Spread of Extensively Drug-resistant Tuberculosis

To the Editor: An emergency has been declared in KwaZulu Natal, South Africa, where an outbreak of 53 cases of a highly lethal form of tuberculosis (TB) has occurred (1,2). This outbreak was caused by an extensively drug-resistant TB (XDR TB) strain.

XDR TB is defined as TB caused by Mycobacterium tuberculosis isolates resistant to isoniazid and rifampicin plus any fluoroquinolone and ≥1 of the 3 injectable second-line drugs (3). XDR TB may be considered an emerging disease but not a new disease. Nosocomial outbreaks of multidrug-resistant TB (MDR TB) occurred in Spain at the height of the HIV epidemic, when 49 TB cases were reported in an HIV ward in Madrid from 1991 through 1995 (4,5). Molecular epidemiology found that a particular strain caused 16 cases in another hospital in Madrid in 1993–1995 (6) and 31 cases in a hospital in Malaga in 1995–1998 (7,8). In total, 22 hospitals from 6 different regions of Spain were affected by this outbreak, which included at least 114 cases, caused by an M. bovis XDR strain (B strain) belonging to the M. tuberculosis complex. The patients included 1 from the Netherlands (8) and another from Canada (9).

The strain responsible for the 1991–1995 outbreak in Spain fits the XDR TB case definition; it was resistant to the 5 first-line drugs, as well as to ofloxacin, aminosalicylic acid, cycloserine, ethionamide, capreomycin, amikacin, and clarithromycin. Isolates were tested for drug susceptibility by the Canetti method on Lowenstein-Jensen medium supplemented with isoniazid, rifampicin, ethambutol, streptomycin, amikacin, and pyrazinamide (6). The isolates were also tested on 7H10 Middlebrook agar for susceptibility to aminosalicylic acid, ethionamide, capreomycin, clarithromycin, and ofloxacin (6). No effective medical treatment was available for these patients. In 2 of the hospitals affected, all patients died, with a short survival time (median of 44 and 49.5 days for the 2 hospitals) between diagnosis and death (6,7). A high rate of reinfec tion (45%) also was noted among HIV-positive patients treated with anti-TB drugs (7). As a result of this outbreak, Spanish hospitals now implement exhaustive control measures, such as maintaining respiratory isolation units under negative pressure; in addition, a national surveillance network for MDR TB was set up in Spain in 1998. From 1998 through 2003, we detected 22 new cases of infection with this strain (10), but no new cases have since been reported to the national MDR TB database.

Our experience indicates that the implementation of more stringent control measures and the use of new, more effective treatments for HIV infection can help to bring XDR TB outbreaks under control in developed countries. However, the outlook is bleak for developing countries like South Africa, in which coinfection with HIV and a highly transmissible and untreatable XDR TB strain could amplify the TB problem to levels unprecedented since the advent of antimicrobrial drugs. These countries urgently require assistance with the establishment of control measures and the development of new drugs and effective vaccines against TB.

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References

A 7-year-old boy was examined in June 2006; he had erythematous-papulose skin and an increased level of alanine aminotransferase (ALT, 796 IU/L) of 1 week’s duration. From October 2005 to May 2006, he had received several courses of combined chemotherapy for a rhabdoid tumor in his kidney. Therapy included carboplatin, cyclophosphamide, etoposide, Adriamycin, and vincristine, and, because of the chemotherapy’s hemotoxicity, the patient required 22 transfusions of concentrated erythrocytes or platelets. Peak levels of ALT and bilirubin were reached 4 weeks after onset of hepatitis (2,001 IU/L and 49 μmol/L, respectively), and ALT levels returned to normal range (8–45 IU/L) 6 weeks later. During a follow-up examination, the boy’s prothrombin index remained >80%, and clinical signs mostly consisted of clinical jaundice. HEV diagnosis was established by detection in serum of HEV antibodies (EIAgen Kits, Adaltis Development Inc., Laval, Quebec, Canada) and HEV RNA with in-house assays. Other infectious or noninfectious causes of acute hepatitis were excluded. HEV immunoglobulin M (IgM) was weakly positive in June 2006 (optical density ratio = 1.6), then strongly positive the next month (ratio = 10.8); IgG remained negative. HEV RNA was detected from serum samples collected in June 2006 by an in-house real-time PCR that targeted the open reading frame 2 region of the HEV genome. Sequences of primers/probe are as follows: HevMrsRTfwd: 5′-AATRATTTTCGTCGGCYYGG-3′; HevMrsRTRev: 5′-ACWGTGCCTCGC CAT TG-3′; HevMrsFam: 5′-FAM-ACCTCYGCG CAGSTYGCTCA-TAMRA-3′.

Serum samples taken from 12 U of blood products that the child received during the 3-month period before onset of hepatitis were tested for HEV RNA; 1 sample was positive. Concentrated erythrocytes (310 mL) from this positive blood donation were transfused to the child in May 2006, 4 weeks after collection and 6 weeks before acute hepatitis developed. HEV IgG and IgM antibodies were not detected in the blood donation, which indicates that the blood donation occurred during the prodromic phase of HEV disease. HEV nucleotide sequences from the blood donor and recipient were identical. Phylogenetic analysis showed that they clustered together and were closely related to genotype 3f, which is prevalent in Europe (Figure [8]).

The blood donor was a 24-year-old man. He did not travel outside metropolitan France for 8 months before donating blood. Anti-HEV IgG seroconversion was observed on a serum sample collected 24 weeks after blood donation, whereas anti-HEV IgM and serum HEV RNA test results were negative. ALT levels were within normal values at the time of blood donation and 24 weeks later. No clinical signs were reported at any time. No other recipient received blood products from this donor.

Our data show that HEV was transmitted from 1 blood donor to the recipient child. On the basis of retrospective HEV RNA detection, 6 other transfusion-transmitted HEV infections, all involving adult blood recipients, have occurred in HEV-hyperendemic and industrialized countries (7). Transfusion-transmitted HEV strains belonged to different genotypes/subtypes that corresponded to those found in the same geographic areas (Figure).

In France, neither HEV antibodies nor HEV RNA are systematically tested in blood donors, and blood donations currently are not tested for ALT. In the absence of systematic HEV RNA testing, HEV diagnosis in blood donations may be hampered by HEV viremia before clinical onset and anti-HEV seroconversion, the possible short persistence or absence of HEV antibodies, and the high frequency of subclinical infections.