

# TB MONITOR™

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### Doubts arising about new short-course treatment

Some TB experts are backing away from rifampin/pyrazinamide, the new short-course regimen recently approved for treating latent TB infection. On top of the death and the episode of serious hepatotoxicity already chronicled, unpublished reports of two more deaths plus other episodes of severe hepatotoxicity have surfaced. At the Centers for Disease Control and Prevention, the Division of TB Elimination (DTBE) has asked jurisdictions to report any incidents of toxicity that appear to be linked to either the use of the regimen or to standard isoniazid prophylaxis. . . . . Cover

### U.S. cases decline for 7th straight year

TB controllers in the United States received a hearty pat on the back with the release of data showing that the eight-year decline in the rate of new cases has reached an all-time low, dropping by 7% from 1999 to 2000. According to figures released by the Centers for Disease Control and Prevention in Atlanta, a total of 16,377 new TB cases were reported by the 50 states and the District of Columbia in 2000, an all-time low, down from 17,531 cases in 1999. Since the peak in 1992, the number of TB cases has dropped 45%, from 10.5 cases per 100,000 people in 1992 to 5.8 cases per 100,000 people in 2000. . . . . 79

### Centers for excellence project planned

The National Institutes of Health has launched a project to expand the organization's ability to do research relating to TB, HIV, and malaria in developing countries. The expansion will take the shape of either three or four new "International Centers of Excellence in Research" based in Uganda, Mali, and one or two other African nations. Along with providing sites for retrials and research, the centers will train in-country researchers, bring in laboratory and communication infrastructure, and provide intensive training for in-country clinicians and researchers. . . . . 82

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## Revisiting RIF/PZA: Toxicity reports give docs the jitters

*Analysis of incidents still under way*

Some TB clinicians are backing away from rifampin/pyrazinamide (RIF/PZA), the new short-course regimen recently approved for treating latent TB infection (LTBI). On top of a death and an episode of serious hepatotoxicity already chronicled in the April 2001 *Morbidity and Mortality Weekly Report* (MMWR), unpublished reports of two more deaths have surfaced, plus other episodes of severe hepatotoxicity. The recent events have left many practitioners feeling decidedly jittery about the regimen.

By late June, some TB experts had decided to meet in Baltimore prior to the National TB Controllers' Association annual conference so they could compare notes on the adverse effects that seemed to be cropping up with use of the regimen.

At the Centers for Disease Control and Prevention in Atlanta, the Division of TB Elimination (DTBE) has asked jurisdictions to report any incidents of toxicity that appear to be linked to either the use of RIF/PZA or to standard isoniazid (INH) prophylaxis. DTBE also is preparing to begin on-site investigations of the incidents. An update on the situation is expected to be published in the MMWR by late summer.

What's known so far suggests that the incidence of serious side effects associated with RIF/PZA may far exceed that for INH prophylaxis, says **John Sbarbaro, MD**, professor of medicine at the University of Colorado Health Sciences Center in Denver. From the start, Sbarbaro has been a vocal critic of the new regimen, predicting that RIF/PZA toxicity might prove unacceptably high.

So far, the deaths from RIF/PZA seem to have occurred among a denominator of perhaps 5,000 patients who have used the new regimen. If that denominator is correct, the rate clearly exceeds that for INH prophylaxis, estimated conservatively by the CDC at about one death for every 10,000 times that regimen is used in TB clinics, Sbarbaro says.

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**Russian TB loan in danger**

An expert on Russia's TB program says the need is urgent for public health experts from around the world to pressure that country to go back to the negotiating table with the World Bank over a \$100 million loan intended to stop Russia's runaway TB epidemic. He especially urges the World Health Organization to take a leading role in getting the talks restarted . . . . . 83

**Project tries to help deportees**

Health workers at two Immigration and Naturalization Service processing centers along the Texas/Mexico border are making efforts to hold onto deportees long enough for them to undergo TB treatment. This includes talking with the appropriate consulate to learn what part of the country the patient is headed for and what treatment resources are available in the area. Then come the tricky jobs of establishing phone contact with a faraway health care facility and educating the deportees about the need for treatment. . . . . 84

