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The Global Burden of Tuberculosis — Combating Drug Resistance in Difficult Times

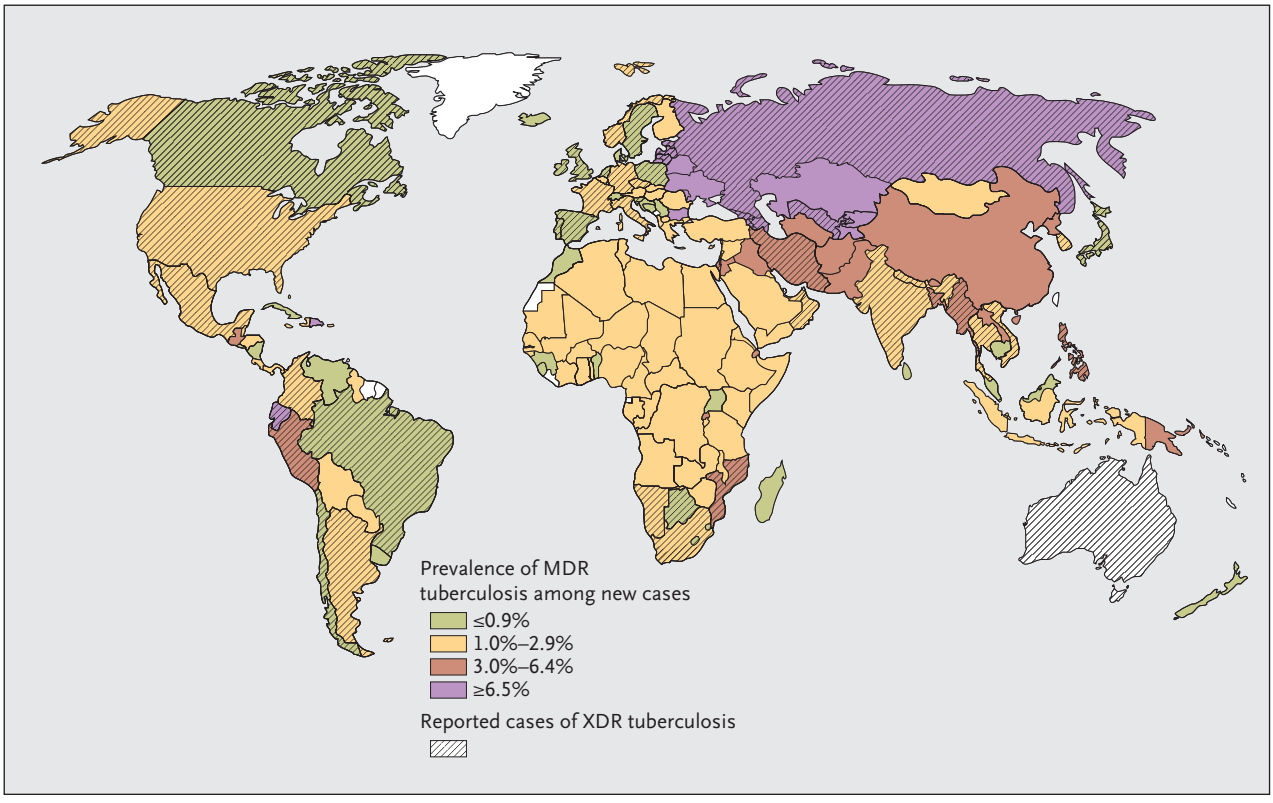
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According to the 13th annual tuberculosis report of the World Health Organization (WHO) — published on World TB Day, March 24, 2009 — there were an estimated 9.27 million new cases of tuberculosis worldwide in 2007 (see interactive graphic).[1] Although this figure represents an increase from 9.24 million in 2006, the world population has also grown, making the number of cases per capita a more useful measure of the problem; this figure peaked in 2004 at 142 per 100,000 and fell to 139 per 100,000 in 2007. An estimated 1.32 million people who were not infected with the human immunodeficiency virus (HIV) died of tuberculosis in 2007, as did an estimated 456,000 people who were HIV-positive. Prevalence and mortality rates appear to be falling in all six WHO regions. Thus, the Americas, the eastern Mediterranean, and Southeast Asia appear likely to meet the Millennium Development Goals target, set in conjunction with the Stop TB Partnership and the World Health Assembly, of halving tuberculosis prevalence and tuberculosis-related mortality between 1990 and 2015. This target will probably not be met by the African and European regions. Nevertheless, do the new statistics, at last, represent the turn of the tuberculosis tide and provide reason for cautious optimism?

Some 22 high-burden countries collectively account for 80% of the global tuberculosis burden. In 2007, the countries with the highest prevalence were India (with 2.0 million cases), China (1.3 million), Indonesia (530,000), Nigeria (460,000), and South Africa (460,000); of the estimated 1.37 million cases in HIV-positive persons, 79% were in Africa and 11% in Southeast Asia. Disturbingly, there were an estimated 500,000 cases of multidrug-resistant (MDR) tuberculosis in 2007 (including 289,000 new cases); of these, 131,000 were in India, 112,000 in China, 43,000 in Russia, 16,000 in South Africa, and 15,000 in Bangladesh; 55 countries had reported cases of extensively drug-resistant (XDR) tuberculosis by the end of 2008. These last figures are reason for considerable concern and highlight a potential threat to our ability to treat tuberculosis, both in individual patients and in the context of a treatment program.

