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From magic bullets back to the Magic Mountain: the rise of extensively drug-resistant tuberculosis

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Extensively drug-resistant tuberculosis (XDR-TB) occurs where health systems have been historically weak; it lays bare the reality of TB as a serious public health problem, especially in areas of high HIV prevalence, and reinforces the need for effective TB control strategies that are coordinated with HIV control. The problem of XDR-TB in high HIV prevalence settings challenges all aspects of the public health and health-care systems, and will require an integrated approach. Failure to act rapidly to contain local outbreaks, develop tools and strategies for identifying and treating XDR-TB, and investing in longer term improvements to TB control could transform the magic bullets for TB into blanks, and assure a return to the grim prospects of the Magic Mountain.

The development of tuberculosis (TB) chemotherapy from the 1940s through the 1970s transformed the deadly 'white plague' into a curable disease, though it was a largely uncelebrated triumph of twentieth century science[1]. But since the dawn of the antibiotic era, TB treatment has been shadowed by the specter of drug resistance. The very first person treated with streptomycin at the Mayo Clinic in 1944 developed resistance to the drug (but was cured with surgery), as did the majority of those treated with the drug in the famous 1948 British Medical Research Council trial that both established the efficacy of treatment for TB and created the paradigm of the controlled clinical trial[2]. Fifteen years ago an epidemic of multidrug-resistant tuberculosis, or MDR-TB—TB resistant to rifampin plus isoniazid—in New York City induced panic and alarm, but a massive infusion of funds into the public health infrastructure turned the tide, at least in the United States, and public interest waned[3,4]. However, the problem of drug resistance has persisted, and efforts to contain it globally have not been sufficient.

Enter XDR-TB. This term refers to disease caused by organisms with resistance to the first-line drugs rifampin and isoniazid, plus key second-line anti-TB drugs (**Fig. 1**). The term XDR-TB was first used in March 2006 by the US Centers for Disease Control and Prevention in a report on XDR-TB compiled from laboratory surveillance from a number of countries[5]. The recognition that XDR-TB existed caused little notice at that time, but a subsequent outbreak of XDR-TB in HIV-infected people in KwaZulu-Natal, South Africa, first presented at the International AIDS Conference in Toronto last August, hit like a bombshell[6].

The Tugela Ferry Disaster

Gandhi *et al.* reported that of 542 people with TB at the Church of Scotland Hospital, Tugela Ferry in rural Kwazulu-Natal province who had *Mycobacterium tuberculosis* cultured from their sputum, 221 (41%) had MDR-TB, a level six-fold greater than the already high levels of MDR-TB in the province[7]. More alarmingly, 53 of these 221 (24%) with MDR-TB had an *M. tuberculosis* strain that was also resistant to the two most clinically useful classes of second-line TB drugs, aminoglycosides (amikacin or kanamycin) and fluoroquinolones—that is, XDR-TB. Among the 53 with XDR-TB, 44 were tested for HIV and all were coinfected (median $CD4^+$ T-cell count 63 cells per mm^3). Fifty-two of the 53 died in a median of just 16 days from the time of sputum collection. Molecular typing of the isolates indicated that 85% were clonally related, implying epidemic transmission of XDR strains, most likely in HIV clinics and hospital wards. Included among the deaths were 15 HIV-coinfected individuals receiving antiretroviral therapy, and two HIV coinfected healthcare workers. The startling lethality of XDR-TB in a setting of high HIV prevalence had a galvanizing effect on clinicians and public health officials. XDR-TB in South Africa seemed to be an emerging epidemic that could reverse a half century of therapeutic gains in TB and cause extraordinary mortality among highly vulnerable HIV-infected individuals.

How did this localized outbreak of XDR-TB emerge? Are similar unrecognized localized outbreaks ongoing elsewhere? How can XDR-TB be controlled? The questions are many, the immediate answers few, and the need for more information urgent.

