Mutation of *Mycobacterium tuberculosis* in resistance to tuberculosis drugs occurs spontaneously and at random, but clinically relevant drug resistance is associated with antituberculosis treatment, appears by selective multiplication of resistant mutants during treatment (acquired resistance), and by transmission of drug-resistant organisms (primary resistance). Proper use of antituberculosis drugs is essential in preventing drug resistance in tuberculosis. The prevalence and trend of drug resistance in tuberculosis is an important indicator of the quality of tuberculosis services.

In 1994, the World Health Organization and the International Union Against Tuberculosis and Lung Disease launched the *Global Project on Antituberculosis Drug Resistance Surveillance*. The objectives of the Global Project are to measure the prevalence of antituberculosis drug resistance worldwide using a standardized methodology, to monitor the trend of drug resistance, to study the correlation between the level of drug resistance and treatment policies in different settings, and to evaluate the efficiency of treatment programs. To date, four global reports on antituberculosis drug resistance in the world have been published.

Guidelines for surveillance of drug resistance in tuberculosis emphasize the following principles:

1. The sample of specimens should be representative of the tuberculosis patients in the country/geographical setting under study and the sample size should be determined to permit standard epidemiologic analysis.
2. The patient’s history should be carefully obtained to determine whether or not the patient has previously received antituberculosis drugs, which is essential to distinguish between drug resistance among new cases and that among previously treated cases.
3. Optimal laboratory performance should be ensured and maintained through links with a supranational reference laboratory.

Several facility-based surveys on drug resistance in tuberculosis in Taiwan were published in past decades. These reports indicated the importance of and the interest in this subject. However, the findings of these facility-based investigations cannot be generalized to the overall population of tuberculosis patients with certainty and have a limited role in monitoring the trend of drug resistance in tuberculosis. Surveys undertaken with a nationwide representative sample may be more widely applicable. An article, published in the March 2008 issue of this journal, which reported increasing drug resistance of *M. tuberculosis* in a medical center in northern Taiwan highlighted the problems.

Su et al reported the prevalence of drug resistance in a total of 611 non-duplicate *M. tuberculosis* isolates from culture-proven tuberculosis cases...
enrolled in a medical center in Taipei. The prevalence of any drug resistance among new and previously treated cases was as high as 55.1% and 61.4%, respectively, while that of monoresistance to pyrazinamide (PZA) was 8.0% and 11.4%, respectively, and that of resistance to at least isoniazid and rifampin (multidrug-resistant tuberculosis [MDR-TB]) was 26.7% and 33.0%, respectively. There were significant increases in any resistance as well as MDR-TB in 2003–2004 as compared with their previous report for the period 1990–1992 in the same hospital. While the increase in the prevalence of drug resistance in the medical center is alarming, the findings reported need further elaboration.

First, the prevalence of drug resistance (especially MDR-TB) among previously treated cases in most settings is substantially higher than that among new cases. Misclassification of previously treated tuberculosis cases as new cases would result in a high prevalence of drug resistance among new cases. According to The Fourth Global Report, the prevalence of MDR-TB among new tuberculosis patients ranged from 0% in Andorra, Cuba, Luxembourg, Malta, Slovenia, Aragon, Spain, and Uruguay to 22.3% in Baku and Azerbaijan. If there was no misclassification of previously treated tuberculosis cases as new cases in Su et al’s report, then the prevalence of MDR-TB among new patients treated in their medical center would be the highest in the world, which is unlikely to be the case.

Second, the number of previously treated tuberculosis cases in most drug resistance surveys is considerably less than that of new cases and thus is prone to bias in sampling. Patients visiting a tertiary medical center is more likely to have been treated with antituberculosis drugs, and the prevalence of drug resistance among previously treated tuberculosis cases in a tertiary medical center is likely to be higher than that observed at the primary health care level because of referral of difficult cases from the latter to the former. The closure in late 2002 of the Chronic Disease Control Bureau, a referral center that specialized in the treatment of drug-resistant tuberculosis cases in Taipei, probably resulted in an increase in the number of referrals of previously treated tuberculosis cases to tertiary medical centers in Taipei, partly contributing to the increase in drug resistance in 2003–2004 in Su et al’s medical center. As they correctly point out, the prevalence of drug resistance among previously treated cases in their medical center is not representative of that in Taiwan overall, which could be obtained in a population-based study. Further, it would be more informative to stratify previously treated tuberculosis cases into the categories of relapse, treatment after default, and treatment after failure.

Third, PZA susceptibility testing is not recommended on 7H11 agar medium because of poor reliability. Performing PZA susceptibility testing on 7H11 agar may explain a substantial proportion of the PZA monoresistance in Su et al’s report. Finally, the quality of susceptibility testing is an important issue. Five rounds of international proficiency testing revealed a high degree of agreement of the testing of isoniazid and rifampin among supranational reference laboratories, but substantial discordant results for streptomycin and ethambutol were identified. It also showed that regular proficiency testing can significantly improve the quality of drug susceptibility testing. Since 2006, the Reference Laboratory of Mycobacteriology of Taiwan has undertaken proficiency testing in several laboratories that perform susceptibility testing of tuberculosis, which has revealed considerable variation in performance with unsatisfactory results in some laboratories (Ruwen Jou and colleagues, from the Reference Laboratory of Mycobacteriology, Research and Diagnostic Center, Centers for Disease Control, Department of Health, Executive Yuan, Taiwan; manuscript submitted).

In conclusion, obtaining a representative sample of M. tuberculosis isolates from the community and ensuring the quality of susceptibility testing are crucial in the surveillance of drug resistance in tuberculosis. It is essential to monitor antituberculosis drug resistance in the fight
against tuberculosis, and, almost without exception, the responsibility of ensuring proper surveillance of antituberculosis drug resistance belongs to the national tuberculosis program.

References


