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Quantiferon a more accurate predictor of TB infection than the TST, trial shows

In its first round of American trials, a promising new diagnostic assay for TB infection seemed able to distinguish between true TB infection and reactions from BCG or atypical mycobacteria. Cultures from cattle show a strong correlation between infectious agents and test results. The triple-reagent assay offers the advantage of being a one-step test, not two steps like the TST. But human trials of Quantiferon threaten to be time-consuming, expensive, and ethically dicey, investigators warn, so don't toss out the vials of tuberculin just yet . . . . . cover

Key to TB persistence found by researchers at Rockefeller and Cornell

Isocitrate lyase, the name of an enzyme that trips a metabolic pathway, doesn't roll exactly off the tongue. But investigators have found that by blocking production of the enzyme, they can prevent TB bugs in vitro from downshifting into a metabolic state that lets them persist in the body for years. The discovery one day may help shorten TB therapy to as little as a few weeks. Researcher John McKinney says he was tipped off to the key one day when he was poking around in the library, looking for work that was too old to have made it onto the Internet. 99

Benchmark suggested for when to treat health care worker who tests positive for TB

Serial skin testing in hospitals is a great way to show what's happening in the facility, but not so useful when you're trying to interpret a positive skin test for a single worried employee, says an Alabama TB expert. In the typical American hospital, where annual conversion rates are apt to be under 1%, chances are greater that a positive test result is false than true. That's due more to limits inherent in any diagnostic test than defects in the TB skin test. One expert says his approach is to explain to the employee what the positive test result probably means and then leave the choice of what to do up to the individual. 101

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Quantiferon looks good, investigators say, but dicey research remains

Don't throw out tuberculin skin tests just yet

Data from the first round of field trials that pitted newcomer Quantiferon against the tuberculin skin test, or TST, have shown exactly what investigators had hoped: Quantiferon, a one-step assay already in use in veterinary medicine, looks like a much more accurate test.

In an ironic twist, the measures of just how good the test may prove are when and how often it disagrees with the so-called "gold standard," the much-maligned TST.

"If you weed out those things known to cause false positives" — namely, cross-reactions from nontuberculous mycobacteria and reactions to BCG — "what you get is increasing agreement between the tests, up to about 90%," says **Jerry Mazurek**, MD, the project officer for a five-site study conducted by the Atlanta-based Centers for Disease Control and Prevention's Division of Tuberculosis Elimination.

Tests agree about 81% of the time

Hospitals and programs shouldn't start throwing out their vials of skin-testing reagents just yet, however, because the last phase of research will be tough going, Mazurek adds.

Here's how the two tests have stacked up against each other so far. "Overall, they agree about 81% of the time," says Mazurek. "If subjects had had a BCG vaccination, there was greater discordance," yielding only about 70% agreement, compared with instances in which there was evidence of atypical mycobacterial infection, he says.

"If evidence showed infection with an atypical [mycobacterium] — usually, *Mycobacterium avium* — the risk ratio is about 3, so if you had evidence of *M. avium*, you were three times as likely to have a positive

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Skin test's positive predictive value takes a licking at IOM hearing
The Occupational Safety and Health Administration has built a case for a new TB standard around skin-test conversions in health care workers. But at a recent hearing of an Institute of Medicine committee convened to mull over the need for such a standard, the skin test came under heavy fire. With TB on the decline in the United States, the chances that a positive result is true are growing smaller, experts testified. Unpublished data suggest atypical mycobacteria may be responsible for more false positives than suspected 102

WHO publishes TB guidelines for health care workers in resource-poor countries
Developing countries have most of the TB, but rich countries have most of the resources. In an attempt to provide some immediate relief and practical guidance, the World Health Organization has published guidelines for how to protect health care workers from TB in high-incidence countries. Opening the window, using a fan, and doing sputum induction outside are some of the low-cost but effective measures recommended in the document 103

Good employees, imaginative incentives help contacts finish their isoniazid
At a TB control program in Long Beach, CA, the customers aren't easy, and the workload is high. Still, the clinic boasts good rates of completion for contacts and other Class 2 patients. The secret sounds simplistic — keep employee morale high, be flexible yet consistent, give stickers and hand stamps to the little kids — but the numbers say the clinic is doing something right 105

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TST and a negative Quantiferon than if you had no evidence of an [atypical infection]," he adds.

The only other time that results varied measurably was when test readers seemed to exhibit what Mazurek terms "digit preference" — that is, when they were more apt to call a reaction a 9 mm than the cut-off point of 10 mm, presumably to spare subjects the trouble of having to get preventive therapy.

"So if we had more nines than 10s recorded at a site, then there was a slightly greater degree of discordance," Mazurek adds.

