46.0)
Resistance to 2 drugs	0.65 (0.52-0.81)†	3.20 (1.54-6.67)‡	2.33 (1.40-3.86)‡
Resistance to 3 drugs	0.50 (0.37-0.66)†	1.64 (0.57-4.71)	4.72 (3.06-7.28)†
Resistance to 4 drugs	0.37 (0.22-0.63)†	2.62 (1.16-5.93)§	6.72 (3.59-12.60)†

*The overall relative risk is adjusted for each country. See "Methods" section for further explanation.
†$P<.001$.
‡$P\leq.01$.
§$P\leq.05$.

Among multidrug-resistant TB retreatment cases, the likelihood of failing (RR, 5.05; 95% CI, 3.36-7.60; $P<.001$) and dying (RR, 3.19; 95% CI, 1.67-6.09; $P\leq.001$) were higher, whereas the likelihood of success was lower (RR, 0.45; 95% CI, 0.35-0.58; $P<.001$), than among susceptible cases. Retreatment cases with any isoniazid resistance other than multidrug resistance were more likely to fail (RR, 2.08; 95% CI, 1.30-3.35; $P=.004$) than susceptible cases. Retreatment cases with single resistance were more likely to fail (RR, 1.85; 95% CI, 1.13-3.04; $P=.03$) than susceptible cases. As with new cases, an approximately linear increase in the likelihood of treatment failures was observed as the number of drugs to which the strains were resistant increased (χ^2 for trend, 89.4; $P<.001$).

COMMENT

This study is the first, to our knowledge, to assess the impact of anti-TB drug resistance on the outcome of SCC administered under countrywide routine control program conditions. The results quantify the degree to which isoniazid and rifampicin resistance and multidrug-resistant TB are obstacles to the success of the WHO-recommended SCC. While 85% of new cases with susceptible TB successfully responded to SCC with first-line drugs, confirming its effectiveness in field conditions, new cases with multidrug-resistant TB, with any rifampicin resistance other than multidrug-resistant TB, and with any isoniazid resistance other than multidrug-resistant TB had a significantly higher failure rate. Rifampicin resistance was the only type of monoresistance strongly associated with treatment failure among new cases. Data available under clinical trial conditions suggested a poor response of SCC in patients with rifampicin resistance.[7] The implications of our findings would support the restriction of rifampicin use to protect the efficacy of this drug. Rifampicin is the most potent first-line anti-TB drug; thus, it should be used under strict direct observation.

The high mortality (9%) and failure (21%) rates of new cases illustrate the negative impact of multidrug-resistant TB on treatment outcomes. Even in the presence of 100% direct observation, treatment success of multidrug-resistant TB cases was only 58% in Peru and 60% in Hong Kong. Although these rates were slightly higher than those in other areas such as Ivanovo Oblast, Italy, and the Dominican Republic, the fact that only a little more than half of the multidrug-resistant cases in Peru and Hong Kong successfully responded to SSC with first-line drugs is worrisome. It is likely that the remainder of the patients would keep spreading multidrug-resistant strains in the community or would die later due to a lack of proper treatment.

These findings suggest that in settings with high rates of multidrug-resistant TB, the current WHO policy of administration of the 5 first-line drugs as standard retreatment regimens needs to be revised according to the availability of resources and DST, the prevalence of multidrug-resistant TB, and the prevailing quality of TB control. In every country facing the problem of multidrug-resistant TB, the first priority is to establish best-practice SCC. In countries with high prevalence of multidrug-resistant TB in which DST is not widely available, a

Table 4. Treatment Outcome of Retreatment Tuberculosis (TB) Cases According to the *Mycobacterium tuberculosis* Drug Susceptibility

