

# Africa Hit Hardest as TB Rates Continue to Rise

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LISBON — This year will be the one with the most cases of tuberculosis worldwide in all of history—and the greatest number of deaths due to the disease, Dr. Peter Godfrey-Faussett said at the 12th International Congress on Infectious Diseases.

This is in part because of population growth and because TB rates continue to rise. Nine million people develop active TB each year, more than one-third of them in China and India. Two million die of the disease annually, and 30% of the world's population is latently infected with *Mycobacterium tuberculosis*, according to Dr. Godfrey-Faussett.



But the news is not all bad. Latest estimates by World Health Organization epidemiologists are that TB rates are actually falling in every region of the world except Africa, noted Dr. Godfrey-Faussett, professor of infectious diseases and international health at the London School of Hygiene and Tropical Medicine.

Within Africa, the highest TB rates occur in countries where the prevalence of HIV is greatest. Traditional Directly Observed Treatment, Short Course (DOTS) programs alone will be insufficient to reduce the burden of TB in areas where the epidemic is driven by HIV, he added at the congress, which was sponsored by the International Society for Infectious Diseases.

Structured DOTS programs have been invaluable in combating TB and have cured more than 10 million people since 1994. And in a famous field study in which Chinese health authorities implemented DOTS in half the country, the prevalence of TB plummeted by 37% in a decade, compared with the rate in the other half of China.

Earlier this year at the World Economic Forum annual meeting in Davos, Switzerland, leaders of the Stop TB Partnership, including Bill Gates and Nigerian

President Olusegun Obasanjo, launched a new TB strategy that builds upon traditional DOTS. The strategy puts a much greater emphasis on HIV, multidrug-resistant TB, and strengthening health systems in developing nations. It also addresses stigma, a big factor in keeping Africans with TB and HIV from seeking treatment, according to Dr. Godfrey-Faussett. Stigma is a particular problem among health care workers in many African clinics, where pay is often poor and morale low.

The new Stop TB Partnership program, which dovetails with WHO's Global Plan to Stop TB 2006-2015, also calls for more intensive case-finding than has been traditional in DOTS programs. "Nobody is suggesting that we get rid of DOTS. But DOTS is much more than watching people swallow pills," he stressed.

"Ultimately we may reach the stage where we do active case finding in whole populations," Dr. Godfrey-Faussett predicted. "Some of the township areas in South Africa and Zambia that we're working in have rates of TB that are no longer measured in cases per 100,000, but in percent. You'll get 1% or 2% of the population per year developing TB. In traditional terms, that's 1,000 or 2,000 per 100,000. When you get rates like that, it becomes possible to think about door-to-door active case finding, but we need to have better diagnostic modalities for that. We badly need new technology. I believe improved diagnosis is the single thing that will make the most difference for TB control."

Dr. Godfrey-Faussett was somewhat skeptical about the TB vaccines now going into field studies. "There's quite a lot of basic understanding needed before we're likely to have vaccines that work. A lot of people aren't that optimistic that the vaccines now going to trials will really prevent a lot of TB. We still have a lot of work to do in terms of better understanding of the immunology and host-pathogen relationships in TB." ■

# New Topical Antibiotic May Thwart Resistance Problems

LISBON — Five days of the novel topical antibiotic retapamulin is as effective in the treatment of uncomplicated skin infections as 10 days of an oral cephalosporin, Dr. Lawrence C. Parish reported at the 12th International Congress on Infectious Diseases.

Patients prefer topical over systemic therapy in this setting by a 3-to-1 margin. When retapamulin ointment becomes available—and GlaxoSmithKline anticipates Food and Drug Administration approval later this year—many physicians will prefer this new option, too, predicted Dr. Parish, a dermatologist at Jefferson Medical College, Philadelphia.

Retapamulin is first in a new class of antibacterials known as pleuromutilins. They possess a novel mechanism of action and an extremely low propensity for development of bacterial resistance. The drug has excellent activity against gram-positive organisms, including the chief pathogens involved in skin and skin structure infections, such as *Streptococcus pyogenes* and *Staphylococcus aureus*, including the methicillin- and mupirocin-resistant strains. In vitro studies indicate the drug has no target-specific cross resistance to other antibiotic classes, so it's highly effective against bacteria resistant to antibiotics. Retapamulin's oral absorption is poor, and has therefore been developed as a topical agent. Allergy to the product is "almost nonexistent," said Dr. Parish.