The bovine 'gold standard'

What makes it tough to interpret results from the 1,500 subjects tested in the first round of the trial is that there isn't a biological correlate, or "gold standard," to back up investigators' hunches about what the tests mean in humans. That means the TST has to serve as the de facto gold standard, even though it falls short, in most peoples' estimates.

Take the instances in which subjects with a history of BCG tested negative with Quantiferon and positive with the TST. As Mazurek puts it, "Is that because people who got BCG were from areas where there was a lot of TB? If so, maybe what the TST was telling us was true. My hunch is that's not the case."

What bolsters Mazurek's hunch is the way there is gold-standard-quality evidence in support of Quantiferon in cattle. "There is a gold standard in cattle, and that's [evidence from] cultures," he explains.

It works like this. Usually by the time animals are brought for evaluation, the disease is well-established. "They can't complain of a cough, obviously, but they usually come in looking pretty sick and having lost weight," Mazurek explains. The animal is tested with Quantiferon for *Mycobacterium bovis*; those that test positive typically are slaughtered, and lymph nodes from as many as two dozen sites are dissected and cultured.

That opens the door for side-by-side skin tests, with a culture available to test results. When CSL, the Australian company that produces uantiferon, has done side-by-side comparisons, Quantiferon has shown greater predictive value than the TST, says Mazurek.

Plus, even though the available evidence so far is slight, in instances where cattle also have been dosed experimentally with BCG vaccine,

Quantiferon again reportedly performs more accurately than the TST, adds Mazurek.

Along with its promise of greater accuracy, Quantiferon offers the prospect of a much speedier skin test than the TST.

That's because the assay depends on a single step — a blood draw — instead of a two-step procedure in which subjects have to return for test readings. Instead of getting an intradermal injection, subjects provide a small amount of blood, which is portioned out into wells and mixed with three antigens: one for *M. bovis*, one for *M. tuberculosis*, and one for *M. avium*.

Specimens and antigens incubate for about five hours. Then the amount of gamma interferon produced by each reagent is measured. Gamma interferon, a cytokine that regulates cell-mediated immunity, is produced by lymphocytes that already have been sensitized, Mazurek explains; thus, the infective agent is presumed to be the one that produces the most gamma interferon.

Even though the news on the newcomer assay is encouraging, measuring the predictive value of the new test will be tough, Mazurek warns. "What we don't know yet is how well [a positive result] from Quantiferon predicts that someone will get TB disease," he says. "Is it one in 10? One in 20? We still need to do that study, and it's going to be hard."

An ethical Catch-22

For one thing, there's the built-in ethical Catch-22: Since the TST is the accepted diagnostic test, how can researchers rightly deny access to preventive therapy to someone who tests positive with the TST but negative with Quantiferon? In theory, researchers could offer such people isoniazid and try to follow those who refused treatment. "But generally, those people are the hardest to follow," he notes.

There's also the sheer scope of the trial. "It would take a tremendous number of people [to do a study], since you'd need to recruit about 4,000 people with a positive tuberculin skin test," he says. "To get that many, you'd have to test about 100 times that many people," given the low incidence of TB infectivity in the United States. Then researchers would have to follow the population for at least several years.

"Some people wouldn't take their INH," concludes Mazurek. "Your only hope is that you'd get enough of them that you'd be able to draw some conclusions." ■

Enzymatic key opens door to quicker therapy

Researcher uncovered clues in 1950s-era studies

Some researchers use the word "persistence" to describe how the TB mycobacterium seemingly goes into hiding. Not quite the same as "clinical latency," the word refers to the bug's maddening ability to duck pharmaceutical bullets, a trick that prolongs treatment to months, even years.

Practically speaking, if a way could be found to shut down the machinery that powers persistence, TB therapy could be shortened dramatically, experts believe — conceivably to just a few weeks.

> "It's very exciting — like the first chink in the wall that lets us peek through and take a look at what goes on during persistence."

All this helps explains the enormous fuss that greeted the article in the Aug. 17 *Nature* that describes a primitive metabolic pathway that's kicked off by an exotic-sounding enzyme called isocitrate lyase, or ICL.

By genetically switching off ICL, a team of researchers from Cornell University and Rockefeller University in New York City found they could effectively shut down the persistence shop. Bugs without the ability to produce the ICL enzyme did just fine during the acute stage of infection but couldn't survive during the chronic stage. Mice infected with bugs lacking the gene to make ICL, in fact, are still scrambling about in their cages and look as if they will enjoy normal mouse life spans.

"It's very exciting — like the first chink in the wall that lets us peek through and take a look at what goes on during persistence," says **John McKinney**, PhD, assistant professor at Rockefeller and head of the university's laboratory for infection biology.

The shift that ICL permits in the TB bug's metabolism is so odd that references to it caught McKinney's eye years ago when he was poking through dusty library stacks, grubbing around in

1950s literature to see what nuggets he might glean from the pre-Medline era.

