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# Multi-Drug Resistant Tuberculosis

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## Abstract

### General level of health in Hong Kong

Not long ago a paradigm of modern medicine's successful battle against infectious disease, tuberculosis (TB) today holds first rank in deaths caused by infectious disease worldwide. Approximately one third of the world's population is infected with Mybacterium tuberculosis, the virulent causative agent. With 8 million active cases and 3 million deaths from TB reported annually, in 1993 the World Health Organization (WHO) declared TB to be a global public health emergency.

### U.S. Prevalence

The years between 1953 and 1984 saw a decline in the annual number of U.S. cases from approximately 84,000 to 22,000, but case rates began climbing again in 1985. The number of new cases reported in 1990-25,701-was 9.8% above the 1989 tally, the single largest increase since national reporting on TB began in 1953.

### Tuberculosis and HIV

The impact of human immunodeficiency virus (HIV) infection has largely fueled these upward trends. The WHO has estimated that 5.6 million persons at a minimum are infected with both HIV and M. tuberculosis, primarily in developing countries. As HIV-associated cellular immunity declines, latent TB infection reactivates or susceptibility to a new infection increases, and the clinical course of TB accelerates. Sharp increases in the number of active TB cases have accompanied the epidemics of HIV infection in Africa, South America and Asia.

### Multidrug-Resistant Tuberculosis

### Epidemiology

Most troubling, multidrug resistance can result from M. tuberculosis being exposed to sub-therapeutic amounts of antituberculous drugs, primary drug resistance or acquiring TB infection from someone who developed primary drug resistance (secondary drug resistance). In some cases, nosocomially acquired tuberculosis has accompanied the increasing incidence of concurrent TB and HIV infections. Multidrug resistance is defined as culture-confirmed TB caused by an isolate demonstrating in vitro resistance to isoniazid

and rifampin. Multidrug resistant TB may be the most virulent of all the HIV-associated opportunistic infections - rapidly progressive, extremely difficult to treat, and often fatal.

Classification of TB as multi-drug resistant depends on a laboratory determination. Despite the need for rapid identification of susceptibility of M tuberculosis, definitions of in vitro resistance, procedures for performing susceptibility testing, and formats for reporting drug resistance have not been standardized. Misdiagnosis of multidrug-resistant TB was reported to be as high as 13% in one study.

**Factors for Transmission**

Changes in patterns of TB transmission have added to the problems of control (Table 1). The incidence of clinical TB within a population is influenced by such factors as intravenous drug use, alcoholism, malnutrition, and socioeconomic status. Different local environments, e.g., degree of ventilation - give rise to markedly varied infection rates; approximately 90% of those exposed never become ill. Infectiousness also varies considerably from one infected individual to another - the frequency of cough and the number of bacteria expectorated in sputum will influence the spread of the disease. On average, a source case will infect ten contacts. Susceptibility to infection varies: Epidemiologic data derived from twin studies indicate that susceptibility to TB has genetic determinants. A significant association has been found between the human NRAMPI (natural-assistance-associated macrophage protein I) gene and the susceptibility of an West African population to TB.

Table 1. Factors Influencing TB Transmission

- Source case
- Environment, including ventilation
- Duration and intensity of exposure
- Contact
- Tubercle bacillus

Sepkowitz K.A. "Clin Infect Dis." 1996;23:954

**Diagnosis**

Although skin response to purified protein derivative (PPD) has long been used to detect latent infection, the test fails to distinguish between latent infection, new infection, and subclinical, but active, disease. The acid-fast bacilli (AFB) smear technique can diagnose most infectious cases, but at least two outbreaks have been associated with a smear-negative source case. Diagnosis of TB has benefited from the development of such molecular techniques as polymerase chain reaction (PCR); DNA and RNA amplification; and identification of restriction fragment length polymorphism (RFLP) (Table 2). Immunologic techniques that augment older approaches (Table 3) have also increased the speed and accuracy of diagnosis of TB. Antibodies appear to be found only in persons with confirmed clinical TBs.

Table 2. Diagnosis of Tuberculosis

- AFB smear or histology
- TB culture
    - 7H10
    - Bactec
    - DNA/RNA probe: Gen-Probe for identification
- Drug sensitivity testing
    - Agar
    - Bactec, primary or secondary
- PCR (polymerase chain reaction)
- Alternative DNA or RNA amplification
- RFLP (restriction fragment length polymorphism)

Table 3. The Diagnosis of Tuberculosis: Expansions of Old Approaches

Tests for the presence of:

- M. tuberculosis
    - Visual
    - Growth
    - DNA from Mb
    - RNA from Mb
- Products of M. tuberculosis
    - Antigens
    - HPLC

Immune response to:

- M. tuberculosis
    - Antibodies
    - In vitro cell-mediated immunity
- Products of M tuberculosis
    - Fragments of antigens
    - New antigens

**Case Management and Treatment**

More than any other factor, management practices that deviate from established guidelines have been responsible for the development of multidrug resistance in M. tuberculosis. Treating with a single drug omitting one or more of the regimen's final dosage-any one of these treatment failures allows a susceptible strain of M. tuberculosis to develop resistance to multiple drugs within a few months. Indeed, a patient's history of treatment for TB is a good predictor of the presence of multidrug organisms.

The initial chemotherapeutic regimen for most patients should include at least four drugs: isoniazid, rifampin, pyrazinamide and ethambutol. All new isolates should be subjected to

routine susceptibility testing. For patients who give evidence of erratic compliance-or noncompliance- with the therapeutic regimen, directly observed therapy is indicated.

## Prevention and Control

Administrative controls, engineering controls, and personal respiratory protection all play a role in the control of tuberculosis. Administrative controls, for example, include implementing effective work practices in clinical settings and screening health-care workers for infection and disease. Engineering controls must be able to deal with contaminated air. Respiratory protection for health-care personnel involved with patient care in cough-inducing procedures and other settings include masks and personal respirators. Some of the measures that can be instituted against nosocomial transmission are listed in Table 4.

Table 4. Nosocomial Transmission Issues

- Respiratory isolation
    - Air exchanges
    - Non-recirculated air
    - Negative-pressure room
    - UV irradiation
- Mask must be worn by staff and patient
    - Surgical mask
    - Particle respirator
    - HEPA respirator
    - Mask fitting
    - HEPA-powered filtration units

Effective treatment is also prevention: The infectivity of those with TB is rapidly reduced with appropriate antimicrobial therapy, which decreases the number of bacilli expectorated and introduces antibiotic into the infectious droplet nuclei.

## Conclusions

New methods must be enlisted against the new challenges with which TB is confronting the medical community (Table 5.). Prompt identification of infection leading to appropriate treatment is the first priority in reversing the current trends in TB incidence. Substantial institutional commitment of effort and resources are necessary to bring outbreaks of multidrugresistant TB under control. New developments in immunology and molecular genetics may assist in identifying those most susceptible to TB and bring new treatments to bear on their disease.

Table 5. The New Faces of TB

- The resurgence of TB
    - Foreign born
    - HIV
    - Children

    - Poor and disadvantaged
- Increased transmission
- Changes in clinical presentation
- Rabid diagnostic tests
- Treatment: 4 drugs
- Directly observed therapy