The origins of drug-resistant TB

Current 'short-course' TB treatment is composed of two months of rifampin, isoniazid, pyrazinamide and ethambutol followed by four months of rifampin and isoniazid. Rifampin has a particularly important role in this first-line regimen: it is highly potent and sterilizing, eradicating intracellular and semidormant organisms that can cause recurrences. Because of this, rifampin cannot effectively be replaced by any other single drug or combination of drugs. Resistance to anti-TB drugs arises from selection of naturally occurring mutants with innate resistance to individual agents in the face of exposure to drugs producing incomplete suppression of growth. Poor adherence to the therapeutic regimen, improper prescribing by clinicians, and drug interactions or malabsorption can result in partial suppression of bacterial growth and the emergence of resistant organisms. Once this acquired resistance develops, treatment is

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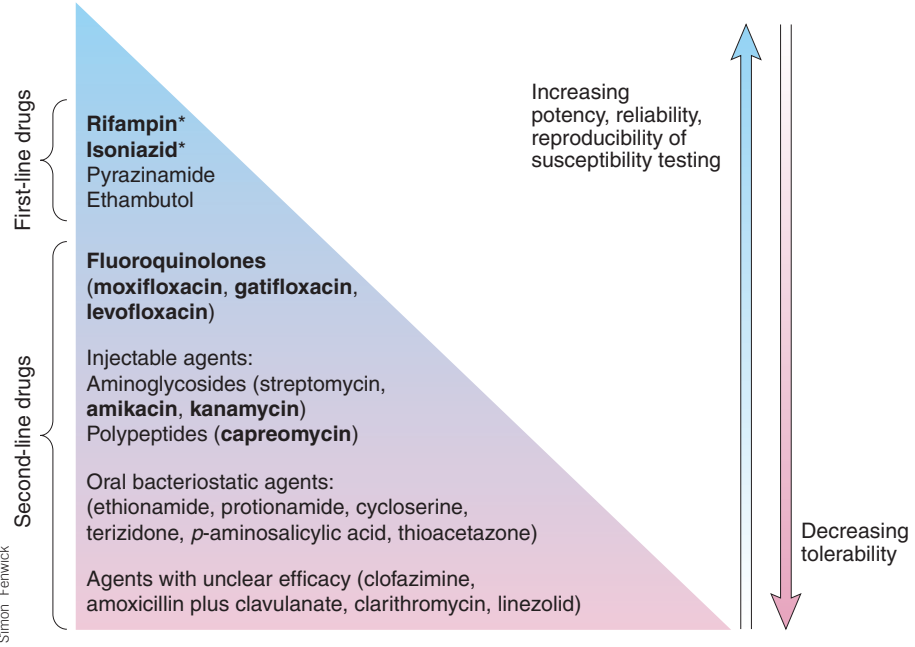

Figure 1 First-line and second-line anti-TB drugs. MDR-TB is defined as resistance (asterisks) to isoniazid plus rifampin. XDR-TB is defined as resistance (boldface) to at least rifampin and isoniazid plus resistance to the fluoroquinolones and to at least one of the injectable drugs capreomycin, kanamycin and amikacin.

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compromised, further resistance can evolve and resistant organisms can be transmitted to others, leading to primary drug resistance that may fail to respond to standard therapy.

Effective treatment and cure of MDR-TB requires prolonged use (typically two years) of a combination of drugs, including second-line drugs that for the most part have lower potency than first-line agents, greater toxicity, or both (**Fig. 1**). For the past six years, a global effort (called DOTS-Plus) to treat people with MDR-TB under strict conditions has been underway, reaching thousands of those with previously untreatable TB. An unfortunate consequence of treating MDR-TB with second-line drugs, however, is the inevitable emergence of further drug resistance. If the same factors that produce MDR-TB remain in force, then MDR-TB becomes XDR-TB.

XDR-TB is defined by the World Health Organization (WHO) Global Task Force on XDR-TB as resistance to at least rifampin and isoniazid plus resistance to the fluoroquinolones and to at least one of the injectable drugs capreomycin, kanamycin and amikacin[8]. Although other second-line drugs exist, the fluoroquinolones and injectable agents are the most potent and tolerable agents, and absent them, treatment of XDR-TB, if it is diagnosed before death, is daunting. XDR-TB is exceedingly difficult to cure, especially in resource-limited settings, since the remaining classes of drugs are very poorly potent, highly toxic, and expensive.

The WHO estimates that the number of new MDR-TB cases in 2004 was 425,000, with China, India, and the Russian Federation accounting for just over 60%[9]. A recent analysis by the Global Project on Anti-tuberculosis Drug Resistance Surveillance indicated that, in the 79 countries or geographical settings studied, median prevalence of MDR-TB among new TB cases was 1.1%, and among previously treated TB cases was 6.9% (ref. 10).

