

Extensively Drug-Resistant Tuberculosis, Taiwan

To the Editor: In Taiwan, the incidence of tuberculosis (TB) was 74.1/100,000 population in 2004 and 72.7/100,000 in 2005; the mortality rate was 4.2/100,000 in 2004 and 4.3/100,000 in 2005 (1). Because of these high incidences and the increasing effects of multidrug-resistant TB (MDR TB), i.e., resistant to at least both isoniazid (INH) and rifampin (RIF), the laboratory-based Taiwan Surveillance of Drug Resistance in TB (TSDRTB) program was established in 2003 (2). Surveillance demonstrated that combined drug resistance rates were 11.3% (2004) and 10.1% (2005) for INH; 7.5% (2004) and 6.2% (2005) for RIF; 4.3% (2004) and 2.1% (2005) for ethambutol (EMB); 10.6% (2004) and 9.8% (2005) for streptomycin (SM); 20.4% (2004) and 18.1% (2005) for any first-line drug; and 5.3% (2004) and 4.0% (2005) for multidrug resistance. These resistance rates are higher than those reported by the third TB global drug resistance surveillance. Global surveillance reported median prevalence of combined drug resistance was 6.6% for INH, 2.2% for RIF, 1.3% for EMB, 6.1% for SM, 10.4% for any drug, and 1.7% for multidrug resistance. TB (3).

Extensively drug-resistant TB (XDR TB) was initially defined as an MDR isolate that was resistant to at least 3 of the 6 main classes of second-line drugs: aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid (4). In October 2006, the World Health Organization (WHO) redefined XDR TB as an isolate "resistant to at least INH and RIF (i.e., MDR TB) plus resistant to at least 1 of the fluoroquinolones and 1 of the following 3 injectable drugs: capreomycin, kanamycin, and amikacin" (5). Clearly, XDR TB is a global threat and the demands

on XDR TB surveillance systems are urgent.

Because no guidelines for drug susceptibility testing of second-line drugs existed in Taiwan before 2007, clinical mycobacteriology laboratories performed drug susceptibility testing of second-line drugs using the agar proportion method by clinicians' request only. Critical concentrations of second-line drugs for drug susceptibility testing were 2 µg/mL for ofloxacin, 6 µg/mL for kanamycin, 10 µg/mL for ethionamide, and 8 µg/mL for para-aminosalicylate. Of the 215 MDR isolates, 92 (42.8%), 35 (16.3%), 34 (15.8%), and 56 (26.0%) were resistant to fluoroquinolone, kanamycin, ethionamide, and para-aminosalicylate, respectively. Of the 116 MDR isolates tested for susceptibility to second-line drugs in 2004, 10.3% (12/116) were XDR TB; of the 99 MDR isolates tested in 2005, 10.1% (10/99) were XDR TB.

With their broad spectrum antimicrobial activity, fluoroquinolones are widely used for the treatment of bacterial respiratory infections in Taiwan. In addition, fluoroquinolones are the preferred oral agents for treating drug-resistant TB that is known or presumed to be sensitive to this class of drugs, or when first-line agents cannot be used because of intolerance (6). In contrast to injectable agents that have a higher incidence of renal and hearing impairment after long-term use, fluoroquinolones have high oral bioavailability, convenient dosing intervals, and a lower incidence of side effects (7). Therefore, despite TB treatment recommendations, some clinicians prescribe fluoroquinolones instead of injectable agents. A previous study by Yu et al. (8) showed that fluoroquinolone-resistant *Mycobacterium tuberculosis* isolates were rare among patients not previously exposed to fluoroquinolones; however, the increased rate of resistance to fluoroquinolones was observed among patients with MDR TB because of in-

adequate treatment regimens or poor compliance (8,9).

