T.B: THE RESURGENT DISEASE

Jeffrey Glassroth, MD

DR. STEVEN BAKER: Our last speaker of the afternoon is Dr. Jeffrey Glassroth who is a Marquardt professor of medicine at Northwestern. He also did his pulmonary training at Boston University prior to a residency at the University of Cincinnati and after a stint with the CDC has been at Northwestern where he's participated yearly in American Thoracic Society and CDC policy committees for management and diagnosis of tuberculosis and he's here to talk to us about what's new in tuberculosis.

DR. GLASSROTH: Thanks. Let me start off and give you a moment just to mentally make the transition from one talk to another by telling you a story that I hope will set the tone for what I'm going to try to do this afternoon.

Imagine, if you will, being parents or one of the parents of a coed off to her first year away at college and receiving a letter after some months of no communication from your daughter, and the letter begins with an apology from the daughter to her parents for not writing for about three months.

It continues on to indicate that she didn't write because she was recovering from her injuries, her head injury and fractures that she sustained in a fire in the dormitory. She goes on to indicate that she probably wouldn't have survived the fire had it not been for a young man named Jimmy who was nearby and pulled her out of the fire.

They got to know each other better and in fact, he nursed her back to health and she began living with him after the event and although he's been in jail and isn't working, he's really a pretty nice guy. And it's very important to her that her parents have this impression of Jimmy because they plan to get married a few months before the baby is expected to be born. The letter concludes by saying sit down and relax.

There was no fire, no injuries, there's no Jimmy, I'm not getting married and I'm not expecting a baby. I did get three D's and an F last semester and I just wanted you to have some perspective on what that really means.

What I'd like to do this afternoon is try to give you some perspective on tuberculosis, particularly in the United States. Much of what I'm going to tell you is bad news, and being an eternal optimist, I look at a lot of the bad news as opportunities for taking some corrective action. It's in 1989 the news actually gets worse and it's just too depressing. There are 16 million cases of tuberculosis worldwide. Actually probably closer to three million deaths in 1984 with HIV upon us.

This is a worldwide situation. A billion infected individuals at risk of developing active disease, and in fact, about eight million new cases moving into the pool of prevalent cases each year. There's exposure to previously uninfected individuals and many of them will move into the infected pool as well.

So this is an enormous public health problem and I would be remiss if I didn't say that no less an authority in the World Bank labeled tuberculosis on an international basis as the number one opportunity for prevention in terms of its impact on worldwide economy and cost effectiveness of the intervention. So it's an enormous opportunity, but right now mostly bad news.

In the United States the situation has been very different, and until a few years ago we were actually looking forward to the day, early in the 21st century, when tuberculosis would actually be eradicated. A model done down at the Center for Disease Control some years ago looked at the number of cases in the US and then modeled the decline with an accelerating tail and in about the year 2065 it was estimated that tuberculosis would cease to be an issue, at least in the United States.

On the way to eradication of tuberculosis, some things went awry. I'll spend a couple of minutes trying to look at some of the origins of the problem. But first I'd like to show you magnitude of the problem. We're actually having more cases than we would expect from about 1984 on. And in fact, the magnitude or the total number of these so called excess cases is almost 52,000 as of 1992, and this is continuing to increase with each year.

In the US the problem is not evenly distributed. I think that's very important for us to consider for a couple of minutes. Among non-Hispanic whites, tuberculosis is a relatively modest problem. There are about 7,000, almost 8,000 cases per year. Non-Hispanic whites account only for about a third of the tuberculosis that we see in the United States each year. So about two thirds of our tuberculosis is now occurring in minority populations or at least populations other than non-Hispanic whites.
Again, an opportunity for us to target some of these populations, some of which perhaps haven't had access to health care, to prevent services and the like.

It's also important to recognize that the epidemic of tuberculosis or at least the prevalence of tuberculosis in white populations and non-white populations is really different. It's in some ways a different kind of disease. There are two points that I'd like to state. The first point is that among non-Hispanic whites, TB is a disease of older adults.

The highest prevalence is really between age 60 and 80. So these are middle aged to older adults among non-Hispanic whites. A very different situation among non-whites, where the peak is really somewhere around age 30. These are younger people. So non-whites were having disease early in life and whites were having it older in life. Obviously this has implications for lost work, for useful years of life lost in those cases that turn out fatal.