**Countries seeking TB control money can do the math**

Relief of the burdensome debt payments on outstanding loans in sub-Saharan African nations would free up \$13.5 billion for other uses. Now a grass-roots organization is attempting to spread that gospel . . . . . 85

**A caveat: Be wary of tuberculosis comeback**

Though finalization of the 1997 proposed tuberculosis standard by the Occupational Safety and Health Administration (OSHA) may be delayed indefinitely or abandoned outright, experts are warning hospitals and other institutions not to slip into complacency and assume TB poses no threat to health care workers. Though TB infection controls may not be regulated, compliance with voluntary guidelines should continue to keep the ancient disease at bay. The history of TB has been described as the "U-shaped curve of concern," meaning that as funding and prevention efforts wane, the disease begins rising again. Such was the case in the United States in the 1980s and early 1990s, when calls began for an OSHA standard to protect health care workers . . . . . 86

**COMING IN FUTURE ISSUES**

- More on RIF/PZA: Fresh updates on the regimen
- Phage therapy: Could it be made to work for TB?
- STOP-TB: Unrolling the blueprint
- The Foegen Connection: The Task Force for Child Survival
- Senate TB bill: Details about the "drop"

Regardless of how the data on frequency eventually pan out, the current problems seem to fall into two types, says **Naomi Bock**, MD, an epidemiologist at the DTBE and an assistant professor at Emory University School of Medicine.

First, using the high end of the dose range suggested for PZA "seems [sometimes] to lead to immediate toxicity," she notes. In such instances, patients beginning the regimen "complain of stomachaches, and then they stop taking the medications," which puts an end to the problem.

That type of experience has already spurred some clinicians to begin using the lower range of the suggested dosage for PZA, she adds.

In the second kind of scenario, problems seem to develop more gradually, with some patients experiencing liver inflammation after taking the regimen for a month or so.

Bock says three issues still need to be sorted out:

- whether either (or both) of the problems is dose-related;
- whether serious toxicity is associated with an underlying history of liver disease;
- whether clinicians will be able to steer clear of trouble by taking steps such as monitoring hepatic enzymes or adjusting the PZA dose.

***Underlying liver disease may be implicated***

In Massachusetts, the Boston city TB clinic and other state providers have treated about 650 patients with RIF/PZA, with three instances of toxicity severe enough to require hospitalization, says **Edward Nardell**, MD, medical advisor to the Massachusetts health department TB control program and professor of pulmonary medicine at Cambridge (MA) University Hospital.

As a result of the three episodes, Nardell has called a temporary halt to use of the regimen in the state. Signs and symptoms in the Massachusetts cases have included vomiting, edema, and high hepatic enzymes in the absence of symptoms.

All three episodes, it turns out, have been linked to an underlying history of liver damage, Nardell adds — though in two cases, patient histories had failed to turn up any clues that pre-existing damage might be present.

"It seems that underlying liver disease may be more of a problem with RIF/PZA than with INH," he says. Getting laboratory baselines might have made a difference in two of the three cases, he adds. Current guidelines call for laboratory

baselines only if patient histories suggest the presence of either liver damage or regular alcohol use.

Evidence from one of the Massachusetts cases suggests that even when baseline hepatic measurements are obtained, things can still go awry. In one instance, Nardell says, a test revealed that enzymes were elevated; but because the patient was a close contact who was judged at risk for developing disease, the decision was made to go ahead and treat. Active symptoms never emerged, but subsequent laboratory tests showed hepatic enzymes were continuing to rise, prompting the physician in the case to stop treatment and hospitalize the patient.

One reason routine lab work is no longer even recommended for prophylaxis is the realization that episodes of so-called “silent liver injury” are findings not infrequently associated with INH prophylaxis, says **John Jereb**, MD, an epidemiologist at DTBE. “Usually, these patients not only never have symptoms, they have complete resolution of the problem,” he says. An estimated 10% to 15% of patients receiving INH prophylaxis probably undergo such episodes, almost always with no symptoms and no lasting effects, Jereb adds.

