

laria, noting that it has assumed drug-distribution tasks that are beyond its capacities and that, as a result, hundreds of thousands of doses of combination therapy have gone undelivered in Angola, where more than 11,000 people died of malaria in 2005. At a time when more money than ever is pouring into global health, the WHO's perceived lack of leadership and the rivalries in which it and other organizations are engaged represent major problems; it would behoove Chan to tackle them.

Jha, for one, believes that Chan may be able to take a first step toward coordinating the efforts of all the rivals if she uses "the WHO bully pulpit," a unique asset. And indeed, Chan, who spent several weeks after her election meeting

with Bill and Melinda Gates, Global Fund Executive Director Richard Feachem, and high-ranking officials at all the major international health agencies, said she had concluded that the WHO should hold a meeting of all the players "to identify priorities and decide who is doing what." In a January 22, 2007, address, she told the WHO executive board that the organization "has a great responsibility to channel [the] enthusiasm, activity, and money" of myriad global health players into a "cohesive and compelling" public health agenda that brings "clear and measurable benefits to countries and their populations."

As colleagues at the WHO will attest, if Chan is holding a meeting, the other players will come.

And that's when her leadership — and her independence — will truly be tested.

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XDR Tuberculosis — Implications for Global Public Health

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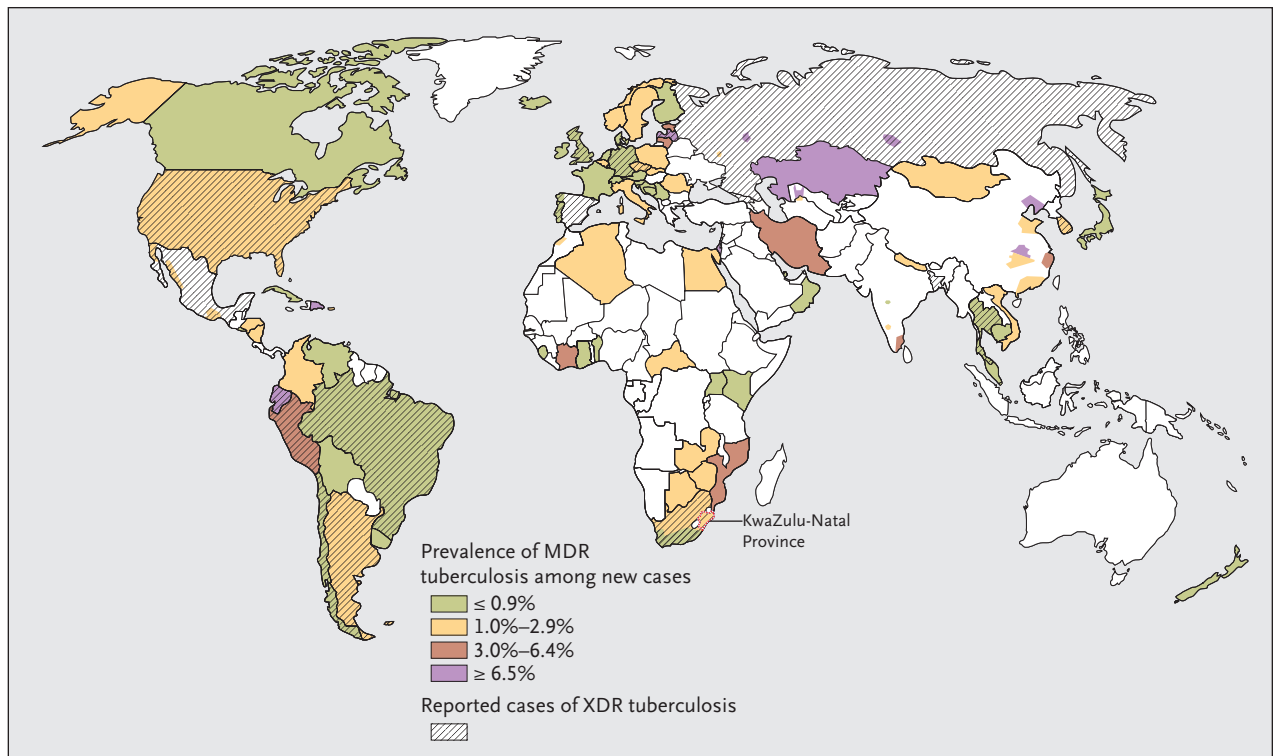
In early 2005, physicians at a rural hospital in KwaZulu-Natal, a province of South Africa, were concerned by a high rate of rapid death among patients infected with the human immunodeficiency virus (HIV) who also had tuberculosis. A study revealed the presence not only of multidrug-resistant (MDR) tuberculosis but also what came to be called extensively drug-resistant (XDR) tuberculosis. XDR tuberculosis is caused by a strain of *Mycobacterium tuberculosis* resistant to isoniazid and rifampin (which defines MDR tuberculosis) in addition to any fluoroquinolone and at least one of the three following injectable drugs: capreomycin, kanamycin, and amikacin. Of 53 patients with XDR tuberculosis, 55% claimed

they had never been treated (implying that they had primary infection with an XDR strain of *M. tuberculosis*); two thirds had recently been hospitalized; and all 44 who underwent testing were HIV-positive. All but one of the patients died of tuberculosis, with a median survival period of only 16 days from the time the first sputum specimen was collected. Genotyping analysis revealed that 85% of the 46 isolates tested belonged to the KwaZulu-Natal (KZN) family of tuberculosis strains, which had been recognized in the province for a decade.¹

