Okay, folks, let's go ahead.

I want to take about 30 seconds to get an update on Hurricane Matthew.

Emergency Preparedness forecasters are still having trouble deciding exactly where it's going to hit along the coast, but in terms of the evacuations that are coming our way, I think you've already all heard that we're getting Flagler evacuations. Some of them are arriving right now. We have 12 of them. We're anticipating another 30. That's a little bit less than initially. Some patients were discharged. Some already expired. So no more will be coming from Flagler.

We are on call for Shands and Jacksonville. They're not sending any at this time, but with changing forecasts they may yet send patients over here later on today or possibly early tomorrow. I'm not aware of any other institutions, Mayo Clinic or Savannah Baptist, that are sending any over at this time or have any plans to. So we're bracing for the worst so that we're not caught off guard. Teaching Services have been incredibly generous taking extra patients on each of the General Medicine services as well as the Gold Team today, Golden Team today is taking several patients. Hospital Medicine has some capacity today. We've also called in a couple of additional hospitalists. We have a lot of folks on reserve, on backup, as well if we need them tonight.

So I just want to thank you all. Stay tuned to your email since information is really constantly changing. But at the moment we're okay.

Mark?

So I just also want to make an announcement that the Celebration of Research thing tonight is being delayed until the 20th. And I'm sorry about that but there's a possibility that we going to close (inaudible).

It's unclear when the rains will pick up and the winds will pick up. It's going to be sometime tonight, and in order to make sure that folks get home safely. So it's been rescheduled as Dr. Brown has mentioned.

Okay, so.

Thanks, Bob.

So I'm Mike Lauzardo the Chief of Infectious Diseases here at UF, and I'm also the Director of the Southeastern National TB Center who is cosponsoring this talk today from Dr. Dick Chaisson. Just so you're aware, we've got folks in the room here, but through the Southeastern National TB Center, we broadcast this to the larger TB community, and so we have about over 400 people registered online, which means there's probably going to be over 1,000 people listening in on this Grand Rounds today as well, both in the U.S. and around the world from our different partner sites.

So it's my distinct pleasure to welcome Dick Chaisson to come and give Grand Rounds today. You know, this is our second time around trying to get Dick here. He got bumped because of the Gatorade Fiftieth Celebration – 50 Year Celebration – last year, and now we tried to undermine his talk again with a hurricane. But he's a trooper and still willing to come.

Dick is truly one of the giants in TB and HIV, globally and TB in the United States. And we think about when we do these introductions we usually talk about how much someone has accomplished and how they've become so accomplished. And that's true of Dick as well. Dick has had over 450 publications that he's had during his time, his career at Johns Hopkins and prior to that.

But I think what's most significant about Dick is not only what he's contributed, but what he's contributed to not only what's happened but what's going to happen in TB. When you look at TB regimens, new drugs, and the care of HIV patients, particularly those who become infected, the influence that Dick has had on our field is hard to exaggerate.

Besides that he's a great guy, and from the more formal standpoint, Dick is, as you can see, both Director of the Center for TB Research and the Center for Aids Research at Johns Hopkins. Been working in the clinical world of TB and HIV ever since the start of his career. And it is our distinct pleasure to welcome Dick to give Grand Rounds to us here today. So thank you very much, Dick, for being here, and thanks for putting up with our weather.

Well thank you very much, Mike. That's a very nice welcome and introduction.

I'm going to start with the disclosure slide, and while you're absorbing that and taking notes, I'll just mention that at the age of six months I was a refugee from a hurricane in Cape Cod and spent three nights sleeping on a teacher's desk in a school room at Falmouth, Massachusetts. My name was in the Boston Globe. And so I've been dealing with hurricanes all my life, but back then we were running away from it. This time I ran straight into it. But thanks for being here in spite of the circumstances where I know at least the residents have 21 admissions waiting for them when they get back.

So I'm going to start with a case presentation of a 53-year-old woman who presented to her primary care doctor with shortness of breath at night and a cough. She had no constitutional symptoms. She wasn't producing sputum. She was a nonsmoker. Didn't have any pets. Didn't have any known exposures to any toxins. But she did have a history of rheumatoid arthritis. She had a questionable history of asthma as well. Depression and cervical dysplasia and kidney stones.

Six years earlier she'd had a tuberculin skin test done and it was positive where it had previously been negative, so she was a converter. She had a chest x-ray at that time which was normal and so no therapy was given to her.

She was taking etanercept, methotrexate, and low-dose prednisone for her RA. And her exam was really completely unrevealing.

Her laboratory evaluation was pretty unremarkable as well including pulmonary function testing. And her chest x-ray was likewise fairly unremarkable though there was some question of whether there might be some widening of the mediastinum, and a chest CT was done. And unfortunately that was lost in the transport, and I don't have it, but the report was that there were multiple hilar and mediastinal lymph nodes.