"I think it was James Watson who said, 'A year in the lab is worth a day in the library,'" chuckles McKinney. "You know, in the preantibiotic era, TB engaged some of the greatest minds of the time. These people didn't have a lot of fancy technology, but they certainly spent a lot of time thinking about how things work."

Obscure researchers and dusty clues

What caught McKinney's attention was a series of papers published starting in 1956 by a now-obscure pair of researchers named Segal and Bloch. Setting out to elucidate the differences between in vitro and in vivo TB bugs, the two compared mycobacteria taken from the lungs of infected mice with bugs grown in standard lab culture. Then they began playing around, offering the two sets of bugs various kinds of "food" in the form of carbon-substrate energy sources.

To the surprise of Bloch and Segal — and, decades later, McKinney as well — the in vivo bugs harvested from mice showed an astonishing dining preference. They completely ignored everything but fatty acids, roughly the gastronomic equivalent of a hungry man in a gourmet pastry shop bypassing the crème horns and tarts and heading for a bag of week-old, rock-hard bagels.

"It was weird, because fatty acids are not a preferred [energy] source," says McKinney. "If the bugs were using it, it was because they had to."

Two labs combine forces

That wasn't the only thing Bloch and Segal turned up that caught McKinney's eye. "They observed in another paper that these in vivo bacteria expressed enzymes in two pathways specifically required for use of fatty acids — the beta-oxidation pathway, which we now study in my new lab, and the glyoxylate shunt." Because it had largely disappeared during evolution, that second pathway is where McKinney decided to begin his own exploration.

By coincidence, McKinney found he wasn't the only one looking at the pathway and at ICL, the enzyme that switches it on.

"[McKinney's lab was] taking the genetic approach, just knocking the gene out, but in my lab, we were looking at what proteins were up-regulated during the shift," says **David Russell**, PhD, chair of immunology and microbiology at Cornell University's College of Veterinary Medicine. "So we decided to combine forces."

Sure enough, Russell and McKinney found that TB bugs lacking the enzyme for ICL couldn't shift into the primitive, carbon-sparing metabolic pathway. But what was prompting the metabolic shift in the first place?

"We felt it represented some sort of transition between the naive host and the immune host," says Russell. "We knew that in the immune host, there are activated macrophages. This seemed to suggest that where there are activated macrophages, the bacterium, in order to maintain an infection, has to metabolize carbon from a different source" by cranking up the glyoxylate shunt pathway.

Same enzyme in other pathogens

What exactly the switched-on macrophage does to make this happen remains to be seen, says McKinney. "Maybe the host immune response is withholding carbon sources, or maybe it's putting the bug into a compartment where it can't get at other energy sources," he theorizes. "What we can say is that the shift is brought about by the host immune response, and *that*, as far as I can tell, is an entirely novel finding."

Drug maker Glaxo-Wellcome, which has helped support McKinney and Russell's work, already has found several compounds that inhibit production of the ICL enzyme, at least in vitro. McKinney says he's cautiously optimistic that animal testing of some of these promising compounds will be under way by the end of the year.

There's an exciting postscript to the story, as well. "Recently, we've seen some unpublished reports in which it's been shown ICL is up-regulated in a number of other pathogens when they enter macrophages," McKinney says. Among them are *Cryptococcus neoformans* and *Candida albicans*, two fungal pathogens; and *Toxoplasma gondii*, a parasite.

Could it be the same host immunity response McKinney and Russell uncovered is driving a metabolic switch in these other pathogens, too? Such a finding would be more than just a chink in the wall. Indeed, it could open up enormous new vistas in research, McKinney believes. "We may have hit on a general theme here," he says. "Anyway, that's our hope." ■

Conversion rates under 2% most likely false

All the same, serial testing still best strategy

The tuberculin skin test (TST) results in more false positives than true positives in most hospital settings in the United States, says **John Bass**, MD, chairman of the department of internal medicine at the University of Alabama at Birmingham.

That's not a slam at the test, either, adds Bass. It's just an observation about the limits of any diagnostic test, coupled with the fact that the test is generally employed in a low-prevalence setting.

If your facility is typical for the United States, you're probably well below that benchmark, and you can assume that whatever apparent conversions you're looking at are probably false positives, he says, because "most places today are down below 1% now, even in New York."

Here's Bass' logic. "For most tests, the false-positive rate is about 2.5%, since 2.5% of results are high and 2.5% are low, for a standard [statistical] deviation of 95%," he says.

There's no biological correlate yet to stack up against the TST, so in a sense, any such line of reasoning is, by necessity, circular, he concedes. "We don't have an independent test to tell us whether the TST is accurate or not. So all we can do is try to estimate the test's sensitivity and specificity. Then you've got what you need to predict the operating characteristics of the test in various populations."