Among non-Hispanic whites the number of cases is declining. It's exactly the reverse among the blacks and Hispanics. In each of these years tuberculosis has actually been increasing. So there's good evidence that certainly among our black and Hispanic populations in the US we have a situation where we have disease and disease transmission even today in the 1990s.

We also have to recognize that we are a net importer of tuberculosis in the United States. About 25 percent, in 1992 27.3 percent of tuberculosis that we see in the United States each year occurs in foreign born individuals, individuals who immigrate to the United States typically from one of the parts of the world where tuberculosis is endemic; Asia, Africa, Central and South America.

Most of the tuberculosis that these individuals – most of the tuberculosis that we see in these immigrants occurs within five years of their entry into the United States. Now, this isn't and shouldn't be misconstrued as an argument against immigration, no problems with that. It's again an opportunity for us to focus on control measures on a population that has a substantial amount of tuberculosis but where prevention is a real opportunity.

Lest we think that this is something that we need to look outside for and become xenophobic about, let me hasten to add that a lot of our tuberculosis is home grown and in fact, much of it is probably the result of failed programs. I'd like to show you one program that's been well studied and well described in Harlem in New York.

First let me mention some data regarding tuberculosis in New York and in Harlem specifically, compared with the US. In the US as a whole, the rates were relatively low but increasing somewhat over that time period.

In New York City as a whole, the rates were higher, substantially higher and again increasing to a peak of just under 50 per 100,000. But in Harlem the rates were phenomenal. They were over 100 per 100,000, increasing to approach 200 per 100,000.

These are third world rates occurring in one of the great cities of the United States today. There's no reason to think that much of this has changed. If we look at the program that provided most of the health care to the central Harlem population, that is the TB Clinic at Harlem Hospital, I think it's easy to see why some of these rates existed and why they're not making any progress.

89 percent of the 178 patients entering treatment at Harlem Hospital during one of those years, were either non-compliant, or lost to follow up within a several month period. Only 11 percent could be construed by any stretch of the imagination as having been retained with the treatment program. Some of those individuals died but they were on treatment. Some of them hadn't yet completed treatment. So it's not clear whether they would ultimately be lost to the treatment.

So we have failed programs. I don't think Harlem is unique. Harlem is simply well studied. They've had the nerve and the courage to actually report the problem that they've been having.

We also have to look for opportunities at other institutions. Nursing homes, it turns out, are becoming more and more important to us as the population ages, are places where tuberculosis occurs and probably where tuberculosis is transmitted.

One large study of 29 states contemplates the relative risk of either being in a nursing home or not being in a nursing home for developing tuberculosis. As you can see, in each of these studies, you're at risk of developing tuberculosis if you're in a nursing home, the relative risk ranging from 1.8 to as high as 5.7.

I don't have time to go into the data but this isn't just a matter of people who are sickly and being already infected perhaps with TB, coming down with TB. We know that there is actually transmission and conversion of skin tests in nursing homes. There is transmission of the disease in nursing homes.

Another fascinating area that we're beginning to appreciate is our nation's prisons. I, like most of you, don't know a great deal about prisons. I've learned some because of my interest in tuberculosis.

We have in the US a phenomenal proportion of our population in the slammer at any point in time, somewhere around one percent of the population. It's a staggering number. Hundreds of thousands of people in jails, prisons, state and federal penitentiaries. It turns out that prisons, in an era of HIV, drug abuse and all the other things that affect the penal system, are tremendous places for the transmission of tuberculosis.

Worse than that, there are places where, by design, we have actually facilitated maximum transmission. We now, in prisons, for example, regularly move people around from one prison to another to prevent gangs from taking hold within the prisons. So if you have someone who turns out to be infectious, they literally ride the circuit and have an opportunity, not only to create
an outbreak in one facility, but with any luck at all, in four, five or six facilities within a year.

A comparison between the non-correctional populations and the correctional population, a survey in 29 states in the mid-80s reported one year case rates of people in prison. Over 30 per 100,000 as opposed to 7.9 per 100,000, a relative risk, almost four times the general population.

We can say, well, it's prisons and damn it, they get what they deserve or something like that, but the fact is that people don't stay in prison most of the time. That's a whole separate discussion on whether that's right or wrong, but they don't. They go back to their communities and we now have documented a number of situations where tuberculosis is contracted in a jail and brought out and transmitted throughout our communities.

