

Infectious Diseases Among Internationally Adopted Children

ABSTRACT & COMMENTARY

Source: Saiman L, et al. *Pediatrics*. 2001;108:608-612.

THIS IS A RETROSPECTIVE STUDY OF A COHORT OF 504 CHILDREN ADOPTED FROM ABROAD FROM JANUARY 1997 through December 1998 evaluated at an outpatient international adoption practice in New York. These children were from 16 countries, although most were born in China (48%) and Russia (31%). The mean age was 1.4 years (range, 1 month to 11.2 years). They showed high rates of positive tuberculin skin tests and *Giardia lamblia* infection. Overall, 75 (19%) of 404 children had tuberculin skin tests ≥ 10 mm, which was associated with bacille Calmette-Guérin (BCG) vaccination (odds ratio [OR] 7.37; 95% CI, 2.19-17.16) and birth in Russia (OR 2.90; 95% CI, 1.68-5.00). However, all children had normal radiographs. *G lamblia* antigen was detected in 87 of 461 (19%) children, and hepatitis B surface antigen was detected in 14 of 485 (2.9%) children. There were no cases of syphilis among 478 children tested, no cases of hepatitis C infection among 496 children tested, and no cases of HIV infection among 490 children tested.

■ COMMENT BY HAL B. JENSON, MD, FAAP

United States citizens adopt more than 15,000 foreign-born children each year. Between 1960 and 1990, most internationally adopted children came from Korea, Latin America, and various Asian nations. Since 1990, greatly increased numbers of adopted children have come from Eastern European countries, especially Romania and Bulgaria, the former Soviet Union (particularly Russia), Kazakhstan, and Ukraine; and also from China, Cambodia, and Vietnam. Many of these children resided in orphanages before adoption. This report indicates changing patterns of infections seen among international adoptees as the countries of origin have changed.

In this cohort, 75 of 404 (19%) had positive tuberculin skin tests ≥ 10 mm. Of the 404 children, 242 (60%) had evidence of BCG immunization, including 220 (54%) by scar, 83 (21%) by vaccination record, and 61 (15%) by both. All children had normal chest radiographs. The rates of positive skin tests and of previous BCG vaccination are substantially higher than reported among earlier cohorts, in which BCG use was uncommon. Some of the positive skin tests could have been due to recent BCG vaccination, although no reliable criteria exist to distinguish infection from BCG vaccination as the cause of the positive skin test. The origin of many children from Russia, where multidrug-resistant tuberculosis is more frequent, is a concern. Consistent with current recommendations by the American Academy of Pediatrics, all skin test-positive children were recommended to receive isoniazid therapy for treatment of latent tuberculosis infection.

The highest prevalence of hepatitis B infection among international adoptees is among Romanian children, with reported rates of 20%. These children can be the source of intrafamily spread, although routine hepatitis B vaccination for all children and household contacts should reduce this possibility. There is not a consensus for reimmunizing adopted children with hepatitis B vaccine, although there is concern about use of outdated or poorly stored vaccine, and sub-optimal responses in malnourished children. In this study, only 29 of 42 (69%) children who had received 3 doses of

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hepatitis B vaccine had detectable HBsAb, which corroborates such concerns.

Reported rates of *G lamblia* infections among adoptees have ranged from 0-18%. The use of *G lamblia* antigen rather than diagnosis by microscopy may have facilitated identification of infection, which was diagnosed in 87 of 461 (19%) children tested. Extremely high rates were found among adoptees from Eastern Europe, particularly Bulgarian (67%), Romania (50%), and Moldovan children (36%). Adoptees from China had a 15% *G lamblia* infection rate.

No infections were identified secondary to syphilis, hepatitis C, or HIV. Infections with enteric bacteria were rare, and included *Campylobacter* (5 children), *Shigella* (3 children), and *Salmonella* (2 children). ■

Two New TB Vaccines to Enter Clinical Trials in Near Future

For both, oft-maligned BCG plays critical part

FOR THE FIRST TIME IN 80 YEARS, TWO NEW TB VACCINES are about to enter human trials. The American-made candidate, which uses a form of BCG engineered to produce extra quantities of a king-sized protein to spark cellular immunity, is being developed by the Rockville, MD-based Sequella Tuberculosis Foundation and is due to begin Phase I trials this summer.

Across the Atlantic, the British contender also uses BCG, but only to “prime” the immune system before “boosting” it with a second vaccine consisting of attenuated smallpox that has been genetically tweaked to make it produce the same big protein. Developers of the British 2-step vaccine are recruiting human subjects for an early-stage trial in England.

The fact that both vaccine candidates use BCG is probably more than just coincidence, say TB experts. But what’s really important is not whether the old TB vaccine proves the key to a better one, but rather that the first round of vaccine candidates has finally graduated from preclinical development.