At 2%, you'd better look harder

Or, you can do what Bass does, which is conduct a posterior analysis of the results of your skin-testing program. "For example, if you have a hospital that skin-tests 1,000 employees a year, and you have seven conversions, that's a conversion rate of 0.7%," he says. If Bass is right about the TST producing a false-positive result about 1% of the time, then "all those [apparent conversions] are false positives," he concludes.

Bass adds that as the number goes up, he starts looking at skin-testing data in a different light. The point at which apparent conversions are likely to represent trouble is about 2%, he says. "If your conversion rate stands at 2% or higher, you're probably transmitting TB. If your rate is less than 1%, you're probably not. And if you're between 1% and 2%, things are sort of iffy."

Most places fall well below that "iffy" zone, he says. "The likelihood of hospital workers becoming infected, especially if you're not in Harlem or Jackson Memorial [in Miami], or else in an unknown outbreak situation, is much less than 1%. So mathematically, at least, almost all the conversions in a serial skin-testing program, where people are tested every year, are going to be false positives."

Debating the need for a federal standard

In his slow, patrician drawl, Bass recently ticked off the same points to members of an Institute of Medicine committee charged with looking at whether a need exists for a federal TB standard. Opponents of the federal standard were quick to seize on Bass' testimony as proof that the Occupational Safety and Healthy Administration (OSHA) is mistaken in its estimates of the TB infection risk to health care workers because, most of the time, under most settings, individuals are probably showing false-positive results.

Because it's bound by precedent and by statutory obligation to show a "reasonable risk" to worker health exists, OSHA is off-base when it adds up skin-test conversions to quantify that risk, they argue.

How to handle those positive results

Whatever the implications for OSHA, Bass says there's no reason for hospitals not to keep using the TST in serial fashion. "The purpose of a skin-testing program is to detect an outbreak of TB in your hospital," he asserts. "It's most valuable for that. The only problem lies in how to interpret the test for a given individual [who tests positive]. What do you do?"

What Bass does first is explain how and why the test result is more likely to be false than true. "Then we give them a chest X-ray to rule out active disease. And then I tell them that isoniazid is relatively innocuous and that they can take it if they like, or they can do nothing."

If the person falls sick with respiratory illness in the next year or so, he adds, "I tell them they should be aware it could be TB, so they should be evaluated." ■

Experts take aim at TST at recent IOM hearings

But, chair adds, OSHA will have its day, too

No one could blame supporters of the federal TB standard proposed by the Occupational Safety and Health Administration (OSHA) if they ran home from a recent hearing by an Institute of Medicine (IOM) committee and grabbed a headache powder and a cold compress.

Held in August, the two-day stint of testimony and discussion was the second meeting for the IOM committee that Congress charged late last year with determining whether TB poses a sufficient risk to health care workers to justify creating a federal standard.

At the end of the second day, session chair **Walter Hierholzer**, MD, professor emeritus of internal medicine at Yale University in New Haven, CT, seemed to acknowledge that the weight of the hearing's evidence was tilting strongly against OSHA. But, he added, "there will be other days" when that won't be the case.

First, OSHA partisans in the audience listened as the opposition dissected the agency's estimates of annual mortality from TB.

When it was time to work over OSHA's estimates of morbidity, which are based on data from skin-testing programs, OSHA opponents traded their scalpels for sledge hammers, as various experts testified to the unreliability of the tuberculin skin test (TST).

Union representatives and experts from occupational medicine, two camps that have spent years advocating on behalf of the OSHA standard, also were on hand. They presented evidence, much of it anecdotal, intended to show that some unscrupulous employers are not abiding by federal guidelines. Only the force of law, they added, will force such facilities to toe the line.

"I actually came away from these hearings with a better appreciation of their point of view. It's true that there are some bad actors out there," notes **Ed Nardell**, MD, chief of pulmonary medicine at the Cambridge Hospital of Harvard Medical School and medical adviser to the TB control program for Massachusetts.

The problem is that OSHA, which must show substantial risk to workers before it can propose and implement federal regulations, has based many of its measurements of risk on TST data. As one expert after another at the IOM hearings argued, the skin test isn't a good indicator of true conversion rates in low-prevalence settings.

"So what do you do?" Nardell asks. "You can't just ignore the science altogether."

In a press conference held after the second day of testimony wrapped up, even OSHA chief **Charles Jeffress** seemed to hedge a bit in his resolve to press forward with the TB standard. Mostly because the ergonomics rule is uppermost in everyone's mind at OSHA, Jeffress conceded that the TB standard probably will miss its latest deadline, set for the year's end.