So she was taken to mediastinoscopy and had a lymph node biopsy performed, multiple biopsies, and they showed non-caseating granulomas and she was given a diagnosis of sarcoidosis. She was treated with bronchodilators for her breathlessness. Her immunosuppressant regimen was not changed, however.

But three weeks later, lo and behold, her biopsy from her lymph node – the material from the lymph node biopsy grew mycobacterium tuberculosis. And luckily she was started on anti-tuberculosis therapy and did very well.

So this case is a nice illustration of some of the challenges of tuberculosis in the U.S. at this time. So even though suppression globally is a very important driver of tuberculosis, particularly HIV, but in the United States, iatrogenic immunosuppression through TNF inhibitors, cancer chemotherapy, transplant medications, is also an important factor in many tuberculosis cases.

Most importantly, this was a totally missed opportunity for prevention. This patient, before starting her etanercept, had a tuberculin skin test done, and it was positive and she should have been treated for latent TB but she wasn't. So this was a blown opportunity.

And diagnosing sarcoid in a patient with positive tuberculin skin test is done at the doctor and the patient's peril. This case turned out well. I consulted on another case recently of a young boy from Nigeria

whose diagnosis of lymphadenopathy was called sarcoid, treated with steroids, and he died of disseminated tuberculosis.

So tuberculosis in the United States is on the decline, although the rate of decline is slowing. It becomes increasingly difficult to eradicate tuberculosis, or eliminate tuberculosis, as we'll talk about, as you get to fewer and fewer cases. You can see that back in the late eighties and early nineties there was a surge of TB, an upswing in cases that was driven largely by first and foremost funding cuts to TB control programs in New York and New Jersey. And then aided and abetted by the HIV epidemic and the emergence of multidrug-resistant TB in hospitals, jails, and homeless shelters.

But with the restoration of funding in 1992, TB case rates have continued to fall, but we're now getting to the point of diminishing returns with just about 10,000 cases of TB a year in the United States.

TB is more common in racial and ethnic minorities, particularly Asians, Native Pacific Islanders, and higher in Latinos and African-Americans than in whites.

An important trend in TB in the United States has been the marked increase in cases of TB in people who were born overseas. Born generally in countries with high rates of TB who come to the U.S. and develop TB when they get here. About half of the cases in foreign-born individuals occur within the first five years of being in the U.S., and the other half occur subsequently.

If you look at the countries of birth of people with TB who come from other nations, it reflects immigration to the U.S. And if we had looked at this ten or 15 years ago, Vietnam would have been a much larger contributor. Mexico has always been a large contributor. The Philippines. And we're seeing increasing numbers of patients with tuberculosis from countries where immigration to the U.S. is increasing such as Eastern Europe, the Middle East, and Africa.

Globally the situation is quite different. Globally tuberculosis incidence is thought to have peaked back in about 2005 at over ten million cases per year. You can see that HIV is an important subset of that but certainly by no means the most important driver of TB.

And you can see that rates of TB are declining agonizingly slowly. The incidence of TB globaly is only going down by about one percent per year.

And if you look at TB mortality, deaths are falling more rapidly than incidences as treatment is becoming better and more accessible.

HIV-related TB accounts for about a quarter of the deaths due to TB – actually upwards of a third of deaths due to TB, but only about 14% of new cases, so there is a disproportional impact of HIV on tuberculosis mortality.

But nonetheless TB incidence worldwide is high. It's the leading cause of death from an infectious disease, ahead of HIV now globally. And challenging this epidemic is very, very difficult.

Now, in spite of those numbers, the World Health Organization last year announced some new goals called the END TB Strategy. And this shows you what their goals are. And the END TB Strategy shown over here. In this column, these are the Sustainable Development Goals, which are UN milestones for health and development.

But in the next 20 years, the WHO aspires to reduce TB deaths by 95%, TB incidence by 90%, and eliminate any economic suffering of families due to the costs of care for tuberculosis. Now if you look at this, and look at where we are and what our trajectory is, you can conclude that is a very nice aspiration but utterly unattainable. Completely fictional. And there are a lot of things that are going to need to be done if we're going to come even close to reaching these milestones. If you look at the short term milestones of reducing TB incidence by 20% in the next nine years, that's a very, very tall order.

So can we eradicate tuberculosis? Well, as you all know, TB eradication is an aspiration, but infectious disease eradication is extraordinarily difficult. So we've eradicated smallpox. Smallpox, like tuberculosis, only had a human reservoir. We had a vaccine for smallpox that worked even though it wasn't ideal. And through very creative public health strategies, including the famous ring strategy for smallpox cases, smallpox was eradicated from earth, and it's the only human infectious disease that has been, though measles has now been eradicated from the Western Hemisphere, though one plane ride of someone coming to Disney World could change that.

