Alarms Sounded over Totally Drug-Resistant Tuberculosis, Gonorrhea

Totally drug-resistant tuberculosis (TDR-TB) last year affected a small group of patients in India, according to Zarir Udwadia of Hinduja National Hospital and Medical Research Centre in Mumbai, India, and his collaborators. Separately, say several U.S. public health experts, “It is time to sound the alarm” about the emerging possibility of “untreatable gonococcal infections.” In both cases, although the alarms are sounding slightly ahead of the dire clinical circumstances that they warn about, these recent drug resistance trends rightly warrant careful attention.

Udwadia and his collaborators, who report their case findings in the December 21, 2011 Clinical Infectious Diseases [doi: 10.1093/cid/cir889], describe four patients who proved resistant to all first- and second-line drugs for treating Mycobacterium tuberculosis infections. They also note that three of those patients previously “received erratic, unsupervised second-line drugs . . . often in incorrect doses.” These clinical researchers reported identifying several years earlier the first patients in India with extensively drug-resistant (XDR) TB.

A separate report from 2009 outlines a similar, albeit somewhat larger, outbreak involving 15 putative cases of TDR-TB in Iran, involving patients from there, Afghanistan, and Azerbaijan. “The isolation of TDR strains from multidrug-resistant-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries,” noted Parissa Farnia of Shahid Beheshti University in Tehran and collaborators there and other institutions, including the Swedish Institute for Infectious Disease control in Solna in that earlier report in the August 2009 Chest, 136, 420–425 [doi: 10.1378/chest.08–2427].

Not so fast, say officials at the World Health Organization (WHO) in Geneva, Switzerland, reacting to the claim from India of TDR-TB cases. WHO officials insist those cases are XDR-TB, noting that “other terms”—that is TDR-TB—“have not been defined by global TB experts.”

For one thing, correlations between in vitro test results for remaining second-line drugs and clinical responses among such XDR-TB patients are not adequately established,” WHO officials note. For another, categorizing...
TB cases as totally drug resistant could well prove premature in the face of ongoing efforts to develop and evaluate new drugs. Nonetheless, with the new term creeping into wider use, WHO officials agreed to convene expert group meetings this March, one “to assess the latest evidence behind a new molecular line probe assay for detecting XDR-TB” and the other to discuss, in part, “possible definitions for ‘totally drug-resistant’ TB.”

Meanwhile, a similar debate is taking shape over drug-resistant isolates of Neisseria gonorrhoeae, the bacteria that give rise to sexually transmitted cases of gonorrhea, according to Judith Wasserheit of the University of Washington, Seattle, Frederick Sparling of the University of North Carolina School of Medicine, Chapel Hill, and Gail Bolan of the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga.

Treatment options for XDR cases of gonococcus are limited to third-generation cephalosporins, and their effectiveness is decreasing rapidly, according to CDC officials. “Though there is no evidence yet of treatment failures in the United States, trends in decreased susceptibility coupled with a history of emerging resistance and reported treatment failures in other countries point to a likelihood of failures on the horizon and a need for urgent action,” Wasserheit says. Details appear in the February 9, 2012 New England Journal of Medicine (366:485–487).

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Lymphatic-Lurking Prions Perhaps More Prevalent than Appreciated

The transmission barrier that keeps prions from jumping easily from one species to another may be far less restrictive than previously thought, according to Vincent Béringue and colleagues at the Institut National de la Recherche Agronomique (INRA) in Jouy-en-Josas, France. Experiments in mice testing several scenarios showed lymphoid tissues as much as sevenfold “leakier” to prions from other species than brain tissue, challenging the widely held notion of absolute species barriers. Details appear in the 27 January 2012 Science (335:472–475).

One way to evaluate tissue-dependent, cross-species transmission is to inoculate mice engineered to express native, or “normal,” sheep prion protein (PrP\textsubscript{W}) with pathogenic prions (PrP\textsuperscript{Sc})—the version of that protein that causes chronic wasting disease (CWD) in deer. This CWD-causing prion invaded only 2 of 29 mouse brains by the end of life, according to Béringue. “In marked contrast, significant levels of CWD prions were detected in the spleens of all but one of the 18 mice tested from approximately 380 days onward,” he says. However, none showed symptoms, raising concern about comparably silent prion “infections” within humans.

Thinking that interspecies transfers of prions in the absence of detectable PrP\textsuperscript{Sc}, Béringue and his collaborators introduced CWD-positive material from asymptomatic mouse tissues into disease-free “ovinized” mice. Not one of the six recipients of the infected brain material developed neurologic symptoms or accumulated pathogenic tissue prions by the end of life. In stark contrast, three of five mice inoculated with spleen material from the CWD donor accumulated pathogenic prion proteins in both brain and spleen tissues—yet all these mice appeared healthy. Thus, CWD prions apparently propagate more easily in spleens than in brains in transgenic mice.

The French scientists inoculated “ovinized” transgenic mice with prions that cause disease in hamsters. Here too, none of the mice developed symptoms, and only 8 of 40 mouse brains tested positive for hamster prions. However, a substantially higher number of spleens harbored replicating hamster prions—18 of 30, suggesting that prions replicate more easily here than in brain tissues.

Béringue and collaborators also challenged transgenic mice expressing human PrP with prions responsible for epizootic bovine spongiform encephalopathy (BSE). Only 3 of those 44 inoculated mouse brains acquired the disease-causing proteins, all beyond 600 days post inoculation. However, the spleens of 26 of 41 of those mice became infected.

“The human species barrier to pri-