	Treatment Outcome, No. (%)							
Region	Cured	Treatment Completed	Died	Failure	Default	Transfer	Total	Treatment Success
TB Cases Due to Pan-Susceptible Strains								
Republic of Korea	47 (61)	1 (1)	0	2 (3)	7 (9)	20 (26)	**77**	48 (62)
Peru	185 (71)	10 (4)	6 (2)	13 (5)	38 (15)	8 (3)	**260**	195 (75)
Hong Kong*	20 (80)	0	1 (4)	0	1 (4)	3 (12)	**25**	20 (80)
Ivanovo Oblast†	31 (52)	7 (11)	8 (13)	2 (3)	12 (20)	0	**60**	38 (63)
Dominican Republic	5 (11)	4 (9)	1 (2)	15 (34)	11 (25)	8 (18)	**44**	9 (21)
Italy	12 (60)	2 (10)	1 (5)	3 (15)	2 (10)	0	**20**	14 (70)
Total	**300** (62)	**24** (5)	**17** (3)	**35** (7)	**71** (15)	**39** (8)	**486**	**324** (67)
TB Cases Due to Resistant Strains (≥1 Drug)								
Republic of Korea	36 (40)	0	1 (1)	21 (23)	5 (6)	27 (30)	**90**	36 (40)
Peru	64 (50)	7 (5)	14 (11)	29 (23)	11 (9)	3 (2)	**128**	71 (55)
Hong Kong*	33 (47)	2 (3)	9 (13)	6 (8)	4 (6)	17 (24)	**71**	35 (49)
Ivanovo Oblast†	14 (30)	2 (4)	9 (20)	15 (33)	5 (11)	1 (2)	**46**	16 (35)
Dominican Republic	2 (4)	9 (19)	1 (2)	16 (34)	15 (32)	4 (9)	**47**	11 (23)
Italy	4 (50)	0	0	2 (25)	1 (12)	1 (12)	**8**	4 (50)
Total	**153** (39)	**20** (5)	**34** (8)	**89** (23)	**41** (11)	**53** (14)	**390**	**173** (44)
Grand Total	**453** (52)	**44** (5)	**51** (6)	**124** (14)	**112** (13)	**92** (10)	**876**	**497** (57)

*Part of the People's Republic of China.
†Part of the Russian Federation.

redefinition of the time frame to consider failure of SCC in retreatment patients and addition of a multidrug-resistant TB-specific treatment option are warranted. The current recommendation is to treat new TB cases that fail first-line treatment at 5 months with a first-line 8-month retreatment regimen.[1] However, administration of an 8-month retreatment regimen, which includes 4 drugs already used in the previous regimen, may result in the administration of monotherapy in a patient who already failed standard treatment and is likely to harbor multidrug-resistant strains. As shown by these data, 67% of the susceptible retreatment cases still responded to the standard retreatment regimen. Thus, 1 option is an earlier decision to treat with a multidrug-resistant TB retreatment

Table 5. Treatment Outcome of Retreatment Tuberculosis Cases According to the *Mycobacterium tuberculosis* Resistance

Region	Treatment Outcome, No. (%)							
	Cured	Treatment Completed	Died	Failure	Default	Transfer	Total	Treatment Success
Any Resistance*								
Republic of Korea	24 (59)	0	0	6 (15)	3 (7)	8 (20)	**41**	24 (59)
Peru	48 (62)	5 (6)	7 (9)	7 (9)	9 (11)	2 (3)	**78**	53 (68)
Hong Kong†	26 (60)	0	4 (9)	1 (2)	2 (5)	10 (23)	**43**	26 (60)
Ivanovo Oblast‡	11 (46)	1 (4)	5 (21)	4 (17)	3 (12)	0	**24**	12 (50)
Dominican Republic	1 (4)	4 (14)	0	12 (43)	7 (25)	4 (14)	**28**	5 (18)
Italy	4 (57)	0	0	2 (29)	1 (14)	0	**7**	4 (57)
Total	**114** (52)	**12** (5)	**16** (7)	**32** (14)	**25** (11)	**24** (11)	**221**	**124** (56)
Multidrug Resistance								
Republic of Korea	12 (25)	0	1 (2)	15 (31)	2 (4)	19 (39)	**49**	12 (25)
Peru	12 (24)	6 (12)	7 (14)	22 (44)	2 (4)	1 (2)	**50**	18 (36)
Hong Kong†	7 (25)	2 (7)	5 (18)	5 (18)	2 (7)	7 (25)	**28**	9 (32)
Ivanovo Oblast‡	3 (14)	1 (4)	4 (18)	11 (50)	2 (9)	1 (5)	**22**	4 (18)
Dominican Republic	1 (5)	5 (26)	1 (5)	4 (21)	8 (42)	0	**19**	6 (32)
Italy	0	0	0	0	0	1 (100)	**1**	0
Total	**35** (21)	**14** (8)	**18** (11)	**57** (34)	**16** (9)	**29** (17)	**169**	**49** (29)
Any Rifampicin Resistance*								
Republic of Korea	3 (38)	0	0	2 (25)	0	3 (37)	**8**	3 (38)
Peru	10 (56)	4 (22)	3 (17)	1 (6)	0	0	**18**	14 (77)
Hong Kong†	0	0	0	0	1 (50)	1 (50)	**2**	0
Ivanovo Oblast‡	1 (33)	0	1 (33)	1 (33)	0	0	**3**	1 (33)
Dominican Republic	1 (14)	1 (14)	0	3 (43)	2 (29)	0	**7**	2 (29)
Italy	0	0	0	0	0	0	**0**	0
Total	**15** (39)	**5** (13)	**4** (11)	**7** (18)	**3** (8)	**4** (11)	**38**	**20** (53)
Any Isoniazid Resistance*								
Republic of Korea	16 (57)	0	0	4 (14)	3 (11)	5 (18)	**28**	16 (57)
Peru	22 (59)	3 (8)	2 (5)	6 (16)	3 (8)	1 (3)	**37**	25 (67)
Hong Kong†	12 (54)	0	2 (9)	1 (5)	1 (5)	6 (27)	**22**	12 (54)
Ivanovo Oblast‡	6 (50)	1 (8)	3 (25)	0	2 (17)	0	**12**	7 (58)
Dominican Republic	0	3 (17)	0	8 (44)	3 (17)	4 (22)	**18**	3 (17)
Italy	4 (57)	0	0	2 (29)	1 (14)	0	**7**	4 (57)
Total	**60** (48)	**9** (7)	**7** (6)	**21** (17)	**13** (10)	**16** (13)	**124**	**67** (54)
Any Resistance Excluding Multidrug, Rifampicin, and Isoniazid								
Republic of Korea	5 (100)	0	0	0	0	0	**5**	5 (100)
Peru	13 (57)	1 (4)	2 (9)	0	6 (26)	1 (4)	**23**	14 (61)
Hong Kong†	14 (74)	0	2 (10)	0	0	3 (16)	**19**	14 (74)
Ivanovo Oblast‡	4 (44)	0	1 (11)	3 (33)	1 (11)	0	**9**	4 (44)
Dominican Republic	0	0	0	1 (33)	2 (67)	0	**3**	0
Italy	0	0	0	0	0	0	**0**	0
Total	**36** (61)	**1** (2)	**5** (8)	**4** (7)	**9** (15)	**4** (7)	**59**	**37** (63)

