

Slides: Double Trouble: The Surprising Connection Between Diabetes and Tuberculosis, NDEP Webinar Series

JM: Good day. Welcome to today's webinar, hosted by the National Diabetes Education Program (NDEP). This is Jude McDivitt, the National Diabetes Education Program director at the CDC, and I will be your moderator. NDEP is a joint program of the CDC and the National Institutes of Health that involves a range of partner organizations from the local to the national and international levels. The goal of our webinar series is to provide those working in diabetes with the latest science and effective strategies to help them address diabetes and diabetes prevention in their communities.

Slide: Objectives for Today

Today's webinar may introduce something that is new to many of you. They will be discussing the connection between tuberculosis and diabetes and also opportunities for collaboration. And we call it "Double Trouble."

Slide: Continuing Education

A few housekeeping details, I am very happy to inform you that there will be continuing education credits for today's webinar. Information about how to claim the credits will be provided in a downloadable handout in a follow-up email that you'll receive after today's program. Today's presenters have no conflicts of interest to disclose.

Slide: Today's Presenters

So, let's get started. Today, we have two diabetes and tuberculosis experts who will present and answer questions. Dr. Sundari Mase is the team lead for Medical Affairs at

the CDC's Division of Tuberculosis Elimination in the Field Services and Evaluation Branch. She supervises all field medical officers' staff. She also serves as a liaison to the four regional training and medical consultation centers for medical consultation activities and provides technical assistance and consultation to all states and local tuberculosis control programs.

Prior to joining the CDC, Dr. Mase was the deputy health officer and physician TB controller at the Santa Clara County Public Health Department. She received her medical training from the University of California in San Francisco, where she also completed her residency.

Dr. Richard Brostrom is the CDC tuberculosis medical officer for the Pacific region and the branch chief for the Hawaii State Tuberculosis Program. Before this, he worked as a family practitioner, caring for many thousands of Pacific Islanders with diabetes. He served for 10 years as the medical director for public health for the Commonwealth of the Northern Mariana Islands, where he restructured the diabetes program and led many advancements for the Department of Health. He has worked to improve care for TB and diabetes patients since 2005. He co-authored the WHO "Framework for the Care and Control of Tuberculosis and Diabetes" and created novel TB-diabetes standards for the Pacific Island jurisdictions. This year marks his 20th year of working in the Pacific Islands.

We will start with Dr. Sundari Mase. So, Sundari, please take it away.

Slide: Double Trouble: Tuberculosis and Diabetes, Opportunities for Collaboration

SM: Okay. Thanks very much. This is Sundari Mase. I'm the medical team lead at the Division of Tuberculosis Elimination in Field Services. And I want to thank the Division of Diabetes Translation, as well as the National Diabetes Education Program for inviting us to speak on this very important topic of tuberculosis and diabetes.

Slide: TB-DM: Opportunities for Collaboration

So, over the course of the next hour and 15 minutes, Dr. Brostrom and I are going to touch on the following topic areas; I'm going to cover a few of the basics about tuberculosis, to sort of set the background, and then I'm going to give an update on the current epidemiology of both tuberculosis and diabetes. Then, Dr. Brostrom will give an update on TB-diabetes literature, as well as discuss current collaborations and future opportunities for partnership. After that, we'll be presenting a few cases.

Slide: What is Tuberculosis (TB)?

So, let's start by talking about what is tuberculosis. Tuberculosis is a disease caused by bacteria that usually affects the lungs--and it affects the lungs in the majority of people, about 85 percent--but TB can affect any organ system in any part of the body. In fact, it's very common to find TB in the lymph nodes, in the brain and central nervous system, the bones, kidneys. And we can even find TB in very unusual places, such as the eye or the skin.

TB disease is entirely curable if it's treated properly with the correct medications and with directly observed therapy, but it can be fatal if not treated properly. In fact, there are approximately 1.5 million deaths reported to WHO annually as a result of tuberculosis.

Slide: How is TB Spread?

TB bacteria is spread from person-to-person through the airborne route and can be transmitted through coughing, singing, sneezing, shouts, laughs-- anything that aerosolizes the organisms. These actions spread the TB germs into the air, where they can then be breathed in by another person and can lead to infection and potentially disease.

Slide: Image of Person Sneezing

Here's a great picture showing what aerosolized particles look like when a person sneezes. And as you can see, you know, billions of particles are let loose into the air when someone sneezes, and TB bacteria can be part of this and can remain in the air for a period of time, during which time others can breathe these organisms in and become infected.