So eradication really isn't going to happen with TB, and I'll show you why in a moment.

Elimination is ending the disease as a public health problem, and for TB that's been defined as getting to an incidence of less than one per million. And that's a log decrease in TB incidence. So it's very, very ambitious.

I'm content with tuberculosis control. And I define that as making it a smaller problem. Making the incidence of TB go down. There was a time in the late 1990s when global health officials said that TB control was working in spite of the fact that the incidence was going up every year. And I don't think you can say that a disease control strategy is working when incidence increases. Incidence is only slowly decreasing, and we need to decrease it a lot more, and that would be good enough for me.

So why haven't we controlled tuberculosis globally? We have the tools, don't we? You know, when I was a medical student we didn't learn about TB because it was assumed it was a done deal. Everything that needed to be done had been done, and people were working on more important things. Except somebody forgot to tell the disease.

So why haven't we done better? Well, globally we've done poorly because global health systems just have not been able to perform. There's been a lack of will. There's been a lack of funding. Lack of commitment. And the health systems that are responsible for controlling TB worldwide just aren't up to the task.

The tools that we have for controlling TB globally are not adequate. They're good, but they're not adequate. The TB sputum smear, which is the most widely used test in the world still, misses half the cases. How can you control a disease if you can't diagnose half the cases?

Adherence to treatment regimens is poor. Treatment for multidrug-resistant TB is very toxic and not particularly good. And the BCG vaccine, the most widely used vaccine in the world, doesn't work. Now you might say it's a good thing – I would say it's a good thing because it prevents child mortality, but it doesn't prevent tuberculosis. It does not prevent pulmonary tuberculosis in adults. It doesn't do anything to stop the spread of TB.

The epidemiologic situation changed in the 1990s and early 2000s with the HIV epidemic and multidrug-resistant TB. And once the genie is out of that bottle there's no putting it back. And for many years global health authorities said we just have to go back to what we knew how to do back in the eighties and nineties and that will solve the problem. Well, the problem changed and now we're confronted with a different reality.

And then finally, for 30 years, global strategies for TB control, unlike strategies for smallpox eradication, were not epidemiologically based. They were humanitarian-based policies. The idea was to save the most lives, and that's a very, very worthy goal, but it's not a disease control strategy because saving lives doesn't necessarily stop the transmission of the disease.

So I'll just quickly review the natural history of TB in individuals and then talk about what that means at a population.

So individuals are infected with TB when they're exposed to an indexed case that has untreated TB. Even though in all of our grant applications we say something different, TB is not that infectious. It's not a highly infectious respiratory pathogen. It's a pretty uninfectious respiratory pathogen. If you have children living in households of TB cases that have gone months without diagnosis, only a third of them get infected. So two-thirds don't. That's awfully good.

Of those who get infected, there can be early progression to disease in the first two years after infection. TB's a slow bug,so instead of an incubation time of 21 days, it's two years. But five to ten percent of people recently infected will develop disease within two years, and 90 to 95% will contain it through host defenses.

For those people who do contain it, over the course of their lifetime if they are otherwise healthy, there's about a five percent risk of reactivating to active TB for late progression of infection. And 85 to 90% of people with TB infection globally never get sick.

So that's the natural history looking at a single exposure and what the course following that might be.

So what are the drivers of this reactivation of tuberculosis? This is something that was done back in 2002 by Ann Oursler, who was one of our Fellows, and she was just interested in the drivers of TB in Baltimore. And you can see that a quarter of our TB in Baltimore at that time was in people with HIV. And we knew that, and we had programs for that. We had outreach. We had screening. We had preventive therapy. But a quarter of it was in people with diabetes and end-stage renal disease. Which we didn't know about. Which we paid no attention to. Which we had no programs for. But diabetes and renal failure are immunosuppressant states. And they're exceedingly common. The prevalence of HIV in Baltimore at that time was less than one percent of the population. The prevalence of diabetes was much higher, and globally is much higher. There are hundreds of millions of people who will have diabetes in the next decade globally. So when you have a underlying condition that increases your risk a little bit compared to HIV which increases it a lot, but it's an exceedingly common condition, you end up with a lot of cases and they end up being important drivers of the epidemic.

So if we look at this in a global sense, we know that we have a reservoir of TB infection of all those people who have been infected but are not yet sick. It's estimated to be about two billion people. I wouldn't quibble about that. It's clearly not accurate. But it's probably correct. It's a pretty decent guess that there are that number of people about in the world who have latent TB.