In this study, 215 MDR isolates were tested; among these, 42.8% (92/215) were fluoroquinolone-resistant, a much higher percentage than the 10.2% (22/215) that fulfilled the definition of XDR TB. Because the adequate use of fluoroquinolones for TB per WHO and national guidelines (either for intolerance or drug resistance) is important, the use of fluoroquinolones is strictly regulated by the National Health Insurance program. Since 2007, clinicians in Taiwan have been required to apply for these and second-line drugs through the Taiwan Centers for Disease Control (CDC) and to accept professional supervision in their administration. Furthermore, these drugs can only be given under the direct observed treatment program.

An outbreak in rural South Africa highlighted the risk of XDR TB for persons co-infected with HIV (10). The current Taiwan TB and HIV Register shows that <1% of TB patients are co-infected with HIV and documents no XDR TB patients who are co-infected with HIV. However, because persons co-infected with HIV and *M. tuberculosis* have the highest rates of progression to active disease, continued monitoring of co-infected patients is essential for control of TB.

The initial purpose of the TSDRTB program was to survey drug resistance of first-line anti-TB drugs in Taiwan. Therefore, our study data are limited; the rate of XDR TB among MDR TB may be an underestimate because we did not have adequate representative cases and methods. The present surveillance system does clearly show the emergence of XDR TB cases in Taiwan, which highlights the need to reinforce diagnosis and treatment strategies recommended by the National TB Control Program. In addition to the established TSDRTB program, Taiwan CDC started an enhanced population-based surveillance of MDR TB/XDR TB in 2007.

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Hantavirus Outbreak, Germany, 2007

To the Editor: Hantavirus disease (for review see [1]) has been reportable in Germany since 2001, according to the Federal Infection Protection Act. In this country, Puumala virus (PUUV) causes most clinical hantavirus cases, although Dobrava-Belgrade virus and Tula virus also circulate (1). From 2001 through 2006, an average of ≈220 cases were reported per year (incidence 0.267/100,000) with a maximum of 448 cases in 2005. In contrast, 1,687 cases were reported in 2007 (2). Whereas in 2005 the highest incidence of infection was in metropolitan areas (3), the current outbreak is focused in the rural areas in southern and western Germany. Clinical case-patients exhibit key characteristics of hantavirus disease (nephropathia epidemica): acute high fever; pain in the back, head, and/or abdomen; proteinuria; rise of serum creatinine; thrombocytopenia; and renal failure (1). The outbreak provided considerable numbers of clinical samples from the viremic phase and thus has enabled a molecular epidemiologic analysis of the circulating virus.

At the National Consultation Laboratory for Hantavirus Infections (Berlin), we received early-phase serum specimens from the outbreak regions for confirmation assays. In enzyme immunoassays and Western blot tests (4), 80 samples from patients during the early clinical phase were positive for PUUV-specific immunoglobulin (Ig) M antibodies. All IgM data were accompanied by simultaneous or subsequent detection of PUUV-specific IgG. The samples were screened for hantavirus RNA by reverse transcription-PCR (RT-PCR) (5). Of the 80 early-phase serum samples, 42 (53%) were RT-PCR positive. For a subset of 14 of the 42 samples, a 557-nt segment of the nucleocapsid (S) gene underwent nucleotide sequence analysis as described previously (6).

The Figure, panel A, shows a map of Germany with the residences of those patients from whom virus sequences were amplified (marked by letter H in front of the specimen number). In the phylogenetic analysis, despite a substantial evolutionary distance to PUUV strains from other parts of Europe, the virus sequences unambiguously grouped within the PUUV species (Figure, panel B). The few previously known human PUUV sequences from individual clinical case-patients in Germany, “Berkel” from Munsterland (7) and “Heidelberg” from a region located between Swabian Jura and Spessart Forest (8), as well as human-derived strains from a small 2004 outbreak in the Bavarian Forest (6), were included in this analysis. The results showed a clustering of the new viral sequences strictly according to residential areas of the patients, forming the following 4 clades: Swabian Jura (SJ), Spessart Forest (SF), Munsterland (ML), and Bavarian Forest (BF). Two different single sequences, Karlsruhe (from a region in northwestern Swabian Jura) and Essen (in southern Munsterland), represent 2 putative additional lineages.