### ***Patients fail to report symptoms***

With RIF/PZA, the evidence so far seems to suggest that when trouble develops, it’s because patients experience symptoms but fail to report them, meanwhile continuing to take the medication, says **John Bernardo**, MD, TB control officer of Boston. Even stern warnings about reporting symptoms and stopping treatment occasionally fall on deaf ears, Bernardo adds. “Some people will deny or ignore symptoms even when they’ve been explicitly warned about them,” he says.

When the short-course regimen was tested in trials on HIV-negative patients in Haiti, few problems with toxicity were reported. If the regimen does prove to be more troublesome for HIV-negative patients, one reason could have to do with PZA’s mechanism of action, says Sbarbaro.

“PZA doesn’t kill bugs,” he says. Instead, it blocks an action whereby the TB microbe converts fats in order to construct a rugged lipid wall around itself. PZA’s prevention of the wall’s construction leaves the microbe vulnerable to assault by anti-TB drugs. But PZA can only do its work in an acidic environment, Sbarbaro adds. It could be that among patients with competent immune

systems — namely, those who are HIV-negative — most circulating TB microbes have been engulfed by macrophages, which lack the acidic environment the drug requires to do its work.

On a more elementary level, Sbarbaro argues that because PZA isn’t active in the continuation phase of therapy, there’s little reason to think it will be helpful for prophylaxis of latent disease. “It’s just common sense,” he declares.

Sbarbaro adds that instead of a retooled version of RIF/PZA, he’d prefer to see more emphasis on four months of RIF, another short-course regimen already available as an option for LTBI treatment. “You can’t have any deaths associated with a preventive regimen and expect people to use it,” he says. ■

## **U.S. cases decline for 7th straight year**

### *New TB cases reach all-time low*

**T**B controllers in the United States received a hearty pat on the back with the release of data showing that the eight-year decline in the rate of new cases has reached an all-time low, dropping by 7% from 1999 to 2000.

According to figures released by the Centers for Disease Control and Prevention in Atlanta, a total of 16,377 new TB cases were reported by the 50 states and the District of Columbia in 2000, an all-time low, down from 17,531 cases in 1999.

Since the peak in 1992, the number of TB cases has dropped 45%, from 10.5 cases per 100,000 people in 1992 to 5.8 cases per 100,000 people in 2000.

The figures were released as part of the National TB Controllers Workshop, held June 18-21 in Baltimore.

“While the 2000 national TB figures highlight the effectiveness of U.S. TB control efforts, the disease still remains a significant health threat in many parts of this country,” said **Jeffrey P. Koplan**, MD, MPH, director of the CDC. “To eliminate TB as a public health problem in the United States, efforts will need to be accelerated in those states and communities most affected by the disease.”

*(Continued on page 82)*

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(Continued from page 79)

The CDC also released figures on the 10 states with the highest TB rates, pointing to several areas where prevention and control efforts must be accelerated.

The top 10 were, in ranking order: Alaska, Hawaii, California, New York, Georgia, Arkansas, Louisiana, Florida, Texas, and South Carolina. (See charts on pp. 80-81 for a complete listing of TB cases and rates by state.)

Seven of the top 10 states had a decrease in TB rates between 1999 and 2000, but three states — Alaska, Arkansas, and Georgia — reported increases in rates.

Alaska had the most dramatic rise in rates, from 9.9 in 1999 to 17.2 in 2000, said the CDC. TB rates in Arkansas climbed from 7.1 to 7.4, and the rates in Georgia increased slightly from 8.5 to 8.6.

Still, the news was mostly good overall compared to the mid-1980s, when TB rates climbed 20%.

But CDC officials warned against complacency, noting that globally, TB continues to grow, with eight million new cases each year, and two million deaths attributed to TB.

“The growing global TB epidemic could impact the declines made in the United States if TB defense systems are not maintained,” said **Helene Gayle**, MD, MPH, director of CDC’s National Center for HIV, STD, and TB Prevention. “Innovative approaches and support, as well as a commitment to global TB control, will be required to eliminate this disease from the United States.” ■

## NIAID to establish intramural trial sites

*Permanent funding will entice partners*

The National Institutes of Health (NIH) has given the go-ahead to an ambitious project aimed at expanding the organization’s capacity to do research and clinical trials relating to TB, HIV, and malaria in developing countries, says **Carole Heilman**, PhD, director of the Division of Microbial and infectious Diseases for the NIH’s National Institute of Allergy and Infectious Diseases (NIAID).