So again, I think we have to look at prisons as an opportunity, indeed an obligation, where we can have an impact on tuberculosis control and prevention. There also are a lot of people that work in prisons and they are also vulnerable.

Another big part of the story in tuberculosis today in the United States and worldwide is HIV. And I'd just like to say a few words about that to complete this epidemiologic survey for you. A now classic paper that was published in the New England Journal of Medicine in 1989 that proved what a lot of people suspected, that if you're HIV infected and you get infected with TB, that is, you become co-infected with HIV and TB, you are at tremendous risk for developing active tuberculosis.

This was a study, a very thoughtful study, done in a methadone maintenance program in New York City where they asked the simple question, who is HIV positive and who is HIV negative in the treatment program. And then they asked beyond that, who is known to have a positive PPD, a tuberculin test, and who is known to be infected with TB. And then they followed these individuals to see what the occurrence of tuberculosis was. The bottom line is that if you were HIV negative and PPD positive, 62 individuals, none of them developed tuberculosis in the two years of follow up that they had.

On the other hand, if you were HIV positive and tuberculin positive, seven of those 49 individuals developed TB within two years, a 14 percent rate of tuberculosis. That's the highest rate of developing the disease for any risk factor that's ever been defined. Some people would go so far as to say that if you're HIV/TB co-infected and nothing is done to treat the TB infection, that, if you live long enough, you will certainly develop tuberculosis. So this is an enormous risk factor for active TB today.

This becomes a tremendous problem because you have to consider the magnitude of the HIV/TB problem. It's a problem in the US but worldwide it's an enormous problem. If you look at the estimate in 1988 for how many individuals worldwide had HIV infection, we had 5.1 million with estimates for the mid-21st century at somewhere between 12 to 18 million individuals with HIV infection. For TB the rates are somewhere between eight and 10 million, with estimates going as high as 96 million by the mid-21st century worldwide. I mentioned earlier that we import tuberculosis into the US and that isn't likely to stop.

So worldwide we have an explosive situation whereby HIV will now act as an amplifier, if you will, of tuberculosis, it will facilitate the spread of tuberculosis in many areas of the world and some of that will almost certainly come back to the US. So as health professionals I think it's imperative that we lead the charge on having our expertise and our experts in these diseases communicating and working with their counterparts around the world because it will come home to the US, without any doubt.

Another aspect of tuberculosis in the late 20th century and another part of the bad news that I'm conveying is drug resistance. We've all read about some of the super strains that are now around. In the 1980s the Centers for Disease Control did regular surveillance of drug resistant TB around the country using a system of sentinel laboratories where they would regularly get resistance data.

Between 1982 and 1988 the national average for drug resistance among people who had never received anti-TB therapy before was just under nine percent. The rate for individuals who had previously been treated and relapsed with their disease, that is, secondary resistance, was around 23 percent. These levels had been pretty stable for a number of years and in a fever of cost cutting, the whole surveillance program was discontinued.

By 1991 there were rumors of increasing rates of drug resistance around the country, so the CDC quickly put together a survey and in 1991 they found that the rate had jumped to almost 14 percent for primary drug resistance and was now 38 percent for secondary resistance. Let me make the point a little more strongly by talking again about New York City which has, unfortunately, been at the forefront of many of our TB problems.

In New York City a survey was done in April of 1991 in which they got reports of drug susceptibility tests that were done at a reference lab at the Centers for Disease Control and they found that 33 percent, 33 percent of all 466 isolates taken just as they came into the city's health department clinics, a third of all of these isolates in patients were resistant to at least one anti-tuberculosis drug, a quarter were resistant to INH which has been a cornerstone of our treatment regimes and 19 percent were resistant to both INH and rifampin which represent the core of our best available therapies.

Twenty three percent of previously untreated patients were resistant to at least one drug. This is a staggering blow for TB control in New York, and a message for the entire country.

They looked at risk factors and I think it's again a message that we all need to consider. There were a number of things that correlated with the likelihood of drug resistance being present. They used an odds ratio, the odds that given a positive culture,
an individual would have resistant strains. The odds were highest if that person had prior therapy. That is not a surprise. But with HIV infection your risk was twofold greater, suggesting that these people were actively being infected by resistant strains and then getting their disease in a hurry.