*Excludes multidrug resistance.
†Part of the People's Republic of China.
‡Part of the Russian Federation.

regimen. Available evidence suggests that the results of smear microscopy at 3 months of treatment correlate well with the treatment outcome.[14] Therefore, in high multidrug-resistant TB prevalence settings, patients could be classified as failures if sputum smear conversion is not achieved after 3 months of a standard retreatment regimen. These patients who are likely to harbor drug-resistant strains can be treated with a multidrug-resistant TB retreatment regimen on the assumption that this is the main cause of failure. Data from Peru suggest that 90% of retreatment cases failing the standard retreatment regimen have multidrug-resistant TB.[15]

While routine DST may not be affordable in many countries with high prevalences of multidrug-resistant TB, its use in selected patients should be considered to recognize multidrug-resistant TB earlier and begin effective treatment. This approach should result in reduction of transmission and, ultimately, multidrug-resistant TB incidence. Available evidence suggests that multidrug-resistant TB responds fairly well (eg, cure rate >80%) to longer regimens (18-24 months) with second-line drugs,[16,17] although other data have shown a low-response rate.[18] To address multidrug-resistant TB effectively in resource-limited settings, formal clinical trials of longer treatment regimens will be needed, as well as the assessment of the feasibility and cost-effectiveness of using second-line drugs at a programmatic level.

Our findings also indicate that strains of *M tuberculosis* with certain patterns of resistance do respond to first-line drugs. Treatment failure was no more likely in new cases monoresistant to isoniazid, streptomycin, or ethambutol, or with any streptomycin and ethambutol resistance than for susceptible cases. The same was true for retreatment cases resistant to rifampicin other than multidrug-resistant TB, or to streptomycin and ethambutol resistance. While the lack of statistical significance in some of these comparisons may be attributable to small numbers of cases, similar results have been reported in clinical trials.[7] Such findings were attributed to the excellent sterilizing activity of both rifampicin and pyrazinamide and to the ability of rifampicin to help prevent the emergence of drug resistance during treatment.[7] Other factors playing a role include the natural history of the disease,[19,20] limitations in the clinical predictive value of in vitro susceptibility testing,[7] and the administration of regimens containing 4 or 5 first-line drugs.