The planned expansion will take the shape of either three or four new “International Centers of Excellence in Research” (ICER). The centers will be based in Uganda, Mali, and in one or two other as-yet-unnamed African nations.

Along with providing sites for trials and other research into the three public-health scourges, the centers will train in-country researchers, bring in laboratory and communication infrastructure, and provide intensive training for in-country clinicians and researchers, says Heilman.

### *Centers won’t have to reapply for funding*

The ICERs (pronounced “icers”) will be funded on a permanent basis, a feature that sharply distinguishes them from extramural projects funded by the NIH, such as Case Western Reserve University’s TB Research Unit (TBRU) in Uganda. The Case Western site, as well another smaller TB site in Brazil, must reapply for funding on a regular basis. The ICERs, by contrast, will essentially operate as permanently funded outposts of NIAID. That feature, along with their work force of in-country investigators and other highly trained staff, means they will be attractive to other potential collaborators, Heilman says.

TB experts inside and outside the NIH are hailing the announcement.

“We certainly welcome greater NIH involvement in this arena, and we are very excited about the prospect for collaboration,” says **Rick O’Brien**, MD, chief of the research and evaluation branch of the Division of TB Elimination at the Centers for Disease Control and Prevention in Atlanta.

NIAID’s decision to expand its overseas intramural research capacity is important for TB research, says O’Brien. “It’s becoming harder and more costly to do TB clinical trials in the U.S. because patients are harder to find,” he says. “It’s also harder for us to address the critical issues posed by HIV for TB treatment — again, because it’s harder to find HIV-infected patients here.”

**Ann Ginsberg**, MD, PhD, chief of the NIH’s Respiratory Diseases Branch, agrees. “It will have a positive impact on TB in this country for two reasons,” she says. “A growing percentage of TB cases here are among people of foreign birth, and that’s led to a consensus that we’ll never control the epidemic here until we control it in the rest of the world. Plus, it’s extremely hard to do efficacy trials here.”

Though she declines to name specific dollar amounts, Heilman says the ICER project will be

the primary beneficiary “of discretionary funds [at NIAID].”

Several events have led to the birth of the ICER concept, Heilman adds. “In the past, international and global research hasn’t been a top priority in the U.S.,” she says. “Now we’re seeing the realization that global health is crucial to American interests — and not just from the perspective of public health, but in many other ways, including economic development and political stability.”

In addition, the NIH has been working to define its role in contributing to the public health goals proposed at the past two G-8 summits. The agency has also worked to define its role in helping attain goals articulated by former President Bill Clinton in his May 2000 Millennial Vaccine Initiative.

The prototype for the ICER model is the NIH’s intramural site for malaria research in Mali, says Heilman. “It’s a great model, and one that’s very worthy of expansion,” she says. “In Mali, we’ve spent a lot of time training investi-

gators and building human capacity. Over the past 10 years, these researchers have become recognized as top-notch by the international scientific community. We’ve also put in a communication system and trained staff in good laboratory and clinical practices.”

What makes the Mali model even more impressive is that the nation is the fourth-poorest country on earth. Despite its poverty, the government has evinced “a gritty determination and the strong belief that health care is important,” she adds. Because the NIH is willing to commit permanent funding to the ICERs, it’s important that the countries chosen as sites express the same high level of commitment, she adds.

Case Western University’s TBRU site in Uganda will definitely be a key player in the ICER planned for that country, Heilman says. “On a recent site visit, we saw clearly that there are untapped opportunities for the TBRU,” she says. “We will expand those opportunities.” ■

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## WHO should push for rethinking of TB loan

*How to shoot yourself in the foot, Russian-style*

With negotiations suspended between Russia and the World Bank for a \$100 million loan intended to fight Russia’s runaway TB epidemic, the need is urgent for public health advocates around the world to pressure Russia to go back to the table, says **Alex Goldfarb**, PhD, director of the Public Health Research Institute’s Russian TB control program.