Drug use was also a factor. Interestingly recent immigration was not. Those people were somewhat less likely to have resistant strains. So we're suggesting that at least in New York, we're making our own drug resistance problem with poor treatment programs, with HIV infection and a number of other factors.

Nationwide in 1992, there was additional reason for alarm, now with multi-drug resistant TB. These are the so called super strains that are resistant to four, five, six, ten anti-TB drugs. Ninety-one to 100 percent of the patients in several outbreaks were HIV positive. That shouldn't be totally reassuring.

I think the reason that we're seeing so many of these people as being HIV positive is simply that they get their disease very quickly after they get infection. We probably have, for any one of these individuals, several others who have more intact immune systems who have been infected with resistant strains and they only become ill with tuberculosis some years later.

Some of these secondary cases I would point out were among health care workers. So this is now a serious occupational risk and it has led to OSHA issuing guidelines that will soon be implemented for air control, masking and respirators. Mortality with these strains is phenomenal. 72 to 80 percent TB mortality with the mean time to death after developing TB being somewhere around three to four months. So not a good situation, certainly not an infection that anyone ought to have.

So much for the epidemiology and for a lot of bad news. Let me talk a little about the good news, because there is some good news. Let me first tell you a little bit about diagnosis and how that's being revolutionized with the tools of molecular biology.

I give you a sense of sensitivity by showing the number of organisms here per milliliter of specimen that you would need to predictably and reproducibly have a positive test, then give you a sense of the speed at which that test can give you an answer.

Our traditional two tools have been the acid fast smear and what I've called the conventional culture, agar culture for TB. These are the tools of really 100 years ago when Caulk was first describing TB. Their sensitivity is fair. You need a lot of organisms, hundreds or thousands of organisms present.

The smear can give you an answer in a few hours but it's not specific. There are other things that can be positive, other micro-bacteria than aren't TB, legionella, nocardia, all can be weakly acid fast positive. So it has problems of sensitivity and although fast, it is not very specific.

Conventional culture is more sensitive but it takes weeks to get an answer. You're stuck trying to determine if the patient really has TB and you often have to make decisions while the culture is cooking and drug susceptibility tests take even longer because they rely on these culture assays to give us answers. So we're often stuck making decisions weeks and even months before we have the kind of information that we'd really like to do these things in a thoughtful way.

Again, technology has been applied here and is really revolutionizing things. Radiometric assays which first came in for conventional bacteriology have now been applied to TB. The backtech system is probably the most well known and familiar of these systems. It uses a radio labeled substrate for micro-bacteria usually palmitate, and the radio label is incorporated by the growing micro-bacteria and then can be read usually by a gamma counter and it has great sensitivity, at least as good as conventional culture, maybe a little better and it can give us an answer in perhaps seven days. These systems have now been modified and adapted to doing drug susceptibility tests.

So with radiometric assays we can get answers in really a week or so and that's very important because it can guide our decision about drug use and help prevent creating drug resistant cases. These systems and the assays cost a little more to run the test but I would submit to you that this is really money well spent because one resistant case saved can save thousands and thousands of dollars in later care.

The really exciting news is down in DNA and RNA probes and particularly those probes that are now combined with PCR or polymerase chain reaction. This is a way of taking now a native specimen, digesting and preparing the specimen and then amplifying the micro-bacteria that are present, the DNA or the RNA in the specimen, multiplying it through the polymerase chain reaction sequence and then probing with very specific genetic probes to identify micro-bacteria.

This has now been done as fast as 48 hours and in theory can find literally a single organism if present. So this gives enormous potential for both sensitivity and speed, and this is truly a revolution in the way we approach micro-bacterial disease and it couldn't come a moment too soon. These prototypes are now being refined and I suspect, at least in large reference labs and probably larger laboratories around the country, will be on line and in use probably within the next couple of years.

There's also some good news about treatment and I think this is important as well. I'd like to refer you one study that uses some of our conventional drugs and just gives them in a somewhat different way, takes advantage of the efficacy of these drugs to allow us a better outcome of our treatment. Let me explain what I mean by this.

The data were reported in the *New England Journal of Medicine*, they come from a Tennessee treatment program for TB and it looked at the results of traditional therapy. By traditional I
mean they gave the best available drugs to the patients and told them to go home and take them every day and come back about once a month for the duration of treatment to be followed up. And they compared that with what happened with directly observed therapy which they began in 1986.