The Stop TB Partnership's Green Light Committee, created in 2000, provides access to preferentially priced second-line drugs to national TB programs, while ensuring rational use through mandatory program review and monitoring. In this context, reports emerged of *M. tuberculosis* isolates resistant to multiple second-line drugs. In response, the WHO and the US Centers for Disease Control and Prevention surveyed an international network of mycobacteriology laboratories in order to estimate the burden of XDR-TB. In a sample of 17,690 *M. tuberculosis* isolates from 49 countries from 2000-2004, 20% were MDR, and 2% (10% of the MDR isolates) were XDR[5]. Population-based data were available from the United States, Latvia and South Korea, where 4%, 19%, and 15% of MDR-TB cases, respectively, were XDR. Overall, this and subsequent reports have documented that XDR-TB is widespread (**Fig. 2**), including occurrence in the US, where TB has been considered under control and overall annual incidence has declined since 1993[11].

A Perfect Storm?

What determinants seem to have fueled the KwaZulu-Natal XDR-TB outbreak? Poor TB control practices, high HIV prevalence, and nosocomial transmission undoubtedly had roles, although limitations in the data preclude definitive assessment of risk factors and their relative weights. In the most recent survey of drug resistance in South Africa, ~7% of *M. tuberculosis* isolates from the KwaZulu-Natal Province were MDR, a number similar to that in several other provinces[10]. Access to some second-line drugs in South Africa predates the Green Light Committee, however, and clinicians and public health authorities were aware of what would now be called XDR-TB cases for a number of years. MDR-TB treatment in some parts of South Africa is weakly managed, with many people receiving prolonged courses of treatment with second-line drugs without supervision, risking noncompliance and further evolution of resistance. A recent analysis of MDR-TB outcomes over a three-year period in South Africa found that 22% of those under treatment defaulted, and mortality was 36% for individuals with HIV infection and 16% for those without (J. Farley *et al.*, unpublished data). In addition, MDR-TB treatment in South Africa (and many other countries) uses a standardized regimen rather than individualized treatment based on susceptibility of the individual's strain. These factors virtually assure the development of XDR-TB in some cases. Propagation of these highly resistant strains through institutional and community spread undoubtedly contributed to the recent outbreak. Indeed, indicate that XDR-TB is more widespread in KwaZulu-Natal, and elsewhere in South Africa, as well.

Transmission of resistant strains to HIV-infected individuals is catastrophic. HIV-infected individuals exposed to drug-susceptible or drug-resistant *M. tuberculosis* progress rapidly to active TB disease, and are more likely to die from TB if active TB develops[12–15]. In sub-Saharan Africa, HIV has fueled large increases in TB incidence, and in eight countries over 50% of those with TB have HIV coinfection[16]. HIV coinfection is likely to have had a major role in the KwaZulu-Natal XDR-TB outbreak. HIV prevalence was high—20% in women in the hospital's maternity ward—and the HIV epidemic was locally mature, such that many HIV-infected people probably had severe immunosuppression[7]. Nosocomial transmission seems to have occurred. Two healthcare workers died of XDR-TB, and two-thirds of people with XDR-TB had been admitted to the hospital in the two years preceding their presentation with XDR-TB.

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Toward controlling XDR-TB

It is clear that there is no magic bullet for controlling XDR-TB, and that addressing drug-resistant TB cannot be divorced from overall TB control efforts. In October, 2006 the WHO's Stop TB and HIV departments convened an XDR-TB task force to review current data, define key issues, make recommendations for short-term actions, and develop longer-term responses at the global level (**Box 1**)[8]. These recommendations, as well as those of the Expert Consultation on Drug-Resistant Tuberculosis, underscore the need for strengthening TB control programs in order to prevent both MDR- and XDR-TB[17]. MDR- and XDR-TB result from poorly functioning health systems and inappropriate management of TB cases. DOTS—the WHO's programmatic strategy for TB control—is necessary but not sufficient in settings in which prevalence of HIV, drug-resistant TB, or both is high[18]. Additional TB control strategies targeted at populations with high HIV burdens are critically important. Such strategies include more widespread use of TB preventive therapy, which is vastly underutilized despite its low cost and known efficacy, and improved TB case detection in HIV-infected people, many of whom die of TB without a diagnosis. Access to HIV care, including antiretroviral therapy, is also urgently needed, and reducing HIV incidence will substantially reduce TB burden over the longer term[19,20].