Slide: TB is NOT Spread by Sharing

TB is not spread by sharing other items, such as papers, pencils, books, desks--you know, certainly not through food or eating utensils. So, we need to be really clear that these are not risk factors for getting tuberculosis.

Slide: There are Two Forms of TB

There are two forms of tuberculosis: TB infection and TB disease. About one-third of the world's population, one out of three individuals, is latently or silently infected with the organism. The organism is very good at living in the human host. Of these, one-third of the world's population, about five percent, will go on to getting active TB disease over the course of a lifetime--5 to 10 percent, that is. And I'm going to break this down for you in a few minutes. And we're going to explore what the difference is between TB infection and TB disease.

When a person has TB infection, they're generally not symptomatic, and they usually have normal exam findings and normal chest X-rays. And they cannot transmit tuberculosis to another individual. But then when a person becomes sick with TB disease, and they're symptomatic with coughing and other--fever, weight loss some symptoms we'll be talking about shortly--they generally have an abnormal chest X-ray if they have pulmonary tuberculosis. And a medical exam could be abnormal. And they can transmit TB to another person.

Slide: TB Infection (Image of Person Receiving Skin Test)

So, TB infection is tested for either using a tuberculin skin test, which many of you, especially those of you in the health care industry, have probably had. And a tuberculin skin test or the blood test--Interferon Gamma Release Assay--will be positive generally when a person has TB infection. This means a person has breathed in the bacteria --that is, by exposure to some other person who has TB and has a test that's positive, either tuberculin skin test or the blood test, but they're not symptomatic, as we discussed.

Slide: TB Infection (Image of Lungs)

When, as we discussed, a person has TB infection, the chest X-ray is generally normal and there is no evidence of TB on the chest X-ray or by exam.

Slide: TB Infection (Image of Granuloma and Tubercle Bacilli)

So, again, to review, the person breathes in TB bacteria, the TB skin test is generally positive--usually, I would say in about 80 to 90 percent. The chest X-ray is normal. The person's immune system has generally contained the TB bacteria on its own, and the bacteria are sleeping. And in fact, you can see, right here, the bacteria that are walled off in a granuloma. A granuloma is formed by the immune system and walls off these bacteria. A person is not sick, not infectious or contagious. And, of note, there is medicine that can be taken at this time to treat the infection, kill all the TB organisms and prevent TB disease from occurring in the future. And that's what we do here in the United States, is we try to find people who are latently or silently infected with the TB organism and the bacteria and treat them to prevent them from ever getting active or TB disease.

Slide: TB Disease

TB disease, however, occurs when a person's breathed in the TB bacteria, but the immune system doesn't contain the TB bacteria. This can happen right away, when the person is exposed and infected, within two years, or it can happen much later in life, when, for whatever reason, the TB bacteria might wake up. This can be due to conditions like diabetes or HIV or other immunosuppressive conditions, but it also can happen in someone who has a completely normal immune system.

So, when a person has TB disease, they breathe in the bacteria. They generally also have a positive tuberculin skin test or blood test. The immune system does not contain the TB bacteria. Generally, in 85 percent, as we saw, they have an abnormal chest X-ray, like this X-ray that we see here. In this X-ray, you can see that there is a lot of disease here, the right upper lung or right upper lobe. And here, you may see the outline of a cavity, which is very common in tuberculosis. And there may even be some abnormality in the other side, with some fluffy sort of white infiltrates here. And there is some volume loss, shifting the trachea to the right side.

So, the person usually feels sick. They're coughing, fevers, weight loss, night sweats, things like that. And if the TB is in the lungs, as in this case, and the sputum is positive for TB, the person may be contagious, or infectious, and is able to give TB to another person.

Slide: Symptoms of TB Disease

Here are the symptoms of TB disease that are most commonly seen: prolonged cough of greater than 2 to 3 weeks duration, often productive, but can also be a dry cough. We consider this a chronic cough. They can cough up blood. We call this hemoptysis. Feel

just generally weak or constantly tired with fever, night sweats, loss of appetite, and as a result, weight loss and even chest pain.

Now, weight loss is one of our very objective findings of TB. In other words, it's something that is measurable. It can be followed in the clinic. But of note, weight loss can happen for many chronic conditions. Tuberculosis is only one of those.

Slide: TB Infection vs. TB Disease