The directly observed therapy uses much the same drugs, usually INH and rifampin and a few other drugs with slight modification in dose, but by using those drugs and adjusting the dose, we know we can give the drugs two or three times a week and have the same efficacy as daily therapy if we use those drugs. When, giving the drug twice a week allows you to bring the patient back for those twice weekly doses and give the drug under direct observation. So you can literally supervise the patients directly and make sure they are taking virtually every one of the pills you’re prescribing, or at least know when they default and know it immediately and take steps to bring them back.

Well, does it work? The experience in Tennessee would suggest that it works very, very well. Between ’80 and ’86 studying 407 patients and from ’86 on, studying 588 patients, failure rate is cut to a quarter of what it was before, relapse rate a quarter of what it was with traditional therapy, resistance, the development of resistance usually due to irregular medication taken is cut to one tenth of what it was in the previous program, multi-drug resistant again a fraction of what it was. But the really interesting thing is there’s a payoff in primary resistance.

These are the people who are presumably coming in to the clinic because they were infected by a resistant strain. In the old situation, about 13 percent of the patients coming in were already resistant before they were ever treated.

In the early years of directly observed therapy, that’s cut in half. Only 6.7 percent of the patients are now coming in, suggesting that the successes over here treating patients means fewer of them are around to transmit resistant bugs to their neighbors in the community. This should only get better if these kinds of results can be sustained.

Where are we now with our current recommendations for treatment? Current recommendations are taking into account the emerging problems with drug resistance and the potential of directly observed therapy. I’d like to just show you quickly where we are in the United States today. If there’s no resistance suspected, your urge to use a six month regime of isonizien and rifampin, given daily or intermittently, supplemented for the first two months or eight weeks by perzinomide, PZA, this combination should allow, if the drug is correctly taken and the organisms are susceptible, a cure rate in excess of 97 percent.

That’s what we think is the capability of the regime itself, if you can actually get the drugs into people. If you are residing or working in a high resistance area that is defined as a rate of resistance of greater than or equal to four percent, or if you don’t know what the rate of resistance is, then you should use the same drugs, 24 weeks, six months of isonizien and rifampin, supplemented by two months of PZA, plus a fourth drug, ethambutol or streptomycin to prevent the emergence of resistance until drug susceptibility test results are available. If you have proven resistance, then we’re urged to use at least two drugs to which the organism is believed to be sensitive and to treat that individual for 18 months or a minimum of 12 months following culture conversion. So these are now the sort of standards of care for the United States.

We get several options for how we can give these drugs. This goes back to the emerging sense that directly observed therapy, twice weekly, could be very helpful. Let me explain this. Option one is the straight forward vanilla option. Eight weeks of isonizien, rifampin, perzinomide, followed by 16 weeks for a total of six months of isonizien and rifampin, add ethambutol or streptomycin if you suspect resistance greater than or equal to four percent.

Option two is an initial phase, two weeks, of isonizien, rifampin, perzinomide plus the fourth drug, followed by six weeks of the three drugs given twice weekly. Followed by 16 weeks, four months, of twice weekly isonizien and rifampin. So it’s dual daily intermittent regime, if you will, largely directly observed therapy, with an initial core of daily therapy to reduce infectiousness and reduce symptoms.

Finally option three, which is recommended for the patients believed to be the most likely to default on therapy. This is a totally observed regime in which we use 24 weeks, six months of twice weekly therapy with four drugs; isonizien, rifampin, perzinomide and ethambutol or injectable agent streptomycin. So we now have a range of options for how we give the drugs and we should be most inclined to give directly observed therapy to those individuals who default or are non-adherent to therapy.

Let me close with several comments about prevention. I think we should not forget that TB is preventable. A lot of what I showed you earlier in terms of programs and defined populations represents opportunities to prevent disease. First of all, improving case prevention is important. One third of minority TB cases are deemed to be preventable; that is, there are people who fall into categories where they would qualify for INH prophylaxis.

So we need to encourage screening in populations where we think we’re going to find infection at a time when we can prevent it. Two thirds of foreign born TB cases are thought to be preventable. So again, a plea for screening our foreign born persons, particularly those from areas endemic for TB.