He reported on 546 patients with secondarily infected dermatitis who participated in a phase III, randomized, double-blind, double-dummy clinical trial conducted at 109 centers in North America, Europe, Asia, and Africa.

The patients, among them 124 children and adolescents, were assigned 2-to-1 to 5 days of retapamulin ointment 1% b.i.d. or 10 days of oral cephalexin at 500 mg b.i.d. in a noninferiority trial involving physicians from multiple specialties. Dr. Parish served as principal investigator.

The primary efficacy end point was clinical response at follow-up on days 17-19. The rates—86% in the retapamulin group and 90% with oral cephalexin—weren't statistically different. Nor were the microbiologic success rates of 87% and 92%, respectively.

Both drugs had 100% microbiologic success in patients with baseline methicillin-resistant *S. aureus*, although there were only seven affected patients, he said at the meeting, which was sponsored by the International Society for Infectious Diseases.

Clinical success rates at the end of therapy were also comparable: 92% in the retapamulin arm on days 7-9, and 94% with oral therapy on days 12-14.

The two therapies were equally well tolerated. No serious adverse events occurred. The most common treatment-related adverse events were treatment-site itching in 1% of the retapamulin group and diarrhea and/or abdominal pain in 1.1% of the cephalexin arm. Participants expressed a 3-to-1 preference for topical over oral therapy for their skin infection.

Dr. Parish said in an interview that the physician preference for oral treatment of bacterial infections and topical therapy for dermatophyte infections isn't based in science. "I've tried to trace where the prejudice comes from, and I haven't been able to," he said, adding he believes many physicians, presented with evidence of equal efficacy, would prefer to use a topical medication rather than expose their patients to a systemic antibiotic.

He predicted that the topical pleuromutilin will fill a role in clinical practice similar to that occupied by mupirocin (Bactroban), which was widely prescribed for the topical therapy of secondarily infected inflammatory skin diseases until resistance became a major problem. Dr. Parish, who disclosed no ties to GlaxoSmithKline, has received payment to conduct clinical research for the company. ■

**In a study of 546 patients with secondarily infected dermatitis, 5 days of retapamulin ointment were as effective as 10 days of oral cephalexin.**

## Special Handling

TB Assays from page 1

Disease Control and Prevention recommended its use in all situations where the skin test has been used, including serial evaluation of health care workers.

The downsides of using these assays in the developing world are that they require living cells and ready access to a lab for enzyme-linked immunosorbent assay.

"This means you have to process blood samples within 12 hours. You have to be careful with the blood. It's sensitive to temperature. You can't put it in the fridge and leave it for the weekend. You cannot leave it out in the car. You cannot mail the blood sample to a lab," she explained at the congress sponsored by the International Society for Infectious Diseases.

For these reasons, Dr. Welding sees the assays ulti-

mately being most useful for latent TB case finding via contact tracing and screening of high-risk groups in low-endemic, highly developed areas such as Western Europe and the United States. The tests should also prove useful in areas with an intermediate TB incidence and good infrastructure, such as parts of Brazil.

In places where TB rates are high, roads poor, and laboratories hard to come by, these tests aren't practical. The ultimate solution in such places is probably an improved skin test that utilizes *M. tuberculosis*-specific antigens rather than the traditional purified protein derivative; such tests, which are simple, low-tech, and low-cost, are now under evaluation in field studies.

Another approach involves serologic antibody tests. These offer several potential advantages. They're much less temperature-sensitive and fragile than the interferon- $\gamma$  tests, they don't require living cells or access to a laboratory, and they yield results in 15-30 minutes.

The newer ones, which utilize *M. tuberculosis*-specific antigens, perform best. They'll never serve as a stand-alone test for diagnosis of active TB—there are too many false-positives in highly endemic areas where uninfected people are often reexposed to TB—but they could have a role as rule-in point-of-care screening tests that trigger a visit to a clinic for definitive testing, she said.

That sounded good to Dr. Peter Godfrey-Faussett.

"I was very heartened by the work on rapid diagnostic tests with serologic agents, because I think eventually—maybe with antigen detection for screening people—that might be the way to go. We've got to be thinking about tests that can be used out in the field at the point of care, because you won't get people to come in to the health center to have a fancy test or x-ray; they can't afford the bus fare," said Dr. Godfrey-Faussett, professor of infectious diseases and international health at the London School of Hygiene and Tropical Medicine. ■