In the OSHA offices in Washington, DC, **Mandy Edens**, MPH, chief project officer for the TB rulemaking process, said she was planning to set work aside for the next two months and devote herself to other tasks.

And, Jeffress added, if IOM committee findings, which are due out by December, go against OSHA, that might — just might — have an effect on what the federal agency does next. "Whatever information comes out of the IOM study, depending on where we are in the process, it might affect what we do," was the way the OSHA chief put it.

The benzene decision sets precedent

To understand the twists in the latest bout of wrangling between pro- and anti-OSHA forces, it helps to go back to the rationale for devising a TB standard — or any standard, for that matter — in the first place.

In 1980, when OSHA was trying to come up with a way to protect workers against the carcinogenic effects of benzene, the petroleum industry sued the agency, accusing it of being too vague in its charges that benzene created a "significant risk" to workers' health. The Supreme Court agreed: OSHA needed to quantify the risk and needed to come up with a risk great enough that a "reasonable person" would act to protect himself, the court said.

With TB, OSHA has tried to quantify two endpoints, says Edens: deaths and the risk of becoming infected. "Obviously, there's a greater risk for [skin-test] conversion than for death, so the focus of our risk assessment has been to get data to quantify the risk to health care workers [for conversion," she adds. "We acknowledge that the available data aren't always the best, but they're

what's available, and you have to deal with the data you've got."

OSHA argues that skin-test conversion, insofar as it signifies TB infection, does constitute what the agency terms "an adverse event."

"Some people argue the skin test is beset with false positives," Edens concedes, "and it's been argued that being infected doesn't impair your everyday life, at least not in the way that losing an arm or a leg does."

Defining 'adverse'

But for some people, becoming TB-infected is an adverse event, she adds. "For one thing, prophylactic therapy carries with it some risks," she says. "For those who can't take isoniazid, there's the risk of developing disease. Plus, there's the emotional concern engendered among people who convert."

Latent infection is construed as an "adverse event" in OSHA's bloodborne pathogens standard, which seeks to protect workers against the risk of contracting hepatitis B virus. "In that case, the main focus of our assessment was not getting the disease itself but becoming infected," she notes.

All this helps explain the weight of arguments — some based on traditional arguments, some on newer data — about the frequency of false-positive results in skin-testing programs. Limits inherent in any diagnostic test employed under low-prevalence conditions explain why the TST probably gives more false than true positives in most places in the United States, says **John Bass**, MD, chair of the department of internal medicine at the University of Alabama at Birmingham.

Fordham Von Reyn, professor of medicine at Dartmouth Medical School in Hanover, NH, presented new and still unpublished evidence that quantifies how, in three sites scattered around the country, cross-reactions with atypical mycobacterial infections appear to account for an increasing number of positive TST results.

At the end of the IOM sessions, Columbia University medical ethicist **Ron Bayer**, PhD, made a closing statement that seemed to reflect the effects of the accumulated testimony accurately. He had gone to the hearings ready to give unions and other OSHA partisans the benefit of the doubt and to support the "little guy," Bayer reportedly told the audience. But the accumulated weight of evidence had worn down his resolve. Now, he said, he was ready to switch sides. ■

TB fight goes global with guidance for poor nations

Emphasis on identifying and separating TB cases

Though declining steadily in the United States, tuberculosis is taking a terrible toll globally that includes nosocomial spread to patients and health care workers in impoverished countries, public health officials warn. To meet the threat, the World Health Organization (WHO) in Geneva is distributing guidelines for the prevention of TB in health care facilities in resource-limited settings.

Written in part by the Centers for Disease Control and Prevention, the guidelines essentially adapt the CDC's 1994 guidance for U.S. health care facilities with few resources.[1]

"The United States and the CDC have the responsibility to work on TB from the global perspective because we can only affect the TB picture in the U.S. so much [by focusing on national controls]," says **Patricia M. Simone**, MD, one of the authors of the WHO guidelines and chief of the field services branch in the CDC Division of TB Elimination.

The TB burden shifts

Indeed, TB is the leading cause of mortality among adults in the world, killing some 2 million people annually. Overall, approximately 1 billion people are infected, the vast majority of them in countries with limited health care resources. Moreover, even as TB has declined steadily in the United States, the proportion of cases occurring in foreign-born people has increased steadily since the mid-1980s, reaching 42% in 1998. Because it appears that TB cases among foreign-born people residing in the United States could soon outnumber cases among U.S.-born people, the CDC and its advisors have concluded that TB elimination in the United States will not be possible without a substantial reduction in the global TB burden.

"It varies quite a bit, but the main problem in the low-income countries is that they have large wards of patients, many of whom have symptoms that could be TB," Simone says. "They also have a lot of HIV-infected patients in these countries. The other big problem is there may not be a rapid ability to diagnosis patients, so there will be

wards with patients who have TB [mixed with] those who don't."