Finally one third of our patients fail to complete TB preventative therapy. So we need to enhance our prevention programs to make sure that the prophylaxis we give is actually taken. I’ve reviewed here just some of the candidates for prophylaxis. I would just also suggest to you that we now have a sense of what the risk is of TB developing if we don’t provide preventive therapy.

I’ve already mentioned HIV/TB co-infection with a risk that’s probably over eight percent per year of developing active dis-
ease, close contacts of potentially infectious diseases of a two to four percent risk in the first couple of years and then some other groups, all are groups in whom we know once they're infected their risk of developing TB is increased but we also know that if we provide prophylaxis with INH or a similar drug for somewhere between six and 12 months, we can lower the risk for their life by about 90 percent.

So these are definable opportunities that all of our health care providers, and to some extent our public health units, should be using to reduce the amount of tuberculosis we have. We have lots of options for providing prophylaxis, isonize daily for six months, isonize daily for 12 months in HIV infected persons. We believe that people who have abnormal X-rays, even when they're bacteriologically negative, that the chances of making a mistake and providing one drug and having resistance involved is so great, that we're now recommending that these people be given more drugs for prevention, but the payoff here is that we can provide prevention very successfully in just four months.

We can greatly reduce the duration of time that prophylaxis has to be taken and substantially reduce the risk of TB in a high risk group. We even have potential, although it's less well proven, for preventing the evolution of active tuberculosis when infection occurs with drug resistant organisms. We can use a variety of drugs other than INH.

We think rifampin is quite effective, rifampin and perzinomide also probably quite effective and for the multi-drug resistant organisms we think that some combinations of quinalones and drugs like perzinomide might be effective. BCG is still a big question mark. In the United States we tend not to use it because the data have generally not supported when tests have been done in the US. We also have, at least until recently, most of our disease in people who have already been infected, BCG doesn't work there. But perhaps BCG or some newer and potentially more effective vaccination may also be of some utility, particularly in treating drug resistant exposure.

Let me just say a couple words about the risk to health care workers for TB. This is an old study from back in the '60s and '70s but I think it brings home the message of what the risk for developing TB life long would be, and the potential for skin test conversion among nurses, people who are very much in contact with patients and with TB.

We know that back in the older days the risk of conversion was probably on the order of five or six percent and that life long risk for the disease was probably somewhere around one or two percent. We have no reason to think that this is any less today but I would point out to you that today we have, given our ADA laws and so forth, we have a situation in which we actually bring health care workers who are particularly susceptible to the disease, health care workers who may have some immune compromising condition, into contact with potentially infectious diseases like tuberculosis.

We are literally prevented from interdicting that kind of exposure other than counseling the individual and suggesting they minimize exposure. So we have to be very thoughtful in terms of exposure to TB and we have to figure out ways to both limit those exposures and to also identify infection when it occurs.

So I would suggest that for one thing we need to really be very diligent about screening staff in high risk facilities on a regular basis. What are high risk facilities? Well, some obvious ones are TB clinics, laboratories that handle mycobacteria, but also as I showed you, nursing homes, chemical dependent treatment programs, correctional facilities.

These are all places where, in some parts of the country, we know there's TB and we ought to get smart about protecting people who work there, obviously to the extent that we can limit infection perhaps using UV lights, good ventilation. That ought to be done as a requirement in these facilities.

Then finally, I think we should learn the lessons of some of the multi-drug resistant outbreaks that we've had and make use of some very straight forward and classical prevention interventions. We have to have a high index of suspicion so that we can isolate these people promptly in our health care facilities. We need to separate patients who have immune compromise from the patients with TB, so we need to use adequate isolation. We need to use adequate ventilation. We need to make sure that hospitals that see these patients have good ventilation systems and know how to use them and maintain them.

We have to avoid lapses in precautions that would occur when, for example, patients are taken out, when we do these things and then send patients all around the hospital for testing when they're still infectious.

Survey groups like the Joint Commission and now state groups are looking very carefully at infection control plans to make sure that they have been updated to reflect our modern views of these problems. And then most importantly we have to identify cases adequately, according to the kinds of regimes I've shared with you today and report cases very promptly so that good contact investigation can go on so that we can identify people who are infected before they develop disease and break the cycle of infection and disease.