“This is what we hope will be the first of many TB vaccine candidates,” says Larry Geiter, PhD, MPH, consultant for the Sequella Tuberculosis Foundation. “We have 3 more vaccine candidates on the runway, and we hope to have our second in trials by the end of the year. We also hope to keep putting 1 or 2 into the development process every year.” Among Sequella’s other starters are a TB auxotroph, designed to shut down after an initial period of replication, and a DNA vaccine that incorpo-

rates a heat-shock protein.

If all goes well, Sequella will conduct early trials in partnership with the National Institutes of Health, he adds.

Geiter’s counterpart in England likewise hails the new phase. “In the TB vaccine world, this is something we’ve not seen since BCG,” says Helen McShane, MD, a Wellcome Clinical Scientist Fellow at the Nuffield Department of Clinical Medicine at Oxford University. “Now the task is to begin looking at all the promising candidates and see which works best.”

A Big Cargo and a Good Carrier

How BCG—long spurned by American TB controllers for the way it muddles the skin test—wound up with starring roles in each of the new contenders makes for an interesting tale.

On this side of the ocean, the story started years ago, in the laboratory of Marcus Horwitz, PhD, a professor in the department of microbiology, immunology, and molecular genetics at the University of California in Los Angeles (UCLA).

Horwitz was tinkering with subunit vaccines, built not from live or killed forms of an entire microorganism but from small, protein-based pieces of TB. Presented alone, the protein pieces got little immune response. They performed much better when teamed with an adjuvant, to enhance the immune response. But despite the high hopes Horwitz’s subunit approach generated in the TB vaccine community, it ultimately failed to deliver the requisite immune-system response.

At length, Horwitz decided to try live vectors as delivery systems, settling after some experimentation on BCG. Its advantages were numerous: As a live organism, it could replicate inside the host, ensuring that whatever freight it carried would get good play. At the same time, it was widely used (except, of course, in the United States) and commonly believed to be safe.

For the cargo for his new vector, Horwitz decided to use the “B” version of Antigen 85, a complex of three look-alike proteins (dubbed A, B, and C) that are manufactured in abundance by TB microbes.

Again, Horwitz had compelling reasons for his choice. At 30 kd in size, Antigen 85 is an 800-pound gorilla among proteins. Plus, because it’s a key ingredient in the construction of cell walls, TB organisms churn out loads of the stuff. Horwitz (as well as many other TB researchers) came to believe that something so big and so abundant must be capable of getting the full attention of the immune system.

Teaming the big protein with the old TB vaccine made sense for other reasons, too. For one thing, regular BCG already secretes Antigen 85, and in such a way that the BCG version is tailored almost exactly the same as the ver-

sion designed by *Mycobacterium tuberculosis*. Altering BCG to make it churn out even more Antigen 85, it follows, ought to induce a brisk immune response, resulting in a rich store of memory T-cells ready for battle against actual TB organisms. So far, data from Horwitz's animal studies show that's what is happening.

When trials begin this summer, Sequella will pit the Horwitz version of BCG against regular BCG. Investigators will also compare the effects of BCG given at birth alone with BCG given at birth and then followed by a dose of Horwitz-styled BCG administered during early adolescence.

Brits Use a One-Two Punch

Back in England, BCG's path to center stage occurred via events that are slightly less convoluted. There, researchers headed by Professor Adrian V.S. Hill, chief of Oxford's Cellular Immunology and Vaccine Development Group, had noticed that smallpox viruses are able to boost previously primed immune responses. "We don't know what it is about pox viruses that make them good at this, but we know they do it. We've seen this in work from other fields, including malaria and HIV vaccine research," says McShane. That work has already entered Phase I trials, she adds.

Even though the malaria and HIV work had harnessed the pox viruses to DNA vaccines to effect the one-two punch, McShane and Hill decided to team a pox vaccine with BCG. For one thing, they reasoned, BCG is not likely to disappear soon from global TB control practices, McShane says. "Most people agree that although BCG is far from adequate, it does afford limited protection, especially to children, so we're a long way from stopping BCG immunization," she says. That made the old vaccine a logical platform from which to try launching a better one.

To direct the boosting to its proper target, McShane engineered her attenuated smallpox virus to secrete Antigen 85. So far, animal data (including results from tests in mice, guinea pigs, and primates) say the two-step strategy gives protection either equal to or better than BCG, depending mostly on what McShane says is the timing of the two vaccine doses.

BCG, named for French researchers Albert Calmette and Camille Guérin, was first used in 1921; since then, over three billion doses have been administered worldwide. Only modestly (and inconsistently) effective, BCG works best at protecting infants and young children from disseminated, often deadly, forms of TB.

From a vaccine developer's point of view, using BCG makes sense in many ways, says Ann Ginsberg, MD, PhD, chief of the Respiratory Diseases Branch at the National Institutes of Health in Bethesda, MD. Since the vaccine does give limited protection, investigators doing human trials could hardly withhold it in countries where it's already given.

