

## Drug-resistant *Mycobacterium* *tuberculosis*, Taiwan

**To the Editor:** Global surveillance of drug resistance has shown that a substantial proportion of tuberculosis (TB) patients are infected with drug-resistant *Mycobacterium tuberculosis* strains (1). Earlier hospital-based surveys have been undertaken in Taiwan, but these lacked systematic sampling and testing methods, which made interpreting results difficult. The combined treatment efficiency and the actual prevalence of drug resistance were unknown. Thus the Taiwan Center for Disease Control initiated the Taiwan Surveillance of Drug Resistance in Tuberculosis program in 2002.

A laboratory surveillance system was established and supervised by the national reference laboratory. The system includes 6 medical centers, 2 TB referral centers, and 1 regional hospital, distributed in 4 regions of Taiwan. The 9 laboratories provide services for healthcare facilities in their own and surrounding areas. Both the national reference laboratory and contract laboratories participated in an external quality proficiency test provided by the College of American Pathologists and the national reference laboratory. Performance was also assessed by the supranational reference laboratory in Antwerp, Belgium.

The population in the first year (2003) of the survey was 22,562,663, the number of confirmed TB cases was 15,042, the estimated incidence was 66.7 per 100,000 population, and the rate of notification of new positive sputum samples was 34.6% (2). A total of 3,699 isolates, ≈50% of *M. tuberculosis* strains isolated, underwent antimicrobial drug susceptibility testing in the system. Since clinical

data were not available, only combined (primary plus acquired) drug resistance rates were analyzed. The survey showed that the combined drug resistance rates were 9.5% to isoniazid, 5.8% to ethambutol, 6.4% to rifampin, 9.6% to streptomycin, 20.0% to any drug, and 4.0% to multiple drugs. Resistance to any single drug was 12.3%, to any 2 drugs was 4.8%, to any 3 drugs was 2.2%, and to any 4 drugs was 0.7%. In the third global drug resistance surveillance report, the median prevalence of combined drug resistance was 6.6% to isoniazid, 1.3% to ethambutol, 2.2% to rifampin, 6.1% to streptomycin, 10.4% to any drug, and 1.7% to multiple drugs (1).

Available historical data from Taiwan are not directly comparable because of different sampling methods and because susceptibility testing methods have been applied in various hospital settings over time (Table, available online at <http://www.cdc.gov/ncidod/EID/vol12no05/05-1688.htm#table>), which limits our ability to monitor trends. The latest drug resistance rates obtained from Chest Hospital, a specialized TB referral hospital, showed that the combined drug resistance of any and multiple drugs were 27.6% and 15.8%, respectively, from January 2002 to June 2004 (unpub. data).

In Taiwan, isoniazid and rifampin were introduced in 1957 and 1978, respectively. Rifampin resistance was first seen in Taiwan in 1982. In recent decades, however, the rates of primary rifampin resistance have increased (online Table), and primary resistance to multiple drugs has increased to 2.4% over time.

Based on patient data collected from Chest Hospital, multidrug resistance occurred in 42.2% of retreated TB patients, and 1.8% of multidrug-resistant isolates were found in new TB patients from January 2002 to June 2004 (unpub. data). In the third

global drug resistance surveillance report, the median prevalence of multidrug resistance was 7.0% (highest 58.3%) among retreated cases and 1.1% (highest 14.2%) among new cases.

Significant declining trends were observed for any acquired resistance (67.0% to 42.6%,  $p < 0.0001$ ) and acquired multidrug resistance (46.0% to 24.6%,  $p < 0.0001$ ) at the Taiwan Provincial Chronic Disease Control Bureau from 1996 to 2001 (3,4). In addition, a decline in combined isoniazid resistance (43.1% to 16.4%,  $p < 0.0001$ ), rifampin resistance (23.4% to 9.5%,  $p < 0.0049$ ), and multidrug resistance (18.2% to 7.8%,  $p < 0.0113$ ) was also reported from Kaohsiung Medical University Hospital from 1996 to 2000 (5). Taken together, data obtained from the Taiwan Surveillance of Drug Resistance in Tuberculosis and those reported previously show that rates of combined resistance to any drugs and multiple drugs has declined in Taiwan.

For retreated cases, the high acquired resistance rates indicated suboptimal initial treatment and insufficient case management of new patients, which raises a challenge to the National TB Control Programme in Taiwan. The direct observed treatment, short-course (DOTS) strategy has consequently been suggested to expand to all patients with newly diagnosed cases. The Taiwan Surveillance of Drug Resistance in Tuberculosis program will be extended to collect each patient's clinical and epidemiologic data, according to principles suggested in the guidelines prepared by the World Health Organization.

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## Enrofloxacin in Poultry and Human Health

**To the Editor:** Following logic similar to that recently used by the US Food and Drug Administration to withdraw approval for enrofloxacin, a recent letter estimated that fluoroquinolone use in poultry could compromise responses to antimicrobial drugs in >24,000 persons per year in the United States (1). However, >99.9% of this estimated risk appears to result from incorrect assumptions. Potentially important corrections include the following: 1) not attributing resistance from foreign travel and human ciprofloxacin use to domestic use of enrofloxacin in poultry (this could reduce the estimated risk by  $\approx 1/3$ ) (2); 2) updating the estimated fraction of human foodborne *Campylobacter* infections caused by poultry to reflect declines in microbial loads on chicken carcasses since 1992 reduces the estimated risk by a factor of perhaps  $1/10$  (3) (the cited 90% estimate by Hurd et al. [1] was intended for use as part of a conservative upper-bounding analysis, not as a realistic point estimate); 3) replacing an assumption that 10% of infected persons would benefit from antimicrobial drug therapy with a more data-based value of 0.6% (4) would reduce the estimated risk by a factor of  $0.6/10 = 0.06$ ; 4) replacing an assumption that fluoroquinolones are prescribed for *all* affected patients receiving antimicrobial drug treatment (rather than, for example, erythromycin) by a more realistic value of fluoroquinolones being prescribed for perhaps  $\approx 50\%$  of patients (2) reduces the estimated risk by a factor of  $\approx 50\%$ ; 5) replacing an assumption that *all* such cases lead to compromised responses with a more data-driven estimate that perhaps  $\approx 17\%$  of patients have compromised responses would reduce the estimated risk by a

factor of  $1/6$  (5); and 6) recognizing that reducing enrofloxacin use may not decrease fluoroquinolone resistance in all *Campylobacter* spp. from food animals (effect not quantified) (6). Together, such changes reduce the estimated risk by a factor of at least  $(1/3) \times (1/10) \times (0.6/10) \times (1/2) \times (1/6) = 0.00017$ , or by >99.9%.

More notably, the calculation in (1) also wrongly assumes that the fraction of patients with fluoroquinolone-resistant infections times the fraction of infections caused by poultry gives the fraction of patients with compromised response caused by fluoroquinolone use in poultry. As a simple counterexample, suppose that 80% of all infections were caused by poultry, with the rest caused by something else (e.g., water), and that all and only the 20% of infections caused by the latter source are resistant. Then the procedure in (1) would estimate (80% of infections caused by poultry)  $\times$  (20% of infections resistant) = 16% as the fraction of resistant infections caused by poultry, even though the correct answer is zero. Thus, the basic logic of the calculation is flawed.

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