Every year, six to seven million of those people will develop active TB from reactivation. They will then expose individuals who are uninfected and susceptible to infection, and two to three million of those will go on to develop disease, and they transmit and so forth. But you have this large reservoir of infection.

For 30 years the only global strategy for TB control was finding cases and treating them with the assumption being if you put people on treatment they'll become noninfectious. That's correct. And transmission will end.

So that's good except that by the time cases are diagnosed, they have usually infected ten to 20 people. And so you stop further onward transmission but you've done nothing about that which occurs prior to diagnosis.

If we had a vaccine that worked, that would be great, but we don't. And so TB preventive therapy, to people with latent TB or recently-acquired TB, becomes a very important strategy for controlling the disease.

And you should think about it simplistically. This is a very, very simple model. But even if we diagnosed and treated people much closer to the time that they got sick, the day before they became infectious, and we treated all of them, and completely eliminated transmission, or had a perfect vaccine that protected

everyone 100%, we'd still have six to seven million cases a year arising from latent infection. And until all of those people died, we would not be able to control TB.

If we could treat the people with latent TB before they got sick, that would end the epidemic.

Easier said than done. How do you treat two billion people? And we'll talk a little bit about that in a moment.

So there have been some modeling exercises looking at what do we need to do to better control TB? The baseline shows you where we are now, 1,000 cases per million. We want to get that down to less than one. And we're not getting there very fast.

If we treat active TB only, shown here, to the best of our ability, we can have an important impact, a dent in the epidemic, but we certainly won't get to elimination or control.

If we mitigate risk factors, and that's shown here. If we just improve our mitigation of risk factors. Treat HIV. Treat diabetes. Prevent diabetes. Treat end-stage renal disease. Prevent people with those conditions from getting tuberculosis, we can have a modest effect.

If we treat latent TB broadly, we can have a huge effect, and obviously we have to improve treatment of active TB and latent TB if we want to reach elimination. But this requires new and better tools than we currently have, so this, again, is an aspiration and not a plan.

To simplify it clinically, the way I like to think about it is there are three steps to TB control. First you have to find the TB that's there. Then you have to treat it. And then you have to prevent TB that hasn't happened yet.

Now why is finding TB that is there important? Well like we said, people who have undiagnosed TB transmit. A third of the cases of TB in the world are not diagnosed. What happens to those people? It used to be assumed that they would eventually be diagnosed, it might just take a couple of years, then they'd get treated and then you'd save their life.

But we now know, particularly with HIV-related TB, that a lot of those people just die. They die of TB without diagnosis and without treatment. So that's not a good strategy. And they transmit. And they propagate TB epidemics while they are undiagnosed. We have to improve TB case findings, TB diagnosis.

And we have to treat TB more effectively. Treatment success rates globally are actually much better than they have been for those who do get treatment. They're up in the mid-80% range. Obviously that leads to the higher treatment of drug-resistant TB is (inaudible).

Finally, preventive therapy is really a critical strategy if we are going to get to TB control. Identifying high-risk populations who are at risk for the progression and giving them preventive therapy. Infection control or controlling transmission in healthcare environments is another important strategy. Controlling susceptibility through treatment of underlying conditions. And if some fine day we had a new vaccine that worked, that would be glorious, but right now we don't.

Now this has been a paradigm shift for global health to think about prevention, even though you would wonder why that could be the case. But I do remember a very, very incredible meeting about 20 years ago at the International Union Against TB and Lung Disease where I proposed that treatment of latent TB in Africa be expanded. And I was told that that was immoral by a leading TB control expert in the world because that would be spending money on people who aren't sick and taking it away from spending money on people who are sick, and that's immoral. And I asked – I just want to get the principle straight. So that means giving polio vaccines is immoral until we have enough iron lungs for everybody who has paralytic polio. Do I understand the concept?

But in public health, it's very difficult to spend money on people who are well and not spend it on people who are sick. And TB control programs globally have become medical care programs, not public health programs, and they have to be both.

So I'm not going to belabor the diagnosis of TB. I think it's something that most internists are familiar with and our biggest error is usually that we forget to think about it. We forget to put it on the differential. But, obviously, most people who present with cough, fever, weight loss and night sweats don't have TB in this nation and this hospital, I'm sure. But some do and we have to think about it. We have to look at their epidemiologic risk factors. Where are they from? We have to look at where they might have had an exposure. If they're on an TNF inhibitor like the patient I presented. And then do an appropriate laboratory evaluation. And oftentimes treat presumptively, although that's changing.

Diagnostic tests have advanced in recent years. I mentioned that the sputum smear is used worldwide and its very insensitive. But with nucleic acid amplification tests, we can really diagnose the majority of TB cases literally within two hours, but certainly within a day or two depending on how the hospital's laboratory load goes.