“When South African President Thabo Mbeke made his infamous statement about HIV not causing AIDS, there was an international outcry,” says Goldfarb. “Everyone, from the press to the scientific community to the international health community, all got onto the South African president. So why not here?”

The World Health Organization, which served as go-between when loan negotiations were initiated, has a particularly important role to play in the situation, Goldfarb says. “Since negotiations were suspended, the WHO has been silent. Now, it’s imperative for them to act,” he says. “After all, the multidrug-resistant TB epidemic isn’t just confined to Russia; this is a global health emergency which threatens the rest of the world.”

All through last spring, opposition to the loan has been building among members of Russia’s pharmaceutical industry. Goldfarb and other Russia-watchers say the nation’s drug manufacturers are fearful that drug manufacturing standards attached to the loan may bar their products from the running when it comes time to purchase drugs for TB projects.

In addition, the Russian press may have fueled industry paranoia with a series of accounts scolding drug makers for their huge product mark-ups. That, Goldfarb notes, has led to the ironically familiar spectacle of the pharmaceutical industry taking yet another drubbing for allegedly predatory pricing.

### *World Bank rep tossed out of meeting*

Whatever the reason, Russia’s version of Big Pharma seems to have successfully put the screws to the Health Ministry, which capitulated in June with an announcement that the government would refuse the loan. The announcement came on the heels of a scandalous incident: In one especially tense meeting, the Russian Health Minister grew so cross that he ejected the Bank’s project representative, a Russian woman, from the room.

The bank, for its part, seems to have thrown up its hands in disgust. **Julian Schweitzer**, head of the World Bank’s Moscow office, says he is “not optimistic” about the fate of the loan.

If the loan does fall through altogether, Goldfarb and other Russian experts warn the fallout will be severe and sustained. "I don't think any responsible agency would fund Russia after watching the World Bank get slapped in the face," he says. ■

## TB Net staff offers lifeline for deportees

*It's not the cigar, it's the microbe*

As readers of *TB Monitor* know, deportees with TB — especially those with multidrug-resistant TB — are a continual headache for physicians working at Immigration and Naturalization Service (INS) processing centers. At present, there seems to be no economic or legal means to do what some INS docs would like to: hang onto MDR-TB patients until they're cured instead of sending them home with no guarantees they'll get treated. (See *TB Monitor*, May 2000, pp. 59-60.)

Since October, however, one small program is taking steps to make sure that's what happens. At two INS processing centers along the Texas/Mexico border — one in Port Isabel, the other in El Paso — two staff members from the Migrant Clinicians' Network TB Net program are putting in long hours to ensure cross-border continuity of care.

### *Contacting foreign providers proves difficult*

Many deportees at the two centers are bound for Central America or Mexico, but patients are also bound back to Russia, China, and South America, says **Jeannie Laswell**, RN, who works in the Port Isabel processing center. Laswell and her El Paso counterpart, **Marta Castro**, spend their days educating patients about TB, contacting foreign providers, and compiling clinical records to send home with the patients.

The two say they start a case by talking with the appropriate consulate or embassy to get an idea of what part of a country a patient is headed for and what treatment resources are available in the area. Then comes the job of establishing phone contact with a faraway health care facility — and here, the job gets tricky, Laswell says.

"We had a patient recently from Honduras, and I'd been on the phone for several weeks trying to get through," she recalls. Despairing of busy signals and recorded messages about downed circuits, Laswell turned to Castro for help.

Castro called the Honduran consulate in Houston and discovered that the consul was headed out the door for a three-week vacation back home. Since he was already saddled with escorting one TB patient, he graciously agreed to take a second patient. In addition, he promised Castro he would take the patient directly to the hospital door and then obtain phone numbers and names of hospital physicians and staff who'd be evaluating the patient.

Compiling patient histories is also tough, says Laswell. "Many of our patients either don't remember having taken TB meds or else didn't understand what they were for," she says.

Helping deportees understand the importance of getting TB treatment is one of the most important parts of the job, say both women. "If you come here illegally because you have a wife and five children to support, the last thing you're thinking about when you get home is getting to the TB clinic," says Laswell. "You're worried about getting back up north so you can make enough money to feed your family."