The guidelines underscore that administration of standard short-course chemotherapy under direct observation by health care workers will cure most TB patients. However, recent studies performed in developing countries have shown that health care workers caring for infectious TB patients are at increased risk of infection and disease. Health care workers are essential in the fight against TB, and they should be protected, the document emphasizes, citing nosocomial transmission cases in health settings in Africa, Thailand, and Brazil.[2-4]

The greatest threat to workers is the undiagnosed and untreated patient. "The data certainly point to nosocomial transmission happening in these settings," Simone says. "It's hard to really say for sure without DNA fingerprinting studies. It's possible that some community transmission is occurring because there is high prevalence of TB in these communities, as well."

Identify, separate, and treat

As a practical approach to the TB problem, the guidelines recommend trying to separate patients into three areas of the health care facility: those with confirmed TB, those with suspected TB, and those who have been ruled out for TB. "Those in whom TB is ruled out can be on the general medicine ward," she says.

But because the use of respirators and corresponding respiratory fit-testing programs are impractical in such settings, the guidelines give primary emphasis to identification, "separation," and treatment of patients. For example, facilities in some countries designate "cough officers" to identify and triage the obviously symptomatic patients in common waiting areas.

"The same principles apply," she says. "The highest priority are administrative controls, which emphasize early recognition of tuberculosis or suspected TB. In the CDC guidelines, we talk a lot about isolation [in terms] of mechanical, ventilated isolation in which the air is actually [under negative pressure vented to the outside]. In these guidelines, we talk more about separation, which is just putting people in a separate place so they are separated by distance to reduce the transmission."

In the absence of engineering controls, the guidelines suggest common-sense measures like opening windows, using fans, and doing sputum induction outside. "The risk of transmission depends on the concentration of droplet nuclei in the air," she says. "[That] can be reduced either by reducing the amount of droplet nuclei generated into the air — by either putting masks on patients or treating the patients so they don't cough infectious germs — or by separating the patients so they can't cough the germs into the air that everybody else is breathing."

Masks vs. respirators

In addition, surgical masks may prevent the spread of microorganisms from a TB patient but do not provide protection to health care workers. Workers may mask in such settings to achieve some limited protection, but they are not as protected as they would be by respirators, she says. "Putting a mask on a [TB] patient is an easy, cheap way to reduce — but not eliminate — the number of droplet nuclei in the air," Simone adds. While respirators protect the wearer from inhaling infectious droplet nuclei, they are expensive and should be reserved for high-risk referral hospital settings, the guidelines recommend.

"We have very limited recommendations for [respirators] in this document, because you can't really implement a respiratory protection program if you don't have the administrative controls in place and you don't really have the isolation rooms," she says. "[If] the air can go either way across the door, for example, then it doesn't make sense for a health care worker to wear a respirator in the room and not outside the room."

(Editor's note: The WHO TB guidelines are available at http://who.int/gtb/publications/healthcare/PDF/WHO99-269.pdf.)

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Three keys to boosting contacts' completion

Capable staff, good morale, and Ninja Turtles

Good contact investigations without good completion rates for preventive therapy are like, well, you fill in the simile. While you're thinking about it, consider that TB control programs are putting tons of creative energy into finding contacts. Evidence for that was abundant at this year's TB Controllers' Workshop in Atlanta, where participants testified about doing contact investigations in schools, crack dens, poultry plants, welfare hotels, transsexual networks, and nearly every other kind of situation imaginable.

Part one of a two-part series

Even so, completion rates for treatment of latent TB infection (LTBI) are just so-so, with the national average standing at about 70%, according to **Patty Simone**, MD, former chief of the field services branch at the Centers for Disease Control and Prevention's Division of TB Elimination.

That falls short of the CDC's 85% completion goal for LTBI contacts, she adds. Completion rates for other groups getting treatment for LTBI are nothing to brag about, either — around 60% for many programs, Simone says, compared with the CDC goal of 75%.

In Long Beach, CA, the TB control program does better than most. Here, completion rates for contacts in 1997, the last year CDC figures were available, stood at a very respectable 87%. Of the 807 other patients who began preventive therapy the same year, 79% managed to complete it.

It would be unfair to say that Long Beach, a gritty urban outpost of Los Angeles with a population of about 450,000, is doing well because it's been dealt an easy hand. Clearly, that's not the case. Demographics in Long Beach include the usual urban ills, plus a heavy sprinkling of foreign-born groups, principally Cambodians.

The program's keys to success, though they may sound simple, aren't necessarily easy to achieve. According to **Barbara Taylor**, RN, public health nurse for the Long Beach TB control program, two of the most important ingredients include keeping an enthusiastic and capable staff on board and using an imaginative array of incentives. Because so many contacts are kids, incentives have come to mean just about anything: dinosaur hand stamps, free toothbrushes, and a Ninja Turtle coloring contest that left the walls of the clinic plastered with images of the four cartoon heroes.