The GeneXpert is a really revolutionary technology that's a molecular biology lab in a cartridge. The cartridge is about the size of an ink jet cartridge that you might have for your printer, but it costs less, as I learned at Staples the other day.

And it's a molecular biology lab that uses PCR in molecular beacons to diagnose tuberculosis and rifampin resistance, which generally equates with multidrug resistance, in about 90 minutes. So this really has had tremendous impact.

The sensitivity is very high. It's essentially perfect for people who have smear positive TB. And it's about 90% sensitive for smear-negative TB for people who have at least three specimens done. But even a single specimen gets 70% of the cases. And there's a new version which is in Beta testing right now that has sensitivity that's essentially 100% for both smear-positive and smear- negative. And if that pans out, then that will truly be revolutionary. We'll diagnose TB the same day in most places.

Another important use of this technology that probably is much more important for us who work in U.S. hospitals is ruling out TB in people. (Inaudible) the differential, but that's not what we really (inaudible) then can we get them out of isolation which, as you know, is extraordinarily expensive.

And this is a study that I'm proud to say my daughter did at UCSF a couple of years ago looking at Xpert, and what she showed was that just using Xpert on sputum reduced hospital isolation days at San Francisco General Hospital from 840 isolation days per year to 35 by using this to rapidly rule out TB where the diagnosis was unlikely but it was possible. So this is a use of this technology that has great benefits for hospitals, actually. It saves money.

The treatment of tuberculosis really hasn't changed much despite my best efforts and others who have been trying to improve it. We really haven't gotten there yet. But the American Thoracic Society, CDC and Infectious Disease Society just published a couple of months ago – actually last month, the updated guideline for treatment of TB. As shown here, there are four regiments, but they're all essentially the same with a little bit of difference in the dosing frequency. But the top regimen, regimen one, is the regimen that's widely recommended and hasn't really changed in about 25 years. It's a six month regimen using a two-month intensive phase with four drugs, and a four-month continuation phase with two drugs. It's recommended that it should be given daily during the intensive phase. It can be given intermittently during the continuation phase, but not for people with HIV or other immunosuppression.

And supervised therapy is recommended DOT.

I want to tell you about another case that presents some other twists. So this was a 27-year-old Mexican man who presented to an emergency room in Baltimore complaining of two weeks of having a cough,

bloody sputum, shortness of breath, chest pain, and a fever. He was a recent immigrant to Baltimore. He had no prior medical history. Said he'd never been sick, never been in the hospital. He said his brother back in Mexico had TB two years ago and was treated.

He was working as a laborer, and he lived in a small apartment with six of his coworkers.

He was on no medications. He was febrile. A little bit (inaudible). His exam was pretty unremarkable, and his initial (inaudible) evaluation in the emergency department was also unremarkable

A chest x-ray showed that he had a left apical (sp) capitary lesion here. And the emergency room doctors placed a tuberculin skin test, collected sputum, which they sent for smear and culture, discharged the patient, and said go to the Health Department Clinic. It was on a Saturday. They said, on Monday go to the Health Department Clinic, and gave him no treatment.

So he came to the Health Department two days later and he had a 35 millimeter tuberculin skin test. His AFB smears were strongly positive on all three of them. But he also had a positive HIV serology. A CD4 count of 268, a viral load of 35,000.

So he was initiated on treatment with a standard regimen. Directly observed therapy. His antiretroviral therapy was deferred because the CD4 count was high. And he did well with conversion of his sputum smears. But his susceptibility testing came back and showed that he had multidrug-resistant TB. He was low-level resistant to isoniazid. Susceptible at high levels. Resistant to rifampin. And susceptible to the other first-line drugs.

So this was a patient with HIV and MDR TB. So his treatment was changed. His isoniazid dose was increased, his rifampin was stopped. Moxifloxacin and streptomycin were added. And after two months he was treated with antiretroviral therapy. And eventually, after about a year, he was cured.

His contacts, which I don't have time to go into today, but they were treated with INH preventive therapy. They were all tuberculin positive. And there is no treatment for MDR TB infection, at least no known treatment, so the hope is that they were infected with a susceptible strain back in Mexico rather than infected by him. But none of them has developed TB yet we know of.

So TB drug resistance has become an increasingly important problem. We define drug-resistant TB as either acquired or primary. Acquired is when someone starts off with susceptible TB, they're treated improperly, either because they don't take all of their medications or they're given the wrong prescriptions, or their drugs aren't absorbed, and resistant mutants are selected and dominate and they eventually become drug resistant. That historically has been the most important route of getting MDR TB.

Primary resistance is where you get infected by someone who has it, and you start off with drug-resistant TB. And this is increasingly important. In the extensively drug-resistant TB epidemic in South Africa, in Kwazulul Natal for instance, over 90% of the XDR TB is transmitted not acquired. People got infected with it, they didn't develop it through bad treatment.

