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Global Epidemiology of Tuberculosis 167
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This article provides an overview of the current scale of the global tuberculosis epidemic. It describes the global tuberculosis situation as measured by reported and estimated cases and deaths. The increasing threats of HIV-related tuberculosis and drug-resistant tuberculosis receive particular attention. There is a brief review of the extent of implementation of effective tuberculosis control using the directly observed treatment, short-course (DOTS) strategy. The article ends with a summary of the approaches needed to accelerate progress in global tuberculosis control.

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Eileen Schneider, Marisa Moore, and Kenneth G. Castro

After decades of decline, an unprecedented resurgence in tuberculosis occurred in the late 1980s and early 1990s. Deterioration of tuberculosis program infrastructure, the HIV/AIDS epidemic, drug-resistant tuberculosis, and tuberculosis among foreign-born persons contributed to the resurgence. Since then, tuberculosis case numbers have declined, but the decline in 2003 was the smallest since the resurgence. Key challenges remain, and efforts must focus on identifying and targeting interventions for high-risk populations, active involvement in the global effort against tuberculosis, developing new tools, and maintaining adequate resources.

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This article reviews the principles, scientific basis, and experience with implementation of the directly observed treatment, short-course (DOTS) strategy for tuberculosis. The relevance of DOTS in the context of multidrug-resistant tuberculosis and the HIV epidemic also is discussed.

The Origin and Evolution of *Mycobacterium tuberculosis* 207
Serge Mostowy and Marcel A. Behr

This article introduces the tools and terminology used for the classification of specific isolates of the *Mycobacterium tuberculosis* complex (MTC). The utility of these tools and

terminology is illustrated by discussing work from independent laboratories that have established a genome-based phylogeny for the MTC. It considers the use of these markers to distinguish atypical isolates not conforming to attributes of traditional MTC members. Finally, it discusses the current genomic evidence regarding the origin and evolution of *M. tuberculosis* in the context of its relevance for tuberculosis control in humans and other mammalian hosts.

Molecular Epidemiology: A Tool for Understanding Control of Tuberculosis Transmission 217
Charles L. Daley

One of the primary goals of tuberculosis control programs is to interrupt the transmission of *Mycobacterium tuberculosis*. The development of several genotyping tools has allowed tracking of strains of *M. tuberculosis* as they spread through communities. Studies that have combined the use of genotyping with conventional epidemiologic investigation have increased the understanding of the transmission and pathogenesis of tuberculosis. This article reviews some of the lessons learned using these new epidemiologic tools.

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Richard Bellamy

Host genetic factors are important in determining susceptibility and resistance to *Mycobacterium tuberculosis*. The etiology of tuberculosis is complex, and several host genes have been shown to contribute to the development of clinical disease. The success of the strategies used to investigate host genetic susceptibility to mycobacterial infections can serve as a model for the investigation of host susceptibility to other infectious diseases.

The Diagnosis of Tuberculosis 247
Daniel Brodie and Neil W. Schluger

Diagnostic testing for tuberculosis has remained unchanged for nearly a century, but newer technologies hold the promise of a true revolution in tuberculosis diagnostics. New tests may well supplant the tuberculin skin test in diagnosing latent tuberculosis infection in much of the world. Tests such as the nucleic acid amplification assays allow more rapid and accurate diagnosing of pulmonary and extrapulmonary tuberculosis. The appropriate and affordable use of any of these tests depends on the setting in which they are employed.

Treatment of Active Tuberculosis: Challenges and Prospects 273
Behzad Sahbazian and Stephen E. Weis

This article reviews the basic principles of drug treatment of tuberculosis, individual pharmacologic agents, current treatment recommendations, and several special situations that clinicians are likely to encounter in medical practice.

Issues in the Management of HIV-Related Tuberculosis 283
William J. Burman

This article focuses on the ways in which HIV infection and the associated immunodeficiency affect the management of active tuberculosis. Controversies in the management of HIV-related tuberculosis can be grouped into issues about tuberculosis treatment itself and

issues posed by the use of combination antiretroviral therapy. The author reviews these controversies and makes recommendations for the management of HIV-related tuberculosis.

Tuberculosis in Children 295
Kristina Feja and Lisa Saiman

The epidemiology of pediatric tuberculosis (TB) is shaped by risk factors such as age, race, immigration, poverty, overcrowding, and HIV/AIDS. Once infected, young children are at increased risk of TB disease and progression to extrapulmonary disease. Primary disease and its complications are more common in children than in adults, leading to differences in clinical and radiographic manifestations. Difficulties in diagnosing children stem from the low yield of mycobacteriology cultures and the subsequent reliance on clinical case definitions. Inadequately treated TB infection and TB disease in children today is the future source of disease in adults.

Treatment of Latent Tuberculosis Infection: Challenges and Prospects 313
Kelly E. Dooley and Timothy R. Sterling

This article reviews the treatment of latent tuberculosis infection in HIV-seropositive and HIV-seronegative persons.

New Drugs for Tuberculosis: Current Status and Future Prospects 327
Richard J. O'Brien and Mel Spigelman

This article reviews two classes of compounds that have advanced into phase II and III clinical trials, long-acting rifamycins and fluoroquinolones, and a number of other drugs that have entered or may enter clinical development in the near future.

The Global Alliance for Tuberculosis Drug Development—Accomplishments and Future Directions 341
Charles A. Gardner, Tara Acharya, and Ariel Pablos-Méndez

The Global Alliance for Tuberculosis Drug Development (TB Alliance) aims to stop the spread of tuberculosis by developing new, faster-acting, and affordable tuberculosis drugs. The TB Alliance is a public–private partnership, a not-for-profit enterprise, that draws upon the resources of both private and public institutions to help address this urgent health need. This article summarizes some of the achievements of the TB Alliance to date and outlines potential future directions.

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