### *Cartoons are a good place to start*

Because many deportees lack education and have a hard time understanding what TB is, Castro says she often starts with a simple booklet from the American Lung Association that features cartoons and pictures. "Then I go to a higher level and use different words to explain the same thing in a different way," she says.

The stories deportees tell her are often heartbreaking, Castro says. Still, it makes her happy to think patients are finally getting the treatment they need. "Sometimes they have no idea that they're sick. They think they're just tired from the border crossing," she says. "At the beginning, they're often angry. Later, they're often very appreciative. They also begin to see how important it is not to spread their disease to others."

Castro tells of a Chinese man bound for deportation who was convinced his illness must be something he'd picked up by sharing cigars he and others smoked during the passage to the United States. Three-way conversations by telephone among Castro, the Chinese patient, and a Chinese translator didn't seem to be advancing

the man's understanding of the situation, Castro says. So she went to her church and found another Chinese-speaking man, took him to the detention center, and tried again. Seeing a fellow countryman face-to-face had a transforming effect, she reports: "His response was amazing." ■

## Forgiveness of debts: A recipe for health care

*TB controllers need to speak up, expert says*

To advocates of debt relief, it all boils down to simple math: Subtract the burdensome debt payments that will siphon \$13.5 billion from sub-Saharan African economies this year, and you've instantly added resources for strengthening desperately needed health care services, they say.

As basic as that sounds, the concept of debt relief — the cancellation of huge debts incurred by poor nations in the 1970s and 1980s — has yet to catch hold of the popular imagination in most places. One well-known American TB expert recalls talking to the head of a highly placed World Health Organization program director about the AIDS epidemic rampaging through Africa. "There's simply no money for treating AIDS," the program director declared.

"Well, but what about debt relief?" asked the TB expert.

The response was less than heartening. "Debt relief?" echoed the puzzled program director. "What's that?"

### *Widespread response needed*

Public health advocates in this country need to become better informed on the subject and speak up about it, says **Jim Kim**, MD, executive director of Cambridge, MA-based Partners in Health (PIH). "One or two people talking about this isn't going to be enough," he says. "It's important for all of us to learn about this issue."

To do some consciousness-raising on the subject, RESULTS International, a grass-roots advocacy group that has taken up the cause of TB, recently held a press conference about debt relief. Featured speakers made up a lively and somewhat unexpected mix, including Jeff Sachs, PhD, director of Harvard's Center for International

Development; Bono, lead singer of the Irish rock group U2; and U.S. Congresspeople **Spencer Bachus** (R-AL) and Barbara Lee (D-CA).

"Debt relief is the most greatest moral and social issue of our time," says Bachus. "These debts were, in many cases, loaned to dictators, and the people in the countries never benefited from the money. Instead, the debts have basically destroyed the health care and educational systems of those countries."

So far, debt reduction programs have managed to write off about 27% of debts in 22 countries, but the gesture hardly counts because the written-off debts were those not being paid anyway, notes PIH's Kim. Fresh analyses of "debt sustainability" offered by the International Monetary Fund and others as proof of their good intentions amount to little more than diversionary tactics, argues Sachs, because the analyses have "absolutely zero to do with what is really sustainable for these countries."

### *User fees: The cruelest cuts*

Last year, Bachus and his colleague Lee succeeded in getting language included in the federal foreign-aid appropriations bill that would prohibit one of the cruelest features of the debt-payment system: the user fees levied by poor countries for basic health and education services. Euphemistically labeled health-care "reform," user fees are an important part of the fiscal-restructuring policies that indebted poor countries must agree to implement to keep the credit flowing.

The rationale for user fees is that they strengthen health care systems and make them more sustainable, says Kim. In reality, they rarely accomplish that goal, but instead cause droves of poor people who can't afford the fees simply to stop seeking health care. The Bush administration has indicated that it opposes eliminating the fees, notes **Joanne Carter**, director of RESULTS.

On the other hand, when user fees are eliminated and debt payments even modestly reduced, poor peoples' lives improve dramatically. In Honduras, for example, modest debt relief has enabled the government to offer three more years of free school. Mali, Mozambique, and Senegal have used savings from debt relief to increase spending on HIV programs, and Uganda has doubled primary-school enrollment while reducing HIV transmission.