And multidrug-resistant XDR TB, as defined here, XDR TB is just further resistance to the second-line drugs making it even more difficult to treat.

Treating MDR TB is challenging because we use bad drugs that we have to give for a long time, 12 to 18 months after conversion. Although recently the WHO has recommended some short course regimens that can be done for nine months, however it's not likely that these would work for most of the patients that we see in this country, and they certainly wouldn't work for most patients seen in Europe. They do work in some developing countries where there's very little background resistance to the second-line drugs.

In recent years there have been two new drugs approved for multidrug-resistant TB. Bedaquiline approved in this country, Delamanid approved in Europe. And they were both shown in placebo-

controlled trials to improve sputum conversion after being added to a background regimen of standard MDR TB therapy when compared with a placebo.

These drugs are right now not very widely used. In this country they're extraordinarily expensive. In our clinic in Baltimore, to use Bedaquiline, the decision has to be made should we treat this patient with Bedaquiline and fire a nurse, or should we try to find something else and keep the nurse because the budget to pay for it is the budget for the TB clinic. There's no separate drug coverage.

Linezolid is a drug that has great promise for drug-resistant TB. And this is a very nice study done in Korea where patients with what was considered untreatable TB, they were resistant to everything, were treated with Linezolid. And there was a delay – they were randomized to get it immediately or have a delay of two months. And it was clearly very, very active. The problem is that it was also toxic, and we usually give Linezolid for as short a time as possible. In this case you can see that 60% of the patients developed neuropathy within about two to three months of being on Linezolid. And we're currently doing studies to try to find more effective ways of giving Linezolid to have antimicrobial activity but reducing the mitochondrial tocicity that results in the thrombocytopenia, the anemia, and peripheral neuropathy that is seen.

So I'm going to turn now from treating to preventing and talk about latent TB. I'm going to give you another case. This one is a quiz. I'm going to give you a quiz because this is a very common situation. So a 31-year-old anesthesiologist from south India had her pre-employment physical and tuberculin test and had 21 millimeters of induration. She said she'd received BCG as infant. She didn't have any known TB exposures but she did training in public hospitals in India, so she had TB exposure.

She was asymptomatic, non-smoker, no problems. She took birth control pills. She had a normal x-ray.

So the question that we got was, what do we do? Would we repeat the skin test in a month? That was one suggestion. Should we do an interferon gamma release assay test? Shall we just offer her treatment for latent TB infection? Or no treatment needed, she had BCG. I think those are my options.

So I'm not going to make you vote, but this was the discussion. So obviously repeating a TST is of no value because she's got a positive one, and what are we going to say? Oh, that was a false positive and it went away in a month? Not likely.

Should we obtain an interferon gamma release assay? That's the real meaty question. A lot of people would like to use the interferon gamma release assay as the tiebreaker. Should we take someone from south India with a positive PPD, do an IGRA, and if it's negative declare them uninfected?

Or should we just offer treatment for latent TB?

The number four was also false. We may decide she needs no treatment, but it's not because she had BCG because that is irrelevant for treatment.

And so the real question is should an interferon gamma release assay be performed. So let's look into that a little.

So how do we test for latent TB? We used to just use the tuberculin skin test. The principles of diagnosis are all the same, it's just the method is slightly different. So with the TST we do an in vivo injection of tuberculin which has TB proteins in it, and that stimulates immune cells. The bio assay occurs in the arm, and after two, three, four days, the reaction is measured. And if there is a measurable reaction, then that's a response showing that the person's immune system is familiar with these antigens indicating likely infection.

The two interferon gamma release assays, the midget, or the T-SPOT.TB, are in vitro assays where we collect cells from the patient, stimulate them in the laboratory, and then read interferon gamma production either by an ELISA or an LE spot and assay.

So the principles are the same. Now the difference is that the QuantiFERON and T-SPOT use antigens that are not found in BCG and are not found in environmental mycobacteria to which many people, particularly in this part of the world, have exposure. So less likely to have false positive reactions.

So for the tuberculin skin test we have the old and tried and true criteria for calling someone positive at five, ten, and 15 millimeters depending on their risk. And for the interferon gamma release assays, we have definitions that the manufacturers have set that approximate what they think the likelihood of a true positive is. There is no gold standard, and so you can't compare it to a gold standard.

And the sensitivity of these tests if very high, 70 to 90% depending on the population. And they have very high specificity. In someone who is immune suppressed who has been exposed to TB, testing really isn't necessary. They should be treated.