In most resource-limited settings, TB laboratory services are woefully inadequate, and laboratory-based diagnosis of TB typically relies on microscopy of stained sputum. This method has poor sensitivity (missing >50% of cases), especially in HIV-positive individuals, and does not provide information about drug susceptibility. Culture is more sensitive than microscopy and can be used for drug susceptibility testing, but *M. tuberculosis* takes several weeks to grow. New diagnostic modalities that could improve TB detection and the identification of drug resistance include nucleic acid amplification tests to detect *M. tuberculosis* in sputum, phage-based methods to detect *M. tuberculosis* and drug resistance in sputum, and rapid molecular genetic tests to detect rifampin resistance in sputum or in cultured bacteria. These tests, however, have generally been regarded as too costly for widespread use in most TB endemic settings. In the absence of laboratory capacity beyond smear microscopy, the approach to diagnosis of drug resistance is generally based on clinical failure to respond to one or more several-month courses of TB treatment. This approach results in unnecessary prolonged morbidity and increased mortality, contributes to continued transmission, and even amplifies development of drug resistance as new drugs are added to an already failing regimen. There is a pressing need to strengthen capacity for prompt, accurate laboratory-based diagnosis of TB and drug resistance. This will require infrastructure development and maintenance, as well as reliable systems for supplies procurement, equipment maintenance and personnel training and retention.

Emergence of XDR-TB also highlights the need for expansion of ongoing drug development activities such as those of the Global Alliance for TB Drug Development. Drugs with new mechanisms of action will be necessary for treating people with MDR and XDR-TB. But the introduction of new drugs into settings where treatment compliance is not assured and where drug susceptibility testing is not available is likely to contribute to even more resistant organisms. Another promise of new agents lies in their potential to enhance the potency of first-line regimens, thereby shortening treatment duration and increasing the likelihood of treatment success, which will prevent the emergence of resistance in the first place.

Box 1 Summary recommendations from the World Health Organization Global task force on XDR-TB, Geneva, 9–10 October 2006[8]

1. Global TB control. Control of TB globally should be strengthened immediately and concurrently with scaling up universal access to HIV treatment and care. The Global Plan to Stop TB should reflect the threat of XDR-TB, and WHO guidelines revised accordingly.
2. Management of patients. The algorithm and revised guidelines for diagnosis and management of patients at risk for MDR-TB and XDR-TB should be finalized and evaluated in countries without delay. Rapid tests for rifampicin resistance should be made widely available.
3. Programmatic management. WHO guidelines for the programmatic management of drug-resistant TB should be updated to address XDR-TB and TB/HIV co-management, and implemented as soon as possible. Countries should consider using the Green Light Committee mechanism to facilitate access to high quality low-priced second-line anti-TB drugs. WHO good practice in legislation and regulations for TB control should be reviewed for adoption and adaptation at the country level.
4. Laboratory services. WHO should disseminate the revised laboratory case definition of XDR-TB. A strategic plan for laboratory strengthening should be developed for global and national levels, with the aim of ensuring that all TB patients have access to timely, quality-assured laboratory diagnostic services; the plan should include deployment of rapid diagnostic tests. Access to second-line drug susceptibility testing should be increased.
5. Infection control. Measures for infection control should be implemented rapidly in health-care settings and other high-risk areas such as prisons, to reduce the transmission of drug-resistant TB. WHO guidelines on infection control should be revised.
6. Surveillance. Rapid surveys should be carried out focused on high-risk patients in order to establish the geographical distribution of XDR-TB. Thereafter, surveillance for XDR-TB must be included within existing drug-resistance surveillance systems.
7. Advocacy, communication, and social mobilization should be enhanced to promote effective prevention, treatment and control of XDR-TB at global and national levels, especially in settings of high HIV prevalence.
8. Resource mobilization. WHO should develop a fully budgeted plan for resource mobilization to meet the short-and long-term needs to address XDR-TB at global, regional and country levels.
9. Research and development. WHO should convene an expert consultation as soon as possible to review research and development issues related to XDR-TB.