Encouraging the staff to keep things interesting by dreaming up new ways to keep kids happy and taking their meds has improved staff morale, Taylor adds. "We have a lot of fun here," she says. "Most people have been here for a long time, and that's important, too, because it means continuity for patients. Patients can match a face to a name, and they can see the same people each time they come into the clinic."

Planting the seed of compliance

There's also the fact that the staff works hard at staying in touch with contacts and letting them know just what's expected of them.

"As soon as the contacts get their positive skin test, we plant the seed by telling them they'll probably be contacted by someone here about starting preventive therapy," assuming that the chest X-ray is OK, she explains. A letter goes out a couple of weeks later, inviting the patients to come in, then a community worker calls (speaking Cambodian or whatever language is appropriate) to remind them of the appointment.

The first time in the clinic, the public health nurse meets with the contact in an educational session, explaining how preventive therapy works and what adverse events to watch for. Because clerical staff members speak several languages, there's usually someone on hand who can translate if needed, Taylor adds.

Making it easier

Next, in a departure from procedure at many clinics, contacts are provided with a list of days and hours when they can return for refills, instead of being given a specific appointment to come back. "That way, if work or some other problem keeps people from coming back on a specific day, they don't have to call us and reschedule," Taylor explains. Likewise, it's OK if patients come in for refills a few days before their month's supply of isoniazid actually runs out. "We try to stay flexible," she adds.

For problem patients, the TB clinic uses a variety of strategies. "Sometimes we get the sense that a mom is really struggling to get meds into her

child, maybe because the child is the age where he wants control," says Taylor. "In those cases, we try to give the child some control: We tell him that if he takes his medicine, there'll be a reward at the end of the month for good behavior."

Rewards run the gamut from coloring books to stuffed animals to toothbrushes. The incentives come from a variety of sources. "People donate things to our clinic from time to time," Taylor notes.

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One woman brings in old copies of the magazine *Highlights for Children.* A former staff member who had business ties to a toothpaste manufacturer managed to get the supply of toothbrushes and toothpaste donated. The toothbrushes, incidentally, have turned out to be a huge hit. "We found that many of our families are so poor there's no toothbrush, or maybe the whole family shares a single toothbrush," says Taylor. "So a free toothbrush is a really great incentive for some kids."

Other rewards cost virtually nothing. "We give out hand stamps to anyone who wants one," says Taylor with a laugh. The kids love the stamps, she adds. It's not unusual to spot children leaving the clinic with their arms and hands gaily decorated with images of dinosaurs, sheep, kittens, and maybe a Mickey Mouse or two, and toting a couple of stickers for good measure. Adds Taylor: "We also try to be generous with praise," another free commodity in good supply around the clinic.

Teenagers, older kids, and even the occasional adult who's having trouble with compliance sometimes get treats, as well. "We don't do this for everyone, obviously, but on occasion we'll give out free movie passes," Taylor says. "That's a very effective motivator for teens and college students."

In what seems to be a growing trend in the state, the clinic added a social worker to its staff a few years ago. At times, simply knowing that Cynthia Brayboy, MSW, is on duty and available seems to be a good incentive for compliance, says Taylor. "Clients absolutely love Cynthia," she says. "They bring her food and other things, and they come in early if they know she'll be here."

Usually Brayboy spends her time helping out with cases, not contacts, Taylor says. But if it looks like troubles with rent money or an empty pantry are interfering with adherence to LTBI, she'll pitch in and do what's needed for a contact, as well.

Finally, having the capability to translate information is important, Taylor says. Long Beach has a potpourri of foreign-born groups, with "more Cambodians than anyplace outside Phnom Penh, I'm told," she says. Knowing that it's important for patients and contacts to get information in a language they can understand, Taylor has outfitted the office computer with a special program that translates letters into Cambodian.

The staff members who speak a foreign language are invaluable, Taylor says. "If you have staff who are knowledgeable about TB and can translate for you and explain your point of view, you can be sure information is flowing between you and the patient is accurate," she says. Without both those components, "it's easy to lose control of the translation process." ■

Targeting social needs with a social worker

Trend is a response to rise in patient problems

Adding a social worker to the mix of staff is one of the best things the TB clinic in Long Beach, CA, has ever done, says **Barbara Taylor**, RN, the public health nurse at the city's TB control program. **Cynthia Brayboy**, MSW, helps patients solve problems that otherwise might interfere with compliance, often more quickly and easily than regular clinic staff can, says Taylor.