So the problem is that the TST and IGRAs appear to measure different things, though they're used for the same purpose. So this is a study done looking at patients who are entering a clinical trial for a biologic. And what we did is we tested them with TST and a QuantiFERON test. And we found that a small proportion of these patients getting TNF inhibitor therapy were positive. And if we looked at all the positives by either test, you could see that there's only a very small overlap of people who were positive by both tests. And if you look at the BCG-vaccinated individuals, then there were a lot more positive TSTs. And if you looked at the non-vaccinated, there were more positive QuantiFERONs.

But there was discordance. So which one are you going to believe? Particularly in someone who has not been BCG vaccinated.

So can you call the QuantiFERON the tiebreaker? Is that going to decide it for you? Who knows. There's no correct answer right now.

One of the problems is that the interferon gamma tests have a tendency to revert from positive to negative. So this is a study that Susan Dorman at Hopkins led that was done by the TB EPI Studies Consortium, which Mike is a member of. I was a participant. I was one of the healthcare workers subjected to these three tests, TST and these two IGRAs. And you can see that for the two tests, these are the people who had positive results. And the positive results were measured by either the ELISA readout in the QuantiFERON test or the number of spots in the LE SPOT plate, the T-SPOT tests.

And you can see that small proportions of these individuals who are positive, the vast majority were negative by both tests. But of those who were positive, a huge proportion reverted when the test was repeated subsequently. I was someone who reverted, but I reverted administratively when they changed the definition of a positive test and they reclassified me from being positive at eight spots to negative at eight spots. Although I'm counted here as positive with my eight spots.

So these tests have limitations. And right now there's a debate raging about whether they should be used for screening healthcare workers. If there's such a high reversion rate, you know, how do we interpret that?

So the tuberculin skin test is a horrible test. You have to inject it. The person has to come back. It has to be read. You can inject too deep. You know, it doesn't create a reaction that can be measured if you inject too superficially, it leaks out all over the skin. It's a crummy test. But these tests are not necessarily the perfect answer. They have limitations. And so you just have to choose and deal with the consequences of the choice. What the CDC recommends is pick one and stick with it. Don't go back and forth between them trying to outsmart yourself.

So talking about latent TB, when you have people with latent TB, treatment of those at high risk is an important strategy for preventing the disease and controlling the epidemic. So clearly we know that the groups at highest risk where the benefit of preventive therapy is greatest is people with HIV. Their risk of TB is hugely increased compared to anyone else in the world.

Contacts of TB cases, we know that they have a high risk of disease, five to ten percent. That's considerable for a disease like TB.

And people starting biologics, TNF inhibitors and so forth.

And then there are these other groups for which the data are less good but where there are instances where preventive therapy is a really good strategy. In Baltimore we've done widespread treatment of injection drug users without HIV and appear to have had a very marked impact on the TB epidemic of drug users in Baltimore. Some cities have done treatment of the homeless. Recently in Seattle there was a nice project to treat the homeless. But the top three groups are the ones who really, really benefit from preventive therapy.

The U.S. Preventive Services Task Force has recommended that TB screening – latent TB screening and treatment – be done for high-risk individuals, and this is important for many reasons including for reimbursement.

The current recommendations from the CDC for treating latent TB are the standard, now 60-year-old isoniazid given for nine months of once a day or six months as an alternative. Not quite as efficacious, but certainly there's better adherence.

Rifampin can be given for three to four months, and that appears very efficacious.

And then the latest addition to the armamentarium is a 12-week course of rifapentine, a rifampin-like drug with a longer half life and greater potency than rifampin, with isoniazid given once a week. And that was shown in a study done by the TB Trials Consortium, a prevent TB study, to be non-inferior to isoniazid for nine months, but as I'll show you in a minute, non inferior is actually better than that. And this was a study done largely in the U.S. in people who were either close contacts of a TB case and a positive tuberculin test. That was about two-thirds of them. Recent converters that included some of the close contacts. And then people with HIV or people who had radiographic scars with fibrosis and a positive tuberculin skin test who we know are high risk.

And they were randomized to these two regimens, about 8,000 individuals.

And this is the TB incidence in this trial. And you can see that the lower line is the rifampin INH regimen. And it was designed as a non-inferiority study saying this is no worse than INH but we can see with a P value of .06, it was morally better. I'm happy to accept .06 as superior. So it was actually superior to INH. And it was less toxic. There was significantly less hepatotoxicity, just a half a percent, versus three percent with isoniazid. And hepatotoxicity is the main reason that many physicians don't like using isoniazid prophylaxis. They don't want to risk someone developing a potentially fatal reaction.

So I'm going to end there and just summarize that there is a global aspiration for TB elimination, but ain't likely in my lifetime, nor in yours. But TB control in the U.S. is certainly attainable. And TB control globally I think could be attainable with more investment.