Prevention and management of XDR-TB

Apparent nosocomial transmission of XDR-TB in the KwaZulu-Natal outbreak is a tragic reminder of the importance of infection control measures—a lesson learned not for the first time during nosocomial outbreaks of largely HIV-associated MDR-TB in New York City[3,4]. How can meaningful infection control measures be implemented in resource-poor settings, given the realities of already overburdened health-care systems where negative pressure isolation rooms, air filtration systems and personal protective respirators are uncommon? Emphasis has been placed on work practice and administrative control measures, which are considered to be the most effective and are the least expensive, and which consist of policies and procedures intended to promptly identify infectious TB cases so that additional precautions and health-care steps can be taken (for example, separation of a contagious individual from others)[21–23]. Such measures, if feasible, will be challenging to implement because of resource constraints

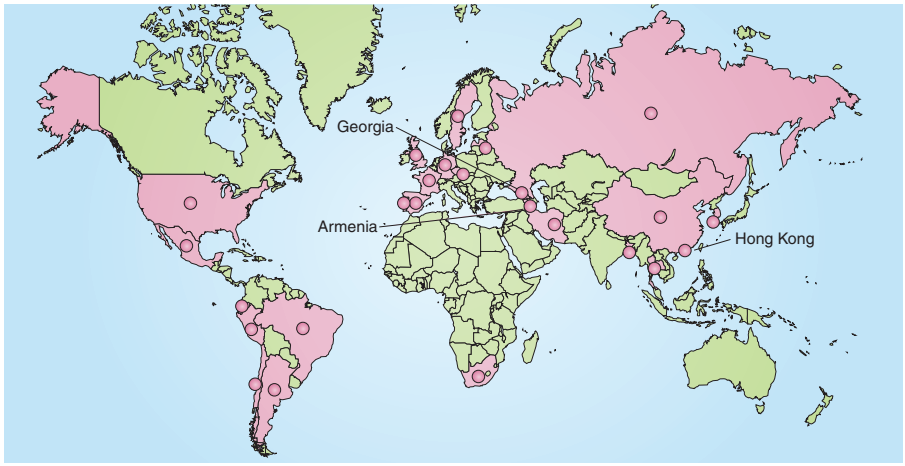

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Figure 2 Countries with confirmed XDR-TB cases thus far (pink). From the World Health Organization, http://www.who.int/tb/xdr/xdr_jan.pdf (accessed 22 January 2007).

and lack of rapid, sensitive diagnostic tools to accurately triage individuals.

The management of individuals with XDR-TB presents formidable challenges, even under the best of circumstances. Can XDR-TB be cured? There is a paucity of data on this point, but data from the United States and from Latvia are somewhat promising. In Latvia 115 people with XDR-TB initiated therapy during 2000–2002[5]. Seventy (61%) were either cured or completed treatment, 30 (3%) died, 27 (23%) failed treatment and 15 (13%) had unknown outcome. In the United States 64 people with XDR-TB initiated therapy during 1993–2002[5]. Thirty-three percent died, and only 31% completed therapy. The South African experience demonstrates the profound impact of coinfection with HIV on survival, however, and underscores the importance of rapid detection of resistance. An algorithm for the initial management of individuals having respiratory symptoms and risk factors for drug-resistant TB has been proposed by the WHO Global Task Force on XDR-TB[8]. This algorithm takes into account HIV status, and it focuses on sputum smear microscopy–positive individuals, who are likely to be most infectious. It also focuses decision-making on results of a rapid test, done directly from the sputum specimen, for detection of rifampin resistance. Although conceptually well-founded, the algorithim is currently available rapid rifampin resistance tests have not been well-validated for use directly on sputum. The Foundation for Innovative New Diagnostics is supporting a large study to determine performance characteristics of two promising rapid rifampin-resistance assays. Of particular importance, the proposed algorithm calls for drug-susceptibility testing of all HIV-positive individuals with TB—this represents a meaningful expansion of drug-susceptibility testing that would benefit individuals and provide important epidemiological information to public health authorities.

There are of course innumerable remaining questions. What constitutes "risk for drug-resistant TB"? What is the appropriate management of "at-risk" smear microscopy–negative individuals (who may have pulmonary TB, extrapulmonary TB or a non-TB diagnosis)? In addition, little is known about the duration of treatment needed to cure XDR-TB, or about drug-drug interactions between antiretroviral drugs and second-line TB drugs. Finally, appropriate infection control strategies that balance individual rights and the protection of contacts may be needed for the care of those with XDR-TB who remain contagious because of medication intolerance, nonadherence or treatment failure.

