The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis

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Global tuberculosis incidence has declined marginally over the past decade, and tuberculosis remains out of control in several parts of the world including Africa and Asia. Although tuberculosis control has been effective in some regions of the world, these gains are threatened by the increasing burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. XDR tuberculosis has evolved in several tuberculosis-endemic countries to drug-incurable or programmatically incurable tuberculosis (totally drug-resistant tuberculosis). This poses several challenges similar to those encountered in the pre-chemotherapy era, including the inability to cure tuberculosis, high mortality, and the need for alternative methods to prevent disease transmission. This phenomenon mirrors the worldwide increase in antimicrobial resistance and the emergence of other MDR pathogens, such as malaria, HIV, and Gram-negative bacteria. MDR and XDR tuberculosis are associated with high morbidity and substantial mortality, are a threat to health-care workers, prohibitively expensive to treat, and are therefore a serious public health problem. In this Commission, we examine several aspects of drug-resistant tuberculosis. The traditional view that acquired resistance to antituberculous drugs is driven by poor compliance and programmatic failure is now being questioned, and several lines of evidence suggest that alternative mechanisms—including pharmacokinetic variability, induction of efflux pumps that transport the drug out of cells, and suboptimal drug penetration into tuberculosis lesions—are likely crucial to the pathogenesis of drug-resistant tuberculosis. These factors have implications for the design of new interventions, drug delivery and dosing mechanisms, and public health policy. We discuss epidemiology and transmission dynamics, including new insights into the fundamental biology of transmission, and we review the utility of newer diagnostic tools, including molecular tests and next-generation whole-genome sequencing, and their potential for clinical effectiveness. Relevant research priorities are highlighted, including optimal medical and surgical management, the role of newer and repurposed drugs (including bedaquiline, delamanid, and linezolid), pharmacokinetic and pharmacodynamic considerations, preventive strategies (such as prophylaxis in MDR and XDR contacts), palliative and patient-orientated care aspects, and medicolegal and ethical issues.

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Introduction

With the notable exception of sub-Saharan Africa, the incidence of tuberculosis has declined over the past two decades in most regions of the world.[1,2] However, gains in tuberculosis control are threatened by the emergence of resistance to antituberculosis drugs. Approximately 20% of tuberculosis isolates globally are estimated to be resistant to at least one major drug (first-line or group A or B second-line), with approximately 10% resistant to isoniazid. WHO has defined multidrug-resistant (MDR) tuberculosis as resistance to at least isoniazid and rifampicin, when first-line therapy is unlikely to cure the disease and a switch to a second-line drug regimen is recommended. Similarly, extensively drug-resistant (XDR) tuberculosis is MDR tuberculosis that is also resistant to the fluoroquinolones and second-line injectable drugs, indicating the probable failure of the standardised second-line treatment regimen. Two modes exist by which patients contract drug-resistant tuberculosis. Primary resistance results from infection with a drug-resistant strain, whereas resistance that develops during therapy is referred to as secondary or acquired resistance. Amplification of resistance might occur when resistance to additional drugs emerges during the treatment course, often in association with inadequate therapy. Globally, approximately 5% of patients with tuberculosis are estimated to have either MDR or XDR types, but the distribution of cases is not uniform; it is substantially higher in some regions, and increasing incidence has been reported in several countries.[1] The high mortality due to most patients remaining untreated is a key reason for this apparently stable estimated global rate of drug-resistant tuberculosis. Approximately 30% of MDR tuberculosis isolates are either fluoroquinolone-resistant or aminoglycoside-resistant, and approximately 10% of MDR tuberculosis isolates can be classed as XDR tuberculosis, or as having resistance to additional drugs beyond XDR tuberculosis (ie, totally drug resistant). This expansion of resistance has