Because the International Monetary Fund (IMF)

## U2's Bono speaks out on debt relief for poor

*'This is our hope, and our prayer'*

**B**ono, lead singer of the Irish rock band U2, has been an ardent activist for debt relief for poor countries for years. He recently had this to say when addressing a press teleconference on the subject:

"I know Jim [Wolfensohn], president of the World Bank. I know him to be a moral man. But what makes me angry is the numbing bureaucracy you meet with whenever you confront this issue. The World Bank points to the shareholders. The shareholders point to the public. And no one seems to be driving the train. The train is just rolling down the tracks.

"If you as an individual go into debt, you will be declared bankrupt at a certain point. The banker takes the hit because he made a mistake in lending you the money. That's just good banking. It's extraordinary that we don't apply the same logic to countries.

"If we could only get some poetry through to the numbers men, this U.S. administration could do something really extraordinary. It would give back Americans faith in the idea of America. It's what this country is supposed to be all about. This is our hope, and our prayer." ■

and the World Bank continue offering new loans to pay off old debts, there's still a long way to go, say debt relief advocates. Astonishingly, for every dollar sent in aid sent to poor countries, \$1.30 flows back to lenders in debt payment services.

Making sure indebted countries use debt forgiveness for health care (as opposed to, say, weapons purchases) shouldn't pose an insurmountable problem, adds Kim. "The IMF and other multilateral lending institutions have a long history of placing conditions on loans," he says. There's nothing stopping them from "conditioning" debt relief, he says.

Bringing more debt relief to poor countries is, simply put, the American way, says Bachus. "We say we want to bring freedom and democracy to these countries," he says. "But we can't do that if they're starving and dying." ■

## A caveat: Be wary of tuberculosis comeback

*'The bottom line is that some risk remains'*

**T**hough finalization of the 1997 proposed tuberculosis standard by the Occupational Safety and Health Administration (OSHA) may be delayed indefinitely or abandoned outright, experts are warning hospitals and other institutions not to slip into complacency and assume TB poses no threat to health care workers.

Though TB infection controls may not be regulated, compliance with voluntary guidelines should continue to keep the ancient disease at bay. The history of TB has been described as the "U-shaped curve of concern," meaning that as funding and prevention efforts wane, the disease begins rising again. Such was the case in the United States in the 1980s and early 1990s, when calls began for an OSHA standard to protect health care workers.

"The bottom line is that some risk remains, and that while on average, it is no greater than the community risk where they live, it is [greater] for certain areas," says **Walter Hierholzer**, MD, chairman of the Institute of Medicine (IOM) panel that reviewed the proposed TB standard.

"It certainly is [greater] if you don't apply infection control standards," he points out. "The report doesn't say that you can forget about infection control because there isn't any risk to health care workers."

According to the IOM panel's report, there does appear to be a risk of TB infection to health care workers in the workplace, and in some job circumstances, that risk may be greater than that encountered in the community. Procedures that generate aerosols are particularly hazardous to exposed employees, the IOM panel warned.

"I would be quite worried about risk and be very careful about infection control if I worked in respiratory therapy, even in areas where TB is not prominent, like the Midwest," Hierholzer says. "Second, the risk varies geographically, as it does in the general population. Certainly, if I worked in New York City, Los Angeles, or San Francisco, I would still be very careful, try to identify all cases, and have a good control program with both engineering and administrative controls."

According to the IOM report, those who reported their occupation as health care workers

within the preceding 24 months accounted for approximately 2.6% of TB cases nationwide in 1999, down from 3% in 1998. During the period from 1994 to 1998, six states — California, Florida, Illinois, New Jersey, New York, and Texas — accounted for 57% of the cases of TB among health care workers and about the same percentage of all TB cases. The six states account for just under 40% of the U.S. population.

Also, from 1994 to 1998, there were significantly higher rates of drug-resistant disease for health care workers (3.2% of cases) than for other workers (1.5% of cases). For the two most recent years, the difference in rates for the two groups was not statistically significant.