The idea of TB controllers hiring social workers isn't exactly new. San Francisco and San Diego added master's-prepared social workers to their staffs about six years ago. But the trend seems to have picked up steam over the past five years, says **Rosa Lee Black**, MSW, social worker for the state health department's division of TB control. The reason is simple: Over the past five years, there's been a marked increase in the number of TB patients with difficult social and psychological problems.

"There was a time when the typical TB patient was an American-born alcoholic," explains **Tony Paz**, MD, program manager for TB control in San Francisco. "But over the years, so many other issues have begun trickling in. Now we have patients who deal with homelessness, poverty,

HIV infection, substance abuse, and mental health issues."

As the number of patient problems began to increase, Paz adds, health care workers in TB clinics responded as best they could. "Many of us began doing social work, but it was pseudo social work, really, given that our training is not in social work." Clinicians began devoting more and more time to this new aspect of their jobs, he notes. "We'd get someone a room after he'd been discharged from the hospital. We'd hand out sandwiches, since folks coming in for their meds need to have something on their tummy. We'd give out juice and bus tokens. We'd provide transportation. After awhile, we just got to feeling that we were out of our league — that what we needed was social services."

Long Beach TB controllers hired Brayboy on a contractual basis two years ago. As a rule, she sees patients referred by clinic staff, after they've spotted troubles that might impede compliance. She sees patients both inside and outside the clinic offices, sometimes heading out to meet someone about to be discharged from jail or the hospital. Other times, she makes home visits when an outreach worker picks up on a patient's distress.

Initial sessions with patients are face-to-face encounters that can take anywhere from an hour to several sessions spread out over two to three days. Brayboy does a mental health evaluation and tries to establish whether there's a history of incarceration, homelessness, or substance abuse. She asks about family and friends and checks for disabilities and eligibility for available services.

She also takes a medical history, even though that's already been done by the time the client has reached her; sometimes, going over the same ground again nets a key fact the patient may have omitted the first time. "They'll say, 'Oh, yes, I forgot to tell the nurse — a few years ago I had hepatitis.'" Names and phone numbers of emergency contacts Brayboy takes down also come in handy when a missing patient needs to be found.

Brayboy says she's certain she saves the clinic staff time. "They'd all like to spend three or four hours with a client, but they just can't do that," she points out. "Because I do, it frees them up to see more patients, and they can do their own jobs more effectively."

Along with helping patients fill obvious gaps in their lives — helping them fill out benefits forms, say, or referring them to a substance-abuse clinic — Brayboy believes she gives her clients something else as well. "Sometimes, people come in feeling so victimized that they feel they have no voice at all. The way I look at it, I can serve as their voice." That doesn't mean doing everything for them, she adds. In fact, during the initial interview, she always asks patients to list their strengths. "Sometimes, they sit there for 20 minutes struggling to come up with some answers. It might be the first time anyone's ever asked them that question."

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Focusing on strengths can be a first step to getting patients to take responsibility for their recovery, she says. "Even though I want to give them a voice, I always stress that whatever we do has to be a partnership. They've got to at least make the effort to do their part."

Paz says having someone like Brayboy around pays long-term dividends, too. "We have patients here for a long time at the TB clinic, and relationships definitely get formed. But what if after treatment is over, the patient goes back to the same environment, the same set of problems? Are we really treating the whole patient?" Making sure TB patients have access to the kind of services Brayboy and other social workers can offer "is a national standard of care. If it's not, it ought to be." ■

CE objectives

After 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. ■

NEWS BRIEFS

Global alliance to be launched in Bangkok

At press time, the Global Alliance for TB Drug Development was expected to be officially unveiled at the International Conference for Health Research and Development — also known as the Karolinska conference — on Oct. 11 in Bangkok.

The launch of the Global Alliance wasn't an official part of the Karolinska agenda but was to have been part of a special presentation, says **George Soule**, public affairs spokesman for the Rockefeller Foundation in New York City. In Bangkok, public health policy-makers from all over the globe were to have met and talked high-level strategy. To read about this year's Bangkok conference, visit the Web at www.Conference2000.ch. ▼

Relief act passed for global TB

Recent congressional passage of a $100 million TB and HIV relief act bodes well for foreign aid funding for TB, say political observers. "This global relief act sets up a framework to allow [those who do the actual work of appropriating the money] to spend more on TB," says **Joann Carter**, head of the advocacy group Results, International. "Passage of the act, like the Sherrod Brown bill, both give tangible evidence of increasing bipartisan and bi-cameral support for money for TB and HIV — and that's good," she says. The foreign aid "approps" bill in the Senate stands at $51 million for TB; in the House, the sum is up to $60 million. Can anything go wrong? Well, yes, Carter says. "We've heard rumors that this might get wrapped into an omnibus bill. In conference committee, where the real money gets locked in, you have more room for details and negotiation. In an omnibus bill, it gets harder to influence the process." ■