"Since any new strategy must work against a background of BCG vaccination, taking advantage of BCG's good properties makes some sense," she explains. In other words, big-scale human trials in the developing world are pretty much stuck with BCG, so why not make the best of it?

Possibly, adds Geiter, American bias against BCG has actually kept researchers from taking what in retrospect seems a perfectly reasonable step. "This is purely my personal belief, but I sometimes think the TB community may have shot itself in the foot a bit here," he says. Just look at the omnipresent lists describing what a new TB vaccine should look like, he says. "Everyone has one of these laundry lists of essential vaccine qualities tucked away in a file cabinet. The problem may be the way the lists all equate essential qualities — like 'safe' and 'effective' — with qualities that maybe would be nice, but which are hardly essential, like 'doesn't mess up the skin test.'"

Maybe, he adds, if those lists had read a bit differently and researchers had been thinking a bit more openly, today's two new candidates would have emerged even sooner. ■

Quantiferon will Sell for \$10 a Dose

Marketing will target prisons, other big-scale users

MAKERS OF THE NEW, ONE-STEP BLOOD TEST FOR detecting latent TB infection are about to start marketing their product to potential U.S. users at \$10 a test. They'll market Quantiferon—which won approval from a panel of the U.S. Food and Drug Administration (FDA) last October—as a straightforward alternative to the tuberculin skin test (TST), says Jim Rothel, PhD, chief scientific officer for Cellestis, Ltd., the Melbourne, Australia-based firm that makes the product.

CDC Suggests Using Test as 'Adjunct' to TST

That plan sounded somewhat at odds with comments from at least one FDA spokeswoman, who told *TB Monitor* she hoped the Centers for Disease Control and Prevention, not Cellestis, would work out procedural kinks before the product hit U.S. shelves. The CDC, for its part, suggested using the test primarily as an "adjunct" to the TST.

Rothel says none of that troubles him. "Well, the FDA asked the panel [that was considering Quantiferon] whether the test was to be considered as only an adjunct to the TST," he says, "and the panel replied essentially, 'Why would you want to do that?' Of course we want to keep working with the CDC. But we definitely see this test not as an adjunct,

but as a straightforward alternative to the TST.”

Marketing would have started already had not the events of Sept. 11 stalled a visa application. Soon, Rothel adds, the company’s American sales representative should be set up in his California office.

In accordance with FDA directives, Cellestis plans to go ahead with trials of Quantiferon in the two groups for whom the regulatory agency didn’t grant approval for use: children and HIV-positive people.

Quantiferon’s U.S. price will run about \$10 a test, says Rothel — or, put another way, \$440 for a kit that tests 44 people. When the cost for labor is factored in, that’s roughly equal to the cost of administering a TST and then returning to read it, he adds.

At least one TB expert says he’s considering switching to Quantiferon. The \$10 price tag “starts to look competitive once you factor in the time it takes to send someone out to read the TST,” says Jim McAuley, MD, MPH, the medical director of Cermak Health Services at the Cook County jail in Chicago. “Not only that, my pharmacy director just informed me that our price for Tubersol is about to go up from \$2 a dose to \$6 or \$7.”

Quantiferon’s logistical advantages are also appealing, McAuley says. As it stands, Cermak places approximately 100,000 skin tests each year, but prison TB nurses manage to read only 25% to 30% of them, he notes. Because it’s a one-step blood test, Quantiferon doesn’t require going back for a return visit.

McAuley is an example of exactly the sort of person Rothel plans to target. “We’re looking at anyone who works in public health where skin testing is done on a large scale, including jails, immigration centers, and that

sort of situation,” he says.

Next Generation of Test Already in the Works

Meanwhile, Rothel says Cellestis is continuing work on an improved version of Quantiferon that might hit the shelves in three years or so. The new version would do a better job of distinguishing subjects who are merely BCG-vaccinated from those who are latently infected with TB, even though CDC trials show Quantiferon already outperforms the TST at that task, Rothel notes.

The next-generation test will work by incorporating recombinant proteins present in TB but absent in BCG, he says. “These are basically pieces of the genome which were deleted when they attenuated *M bovis* to make BCG,” he explains. “ESAT-6 is the main one you’ve probably heard of.”

For now, Cermak’s McAuley says his real challenge will be to figure out how to persuade his labor force to accept the new technology. “It’s always painful when you introduce new technology,” he says. Not that using Quantiferon is that hard, he adds: “I’m not a lab guy, and even I can do an ELISA,” the basis for the assay, he says. “It’s just that change always comes hard.”

McAuley adds that one thing he’s not worried about is whether the test works. “I read the *JAMA* article [detailing results of the CDC trials], and I listened closely to the FDA testimony, and I’m convinced it’s a good test,” he says.¹ ■

Reference

1. Mazurek GH, et al. Comparison of whole-blood interferon assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. *JAMA*. 2001;286:1740-1747.

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