Internists and primary care doctors I think play a really important role, and particularly in this country at this time in the epidemic. That we have to diagnose active TB in the people who have it, but that's a rare event for most clinicians. And what's more important is identifying people at risk and diagnosing and treating latent TB infection in those individuals. And that is what is likely over the long run to have the biggest contribution to controlling TB here in the U.S. and controlling it globally.

So with that, I'll end, and thank you very much for having me.

So we'll take any questions. Nicole?

Yes, hi. Thank you Dr. Chaisson.

So just in that very last graphic you showed, it shows that dual therapy was superior. The curves are still showing up, but in the direct curve there it is definitely flatter though. But this is still going out to the INH so that suggests that we have perhaps low-level resistance that's going on that's accounting for that?

Not in this study, no. Oh, I'm sorry. I'm going to repeat the question.

Yes, sorry. For those of you at home – I'm sorry. For those of you at work, the question is, in this rifapentine versus INH study, the curves are going up and was that a result of low-level resistance or resistance. And the answer is no, not in this study.

You know the risk – this was a study that only followed people for two-and-a-half years, and after two-and-a-half years, you know, that was the end because the risk is thought to be within two years. So there was a bit of a margin given. But when you have the HIV-infected people, their risk is not within two years, so that was a limitation to the study. And you have people with abnormal chest x-rays, their risk is not within two years, it's really within five or more. So there is continuing occurrence of disease. And for the INH group in particular, a lot of that is in people who never actually completed it. So you're seeing them continue to develop disease, and a lot of them – the completion rates for the INH were only about 60%. Which is what happens in the real world, because it was a real world study.

(Inaudible) so how good is the data for (inaudible)? And what drugs, how long to treat, and how good is the data in that situation?

Okay, so the question is how good are the data for people starting on therapy with a TNF inhibitor and getting treatment for latent TB. They are pretty good. And the experience was that when drugs like the etanercept and adalimumab were first used, there were all these reports of disseminated TB, fatal TB, and people who were getting it. And so the American College of Rheumatology started issuing guidelines for screening and prevention. And the companies that were developing these drugs and doing clinical trials implemented screening as part of them, and in the clinical trials, I was asked to help with a couple of them because, you know, these were rheumatologists who didn't think about TB and didn't know what to do but knew that these drugs were wonderful and hated to see them ruined by people getting TB.

And when screening and prophylaxis with isoniazid for six to nine months was instituted, essentially it eliminated the cases. You just don't see them. You only see them when people don't get latent TB treatment.

And in the clinical trials, the only requirement was the people be screened and put on treatment before they start their drug. Didn't have to complete it. So that's what's recommended. The CDC recommends that. The American College of Rheumatology recommends that. Screen them and start treatment and then you can give them their biologic and the risk is essentially eliminated. There's no such thing as always eliminated. But very, very effective. I think the data are pretty good.

Peter, you've been waiting patiently. Go ahead.

(Inaudible.) in Nashville. Every new patient that was admitted to our teaching hospital, our city hospital, and VA who were not known to have been convertersreceived a skin test. Now, of course, not so much. The question I have for you, given the fact that our population of inpatients now is so rich with immunosuppressed patients, such as patients with diabetes, do we need to go back to the 1970s?

So should we go back to the 1970s and test everybody who is admitted to the hospital? Well, I think the answer to that question lies in the CDC guidelines that were published in 2000. They're being updated. You're involved in that, I know, so –

They're in clearance.

well, I shouldn't say. We're broadcasting live.

The new guidelines have been in development for four to five years, and there have been great battles. But the wisdom of the last set of guidelines in 2000 was only test people in whom you're going to do something. If you're not going to do anything about it, don't test them. You wouldn't get, you know, an exercise EKG, or, you know, a test in someone you weren't going to do anything about. That you don't think has the disease. So only test people where if they have a positive test you will treat them. And so the question is for people who we admit who are on biologics, should we test them. Yes, if they haven't been already. Someone who is on, you know, etanercept or one of those drugs, I say etanercept because it's the easiest one to pronounce, then if they haven't been tested, they should be because they're at risk if they're infected and we can do something about it.

What about diabetes? There's a big debate right now, and the WHO and the CDC have decided at this point, although the new guidelines may change that, I'm not involved so I don't know, but that diabetes per se is not yet an indication for treating latent infection despite the data showing that it's an important driver of TB globally. And it's largely because there's an absence of studies on the efficacy and on the safety of that population.

So you could do that as a clinician, you might say, boy, this patient has diabetes, they have latent TB, particularly if they are from a high-risk environment, if they're an immigrant from a high-burden country, sure, that would be very, very reasonable to do. Should you do it for everybody? It's not currently recommended. And we did a study at Hopkins (end audio)