Enhanced surveillance of XDR-TB is needed to better understand the scope of the problem and plan appropriate responses. The Global Project on Anti-tuberculosis Drug Resistance Surveillance has collected information on prevalence, patterns and trends of drug resistance since 1994. This important activity has focused on resistance to first-line drugs and has contributed much to our understanding of MDR-TB prevalence[10,24]. So far, however, surveillance for XDR-TB has been more limited, as drug susceptibility testing for second-line drugs is not well-standardized and for some drugs is poorly reproducible, and few countries perform such testing within the context of their national TB programs[25]. Priorities for XDR-TB surveillance include facilitating access to reliable susceptibility testing to second-line drugs and incorporating this into existing surveillance systems, and incorporating information about HIV testing into TB surveillance activities.

Last, but certainly not least, the role of effective advocacy for a more vigorous response to the global TB epidemic cannot be overstated. While alarmist messages may increase stigma in some settings, informed and evidence-based advocacy must seek to mobilize the money and commitment required to sustain and expand TB programs and research. The Global Plan to Stop TB conservatively estimates a gap of $32 billion between available and needed funds to meet the Millennium Development Goals for TB. Funding of research on TB is improving after decades of neglect but still lags far behind that of other diseases such as HIV[26].

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COMPETING INTERESTS STATEMENT

The authors declare competing financial interests (see the *Nature Medicine* website for details).

1. Ryan, F. *The Forgotten Plague: How the Battle Against Tuberculosis Was Won—and Lost* (Little, Brown; Boston, 1993).
2. British Medical Research Council. *BMJ* **2**, 769–782 (1948).
3. Frieden, T.R. *et al. N. Engl. J. Med.* **328**, 521–526 (1993).
4. Frieden, T.R., Fujiwara, P.I., Washko, R.M. & Hamburg, M.A. *N. Engl. J. Med.* **333**, 229–233 (1995).
5. Centers for Disease Control and Prevention. *MMWR Morb. Mortal. Wkly. Rep.* **55**, 301–305 (2006).
6. Gandhi, N.R. *et al.* Abstract THLB0210, Late Breaker Session, XVI International AIDS Conference, 13–18 August 2006. .
7. Gandhi, N.R. *et al. Lancet* **368**, 1575–1580 (2006).
8. Report WHO/HTM/TB/2006.375 (World Health Organization, Geneva, 2006).
9. Zignol, M. *et al. J. Infect. Dis.* **194**, 479–485 (2006).
10. Aziz, M.A. *et al. Lancet* **368**, 2142–2154 (2006).
11. Centers for Disease Control and Prevention. *MMWR Morb. Mortal. Wkly. Rep.* **55**, 305–308 (2006).
12. Antonucci, G., Girardi, E., Raviglione, M.C. & Ippolito, G. *J. Am. Med. Assoc.* **274**, 143–148 (1995).
13. Selwyn, P.A. *et al. N. Engl. J. Med.* **320**, 545–550 (1989).
14. Daley, C.L. *et al. N. Engl. J. Med.* **326**, 231–235 (1992).
15. Kang'ombe, C.T. *et al. Int. J. Tuberc. Lung Dis.* **8**, 829–836 (2004).
16. Report WHO/HTM/TB/2005.349 (World Health Organization, Geneva, 2005.
17. SA HealthInfo. <http://www.sahealthinfo.org/tb/expert.htm> (2006).
18. De Cock, K.M. & Chaisson, R.E. *Int. J. Tuberc. Lung Dis.* **3**, 457–465 (1999).
19. Currie, C.S., Williams, B.G., Cheng, R.C. & Dye, C. *AIDS* **17**, 2501–2508 (2003).
20. Nunn, P. *et al. Nat. Rev. Immunol.* **5**, 819–826 (2005).
21. Nardell, E.A. *Semin. Respir. Infect.* **18**, 307–319 (2003).
22. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings (World Health Organization, Geneva, 1999).
23. Centers for Disease Control and Prevention, World Health Organization, International Union Against Tuberculosis and Lung Disease. <http://www.who.int/tb/publications/2006/tbhiv_infectioncontrol_addendum.pdf> (2006).
24. Cohn, D.L., Bustreo, F. & Raviglione, M.C. *Clin. Infect. Dis.* **24** (suppl. 1), S121–S130 (1997).
25. Heifets, L.B. & Cangelosi, G.A. *Int. J. Tuberc. Lung Dis.* **3**, 564–581 (1999).
26. Feuer, C., Sayed, J. & Harrington, M. *Tuberculosis Research and Development: A Critical Analysis* (Treatment Action Group, New York, 2006).

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