These alarming findings attracted much attention at the International AIDS Society conference in Toronto in August 2006. But this was not the first time

that XDR tuberculosis had been identified. A March 2006 report by the Centers for Disease Control and Prevention and the World Health Organization (WHO) documented the presence of XDR tuberculosis in at least 17 countries. Though not representative, the data showed that 10% of MDR tuberculosis isolates were in fact XDR tuberculosis. More representative data from the United States, the Republic of Korea, and Latvia showed that 4%, 15%, and 19%, respectively, of MDR tuberculosis isolates were XDR strains.²

In the fall of 2006, international experts agreed on the laboratory case definition of XDR tuberculosis; a framework for action on the clinical management of suspected XDR tuberculosis;



Prevalence of MDR Tuberculosis among New Cases of Tuberculosis, 1994–2002, and Countries with at Least One Reported Case of XDR Tuberculosis as of January 2007.

Data are from the World Health Organization.

implications for national tuberculosis-control programs; protection of health care workers; surveillance; and advocacy, communication, and social mobilization.³

The global threat of XDR tuberculosis has great significance for the public health field. For one thing, its very existence is a reflection of weaknesses in tuberculosis management, which should minimize the emergence of drug resistance. Early, accurate diagnosis and immediate, proper curative treatment, supported and supervised so that drugs are taken for the appropriate duration, are key to tuberculosis control. Inadequate drug regimens select out drug-resistant strains, which then proliferate. Further treatment errors repeat the cycle, leading to strains that are resistant to other drugs, until MDR tuberculosis is created.

The recipe for XDR tuberculosis is the same — the inappropriate use of second-line drugs in a patient for whom first-line drugs are failing. Patients then spread the infection to close contacts, who acquire primary XDR tuberculosis. Multiple errors have probably contributed to the development of XDR disease in South Africa.

Solutions that interrupt this cycle are urgently needed. The most basic requirement is an effective disease-control infrastructure, starting with much-strengthened laboratory capacity. Diagnosis based on sputum-smear microscopy and rapid liquid-culture methods followed by the provision of appropriate support for patients and strict supervision of treatment until cure are the basis of tuberculosis control. Compli-

ance must be maximized to prevent the emergence of drug resistance.

Prevention, however, is insufficient once drug-resistant tuberculosis has spread. Immediate detection through rapid drug-susceptibility testing is necessary to ensure that patients receive a quick diagnosis and adequate treatment and that transmission of the disease is thereby interrupted. Such treatment requires access to second-line drugs, which are more costly, more toxic, and weaker than first-line drugs. Second-line treatment must be given for at least 18 months under strict monitoring and supervision, and patients must receive counseling and support, since further development of drug resistance would render them virtually untreatable.⁴ New classes of anti-

tuberculosis drugs are unlikely to become available for at least another few years.

XDR tuberculosis also has major implications for the care of patients with HIV and for HIV control, because a high prevalence of HIV predicts extreme vulnerability to tuberculosis. All available public health measures must be implemented when these diseases converge, starting with DOTS, the essential package of tuberculosis-control intervention based on diagnosis and treatment of infectious cases, and HIV–AIDS prevention and treatment. Antiretroviral drugs protect against tuberculosis by restoring patients' immunocompetence. Tuberculosis screening and chemoprophylaxis are essential in patients who are HIV-positive, as are antiretroviral treatment and the use of trimethoprim–sulfamethoxazole for patients with tuberculosis. Furthermore, hospital infection-control measures must be strengthened to prevent transmission among hospitalized patients and health care workers.

The development of XDR tuberculosis reveals weaknesses in primary care diagnostic services. Patients with cough often present at the nearest clinic, and if they have tuberculosis that is not promptly diagnosed and treated, they will spread the disease. And if tuberculosis isolates are not tested for drug susceptibility from the outset, resistance may be detected too late to permit a cure. These interventions require substantial primary care capacity and training of health care workers in recognizing suspected cases of tuberculosis, making diagnoses, supervising treatment, and counseling patients. Well-trained laboratory technicians are also of

paramount importance for ensuring proper diagnosis.