So in the 1990s the issues with respect to tuberculosis relate to, I think these four items. The interaction of tuberculosis and HIV infection and the amplification that HIV infection has for TB, the problems with multi-drug resistance in several areas around the country, the good news about the emerging high tech innovations and what that will allow us to do with TB and then finally, not forgetting some very traditional standard interventions and control programs and strategies that can still have a major impact on tuberculosis. Thank you for your attention.

(Applause.)
AUDIENCE MEMBER: I thought it was a wonderful talk. I've got a question. Years ago when I went through medical school and went through my post-graduate training, we all worked in a TB sanatorium and it was standard practice that all physicians had BCG, all health care personnel had BCG and we didn't have a real problem with exposures.

We were all exposed but no one seemed to have gotten tuberculosis. I wonder if you could comment on whether there are controlled studies in the United States on health care workers who have received BCG and those that haven't in terms of the development of tuberculosis.

DR. GLASSROTH: There have been a lot of studies of BCG efficacy, not specifically in health care workers, but studies of BCG nonetheless, several of them in the United States. The problem is the efficacy of the BCG in these studies has ranged from zero, and the worst results have actually occurred in the US, to as high as 89 percent elsewhere in the world. The most recent study which was done in Shinglupth in south India about ten years ago actually was a very disappointing study that showed a very low rate of protection. Now, there's a couple of caveats with respect to those studies.

Number one, there isn't one BCG the way there's one penicillin. There really are BCGs. The Serum Institute in Copenhagen makes BCG. The government of Mexico makes BCG. The Pasteur Institute makes BCG. Until a few years ago the University of Illinois had a BCG Institute that made BCG.

So you're looking at a lot of different preparations, standardization is all over the place and there are a number of other factors that effect the take of the vaccine. So it's really unclear just what the efficacy is. I think most people would agree, even those people who are not BCG advocates, but probably grudgingly agree that BCG, if it doesn't prevent disease, probably does prevent the worst of the disease, meningitis, miliary disease and so has some advantage there.

Now, what BCG doesn't do and the biggest proponents of BCG would agree with this, is it doesn't prevent disease. It has no effect whatsoever once someone is infected. Once you're infected, BCG doesn't work. Everyone agrees with that. Now, the real problem occurs with what BCG does to the skin test. When you get BCG there's a good chance you'll convert your skin test. Once that happens, there's no way to know whether that skin test reaction is from a virulent infection with TB that happened to occur at that point or due to the BCG. So prevention strategies using, for example, INH really become very hard to implement.

So in this country where most of our disease has traditionally come from people who are already infected, our major push has been to use the skin test INH as opposed to BCG. That's all being rethought as we have these drug resistant cases where INH probably isn't going to work and other drugs may not work either.

But I think most people would agree that it would be wonderful to have a vaccine that we could all agree really did what we hope it would do. And there actually is some potential for that occurring, again using the tools of molecular biology to help develop those vaccines. So there's still no good answer with respect to BCG.

AUDIENCE MEMBER: I wonder, with this resurgence of TB, if you think the HIV control programs are going to become a little more consistent with our idea of a public health policy, so that we can identify these cases and we can really find out where we have co-morbidity because right now we really have our hands tied to be able to take care of these people.

DR. GLASSROTH: That's a good question. I have no easy answer. I suspect we won't because as I said, even something that seems as overly obvious as not taking someone whose HIV infected and allowing them to work in a TB unit, you can't do that. I mean ADA will preclude you, there would be problems with that. What we get now is aggregate data. We can match up, and we know that in some areas HIV and TB co-infection are a big part of the TB that we see. What we can't get is the patient specific data. I don't see any of that changing.

I think we're still in an era where we protect individuals' rights at all cost, that's very important. The insurance issues, which all of you are well acquainted with, obviously give a lot of pause for concern to the insureds who might be affected by this. We don't have good strategies for protecting confidentiality. Even when we try to transmit data confidentially, it often leaks.

So I don't have any simple answer. I don't see that changing. I think the message has already come home. I think the answer that we've gotten is probably the one that we're going to get for some years to come. They're not going to give us that information. Thank you.

(Applause.)

DR. WILLIAM BAKER: So in closing, we thank our participants from the Northwestern Medical Center this afternoon. I think we've had a very excellent, well done informative afternoon. I want to thank all four of them and thanks, Steve, for taking us through the afternoon. We'll see you at the dinner dance tonight, the reception at 6:00 and here again at 8:30 tomorrow morning. Thank you.

(The meeting was recessed.)