In settings in which the national TB program struggles to perform adequately, such as in Ivanovo Oblast in Russia and in the Dominican Republic, low rates of treatment success in both susceptible and resistant cases were observed. Furthermore, the proportion of defaults among newly susceptible (10% and 21%) and newly resistant (13% and 19%) TB cases in these 2 settings were the highest of the 6 participating countries. The DOTS program in Ivanovo Oblast is relatively new and faces major difficulties because of the nature of an important fraction of the patient population (eg, alcoholism, ex-prisoners, and long-term TB cases).[21] In the Dominican Republic, the DOTS strategy was not in place at the time of the study.[22]

Our study has several limitations. First, we cannot rule out the possibility of misclassification of retreatment cases as new cases, and of treatment outcomes in some countries, especially in those settings in which program activities are not well organized. Second, treatment outcome results were available for a limited number of patients enrolled for DST in Hong Kong and, to a lesser extent, in Italy. Treatment outcome data for patients with TB are not collected on a routine basis in Hong Kong and Italy. Because these 2 settings have second-line drugs available, the likely effect of the missing cases would be an underestimation of the treatment failures among drug-resistance cases. Failing patients may be switched earlier to second-line drugs based on the susceptibility pattern before they are declared treatment failures. An underestimation of the failure rates, however, would only suggest a more severe problem. Third, an underestimation of the failure rates is also possible if smear microscopy is used as the criterion standard to assess treatment outcomes, as our study did. While quality assurance programs are in place in the participating countries, the quality of smear microscopy is unknown in settings in which a high number of patients completed treatment without bacteriological confirmation. Ideally, assessment of treatment outcomes should be based on sputum culture to increase sensitivity; however, culture is not widely available in developing countries. The reliability of smear microscopy to assess response to therapy in patients with drug-resistant TB has not been determined. Fourth, due to the nature of the study, which assessed results at the end of treatment but could not provide longer follow-up information, we were not able to evaluate relapse rates among successfully treated drug-resistant cases. It is possible that presumptively "cured" cases could have presented as relapses a few weeks or months after the study ended. In such cases, treatment success would have been overestimated. Finally, the number of HIV-positive patients available was too small to evaluate the relationship of drug resistance and HIV. Unfortunately, the global project on DRS, from which the samples studied in this investigation were generated, does not include a formal component for HIV testing in patients enrolled for DST.

These potential limitations notwithstanding, 5 major findings of our study are worth emphasizing. First, we have confirmed that cases with drug-susceptible strains of *M tuberculosis* respond better to SCC than cases with resistant strains. Second, multidrug-resistant TB cases have the highest rates of death and treatment failure in both new and retreatment cases. Third, any isoniazid resistance other than multidrug resistance is associated with lower treatment success and higher failure rate in both new and retreatment cases. Fourth, resistance to rifampicin alone

is associated with a higher treatment failure rate among new cases. Finally, treatment failure increases steadily as the number of drugs to which the strains were resistant increased.

To allow TB case management in countries with high prevalence of multidrug-resistant TB, the DOTS strategy should be adapted. Treatment regimens with second-line drugs should be incorporated as an option for use, provided that high cure rate and low defaulting rate of new cases are guaranteed. In addition, reassessment of the recommended standard retreatment regimen with 5 first-line drugs also should be considered, especially for new cases failing the standard treatment regimen with 4 first-line drugs. Moreover, DST should be implemented at least for patients failing the standard treatment regimen with first-line drugs. The introduction of feasible and inexpensive rapid testing for rifampicin resistance also should be explored. If DST is not possible, smear microscopy could still be used to change to a multidrug-resistant TB retreatment regimen.

The best way to prevent the development of multidrug-resistant TB is to encourage countries to adopt DOTS and to provide standard SCC to new patients who will be the source of multidrug-resistant TB if not treated properly. Rifampicin, in particular, needs to be administered under strict supervision. Otherwise, therapy should be based on the administration of an 8-month treatment regimen for new cases of TB, in which the unsupervised continuation phase does not include rifampicin. Regimens including isoniazid and ethambutol in the continuation phase have been shown to achieve high cure rates.[23,24] Finally, our results also suggest that any good TB control strategy should allow for the use of second-line drugs provided all possible measures are taken to ensure strict adherence to treatment, thus preventing the development of further drug resistance.

Author Affiliations: World Health Organization, Communicable Diseases Programme, Geneva, Switzerland (Drs Espinal, Kochi, Dye, and Raviglione); Korean Institute of Tuberculosis, Seoul (Dr Kim); National Tuberculosis Control Program, Lima, Peru (Dr Suarez); Hong Kong Department of Health, Pathology Service, Hong Kong Special Administrative Region, People's Republic of China (Dr Kam); Tuberculosis Research Center, Moscow, Russian Federation (Dr Khomenko†); Foundation Salvatore Maugeri, Care and Research Institute, Tradate, Italy (Dr Migliori); Research Center on Maternal and Child Health, Santo Domingo, Dominican Republic (Dr Baéz).
†Deceased.
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