In addition, the need to contain XDR tuberculosis places major demands on surveillance systems. Most current information on drug resistance comes from surveys, since routine drug-susceptibility testing has been the privilege of rich countries. This situation must change rapidly in areas affected by XDR tuberculosis. Information is essential for building and monitoring a response, and only computerized information systems allow sufficiently rapid exchange of information within and between countries. The 2005 International Health Regulations, which take effect in June 2007, provide a framework that identifies the roles of the WHO and national governments in identifying and responding to public health emergencies and sharing relevant information. Effective implementation of these regulations requires much more effective national surveillance and response systems — and therefore the mobilization of resources.

XDR tuberculosis has exposed the dearth of new tools for tuberculosis control. Although the current diagnostic tests and drugs can control tuberculosis if rigorously applied, the lack of easy-to-use tests that produce rapid results reflects a lack of awareness of the magnitude of the problem. Ideally, if tuberculosis is suspected, it should be diagnosed at the point of care, and information about drug susceptibility should be obtained rapidly to guide treatment decisions. In most countries, this ideal is not achieved because of insufficient primary care services and the lack of adequate laboratories and of tools permitting easy, prompt detection of

drug resistance. To correct these deficiencies, governments and international aid partners must invest in building a proper care and laboratory infrastructure, and research on better diagnostics must be intensified without delay.

Similarly, the lack of new classes of antituberculosis drugs has made treatment of drug-resistant tuberculosis challenging. New treatment regimens probably will not be available for several years — hence the imperative to preserve the effectiveness of current drugs by making sure that no second-line drugs are used without proper supervision. An effective vaccine would be the most powerful tool for preventing tuberculosis and drug resistance, but a vaccine is not anticipated anytime soon. We must invest in research and development for better tools while maintaining the efficacy of the tools we have available today.

All evidence suggests that XDR tuberculosis reflects a failure to implement the measures recommended in the WHO's Stop TB Strategy.⁵ This strategy emphasizes expanding high-quality DOTS programs, addressing HIV-associated tuberculosis and drug resistance, strengthening health care systems and primary care services, encouraging all providers to follow good practices, empowering patients and communities to improve health, and enabling and promoting research. These measures ultimately require political commitment and will, and in many countries, health is still not a top priority. But we now have an opportunity to prioritize tuberculosis control and research efforts, energized by the appearance of highly resistant strains that may not be halted unless imme-

diate investments match the challenges we face.

An interview with Dr. Smith can be heard at www.nejm.org.

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FOCUS ON RESEARCH

The Riddle of Kawasaki Disease

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Two generations of clinicians and researchers have been stumped by the riddle of Kawasaki disease. How can an illness look like an infectious disease but not have a recoverable agent; look like an immune-mediated vasculitis but not be easily treated with corticosteroids; and look like a benign, self-limited illness but be the leading cause of acquired heart disease in children? The answers to the riddle continue to elude us.

Kawasaki disease affects children of all ethnic backgrounds throughout the world, although susceptibility is shaped by genetic influences. Japanese children have the highest incidence of the disease, with an attack rate that has reached 175 per 100,000 children younger than 5 years — a prevalence of approximately 1 in every 185 Japanese children — according to Yosikazu Nakamura and Ritei Uehara of Jichi Medical University in Tochigi, Japan. In the United States, it is difficult to estimate the national burden of the disease, because the reporting of cases to the Cen-

ters for Disease Control and Prevention has been sporadic. However, regional estimates in a multiethnic U.S. population suggest an attack rate of 20 to 25 per 100,000 children younger than 5 years. Generalizing this rate and applying it to U.S. population estimates for 2005 predicts at least 5000 new cases of Kawasaki disease each year.

There is no diagnostic test for this acute vasculitis of unknown cause. The illness begins with the abrupt onset of fever. Typically, the clinical signs appear over the course of several days and include conjunctival injection without exudate; erythema of the lips, tongue, and oral mucosa; rash; edema and erythema of the hands and feet; and in a minority of cases, cervical lymphadenopathy.¹ These signs are accompanied by a dramatic acute-phase response manifested by an elevated white-cell count with neutrophil predominance, anemia, an elevated erythrocyte sedimentation rate, an elevated C-reactive protein level, and thrombocytosis. Coronary-artery aneurysms develop in as

many as 25% of untreated children and can lead, over time, to ischemic heart disease, myocardial infarction, and rarely, death (see images).

Clinical experience in Japan suggested that high doses of intravenously administered immune globulin were effective in abrogating the acute inflammation and reducing the risk of coronary-artery damage. Randomized, prospective clinical trials conducted in the United States in the 1980s established that intravenous immune globulin was an effective and safe therapy that reduced the rate of coronary-artery aneurysms detectable on echocardiography to 3 to 5%.² The mechanism of action of this treatment has never been clearly delineated, although the beneficial effects of specific antibodies (antiagent, anticytokine, and antiidiotype antibodies), cross-linking of inhibitory and stimulatory Fcγ receptors, and binding of complement have all been proposed. Aspirin is also administered, initially in high doses for the antiinflammatory effect and subsequently in low doses