Studies suggest recent occupational TB infection risks of about 0.5% to 1% per year for hospitals in low-TB-incidence areas and about 1% to 5% a year for hospitals in high-incidence areas. Those risks fall steadily as influenced by implementation

of infection control measures. In addition, the report clarified that attack rates among tuberculin reactors are substantially lower than the oft-stated 10%. Studies suggest a 3% to 5% rate may be more accurate, the report states.

“We had newer data than OSHA had,” Hierholzer says. “The newer data would seem to suggest that some of the levels of risk that OSHA originally proposed in 1997 were higher than we saw now. Whether that will continue is unknown. There still is some risk there, but it is very geographical and related to community risk. It is very variable by worker.”

The committee also determined that respiratory protection is important when dealing with TB cases, he adds. “There were some suggestions a while back that if one had very good engineering and administrative controls, then one would not need to wear a mask,” he says. “We think that is imprudent and probably dangerous.” ■



## Treatment of MDR-TB meningitis

By **Carol Kemper, MD, FACP**  
Clinical Associate Professor of Medicine  
Stanford University  
Stanford, CA

**Source:** Berning S, et al. *Clin Infect Dis* 2001; 32:643-646.

**B**erning and colleagues at the National Jewish Medical Center in Denver describe an unusual case of widely disseminated multidrug-resistant tuberculosis (MDR-TB) resulting in meningitis in an HIV-positive man. The patient ultimately responded to intrathecal administration of levofloxacin and amikacin, in addition to systemic therapy.

During initial treatment with a 5-drug regimen including INH, ethambutol, pyrazinamide, cycloserine, and capreomycin, the patient developed progressive central nervous system disease with positive cerebrospinal fluid cultures, despite evidence of improvement in the lungs. Initial

attempts at treatment with parenterally administered levofloxacin and amikacin were not successful. Ultimately, intrathecal treatment via an Omay reservoir with both levofloxacin (maximal dose 1.5 mg) and azithromycin (maximal dose 5 mg), titrated to patient tolerance, on alternate days, resulted in improvement in CSF parameters within 8 days. Although CSF levels of the 2 agents were lower than target levels, they exceeded the MIC of each agent. CSF:serum ratios of both agents were higher (82%-99% for levofloxacin and 43% to > 200% for amikacin than published reports. The patient was doing well 12 months later, still on therapy. Therapeutic drug monitoring of CSF and serum levels proved helpful in making dosage adjustments. ▼

### CE objectives

**A**fter reading each issue of *TB Monitor*, health care professionals will be able to:

- Identify clinical, ethical, legal, and social issues related to the care of TB patients.
- Summarize new information about TB prevention, control, and treatment.
- Explain developments in the regulatory arena and how they apply to TB control measures.
- Share acquired knowledge of new clinical and technological developments and advances with staff. ■

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## Editorial Questions

For questions or comments, call Alice Alexander at (404) 371-8067.

# What to do when AFB culture is lost?

By **Alan D. Tice, MD, FACP**  
Infections Limited  
Tacoma, WA

**Source:** Patnaik M, et al. **Rapid detection of smear-negative *Mycobacterium tuberculosis* by PCR and sequencing for rifampin resistance with DNA extracted directly from slides.** *J Clin Microbiol* 2001; 39:51-52.

**P**atnaik and associates of the research department of Specialty Laboratories in Santa Monica, CA, seem to have perfected a way to detect *Mycobacterium tuberculosis* from slides of expectorated sputum using polymerase chain reaction (PCR). They can even detect the gene for resistance to rifampin.

They studied routine specimens sent to their laboratory for mycobacteria stains and cultures. They also used a technique of eluting mycobacterial DNA from sputum slides, then sequenced the rpoB gene to determine rifampin resistance as well. The nested PCR method could be done with a turnaround time of 48 hours.

Of 47 sputum specimens submitted for acid-fast bacilli (AFB) smears and culture, 24 (51%) grew *M. tuberculosis*. Only 14 (58%) were detected by microscopic methods. All 24 were positive by the PCR technique. There were no false positives. PCR also detected all 5 strains with rifampin resistance.

If more specimens confirm these numbers, it could also be used for much more rapid results for the detection of *M. tuberculosis* as well as susceptibility testing. ■