In early April in Beijing, at a ministerial meeting of countries with a high burden of MDR or XDR tuberculosis, it was forecast that to achieve the target set out in the Global Plan to Stop TB, treatment of 1.4 million cases of MDR or XDR tuberculosis will be required in the 27 countries with the highest burden between 2009 and 2015. The cost of diagnosing and treating these cases was estimated at $16.9 billion, with annual costs increasing from $700 million in 2009 to $4.4 billion in 2015; the latter figure is 61 times the funding that is available in 2009. In higher-burden regions, the proportion of tuberculosis cases that are multidrug-resistant may range from 1 to 14% or more.[2] Of these cases, the proportion that are extensively drug-resistant may be as high as 21%.[3] Even in the United States, where the number of MDR cases appears to be declining, the number of XDR cases is increasing. Although countries in Eastern Europe, the former Soviet Union, and China have a large number of MDR cases, reporting suggests that sub-Saharan Africa has a relatively low proportion of drug-resistant cases. However, the incidence of primary drug-resistant cases indicates that these areas may have the highest rates of transmitted MDR tuberculosis in the world.[2] Furthermore, we know that reinfection and multiple infection are common in high-incidence areas, and thus that many so-called recurrent cases are the result of a new infection and should be add-

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Prevalence of MDR Tuberculosis among New Cases of Tuberculosis, 2007, and Countries with at Least One Reported Case of XDR Tuberculosis as of December 2008.

Data are from the World Health Organization.

ed to the primary cases to give a true picture of the growing burden of transmitted MDR and XDR tuberculosis.

Tuberculosis is a disease of poverty, and the declining incidence in many relatively wealthy areas is not unexpected, but there are other parts of the globe where health systems are defective or simply overwhelmed and cannot cope, because of either a lack of funds and personnel or dysfunctional politics, which lead to the sloppy implementation of directly observed treatment (DOTS) programs and exacerbate the tuberculosis problem. Resistance to any agent emerges rapidly if there is overt or covert monotherapy or noncompliance. Under less than ideal conditions, isoniazid monoresistance also emerges rapidly. And in the absence of isoniazid, our most powerful bactericidal agent, the risk of resistance to rifampin, the next-most-powerful bactericidal agent, increases, since neither pyrazinamide nor ethambutol (nor streptomycin) is particularly effective in preventing resistance in companion drugs. Once MDR tuberculosis has developed, there is little to stop the rapid acquisition of resistance to the remaining agents. Further progression to pre-XDR and XDR tuberculosis becomes only a question of time. Since this process will take place over some months, or even years, the patient remains infectious, and it is not surprising that transmission of MDR and XDR tuberculosis occurs, particularly in communities with a high incidence of HIV infection.

Since we now know that many of the tuberculosis infections in high-incidence countries have been transmitted recently, our failure to contain MDR and XDR tuberculosis also reflects our inability to diagnose the problem quickly enough to prevent transmission while continuing to prescribe an ineffective standardized regimen.[4] Individualized therapy could optimize multidrug treatment and limit the further acquisition of resistance. However, in the face of limited resources for the necessary testing and decision making, we have been forced to adopt a standardized approach, which contributes to further treatment failures in MDR tuberculosis. Reinfection is treated as "relapse" according to standardized protocols, and the drugs that are add-

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ed to the regimen only provide the bacterium with new opportunities for developing additional resistance. The Case Record appearing in this issue of the *Journal* (pages 2456–2464) provides a vivid example of the deadly consequences of prescribing a standardized regimen in a severely ill patient without knowing the drug susceptibility of the causative organism.[5] Recognizing the urgency of this problem, the Stop TB Partnership has defined one of its major objectives as the improvement of laboratory facilities and services and the training of personnel to permit the introduction of new, rapid diagnostic tests for MDR tuberculosis.[1]

The threat of MDR and XDR tuberculosis could hardly have come at a worse time — in the midst of the worst economic conditions in a century. In theory, the cost burden to developing countries for treatment of MDR and XDR cases may far exceed their total budgets for health care, and aid from the Global Fund to Fight AIDS, Tuberculosis, and Malaria or other sources will be essential for some time if we are to try to control this problem.

On a note of optimism, the Stop TB Partnership has established the Global Laboratory Initiative to promote the availability of new diagnostic tools in countries with a high MDR burden, country-specific budgets are being prepared, and funding could become available through the Global Fund and through UNITAID (an international facility for the purchase of drugs against HIV–AIDS, malaria, and tuberculosis). A number of new antituberculosis agents are in the developmental pipeline, many under the aegis of the Global Alliance for TB Drug Development, and some have already entered clinical evaluation in studies of early bactericidal activity and the treatment of MDR tuberculosis. However, it must be recognized that the development of a new antituberculosis agent is a long, expensive process; if these agents are distributed in places with dysfunctional health services, where the need is probably the greatest, the development of resistance could leave us worse off in a decade than we are now. "Self-supervised DOTS" is not DOTS, and if health systems remain dysfunctional, any new drug will follow the same path to resistance that our current drugs have taken.

The tuberculosis tide has turned, but maintaining the momentum will require a financial and political commitment that may be beyond the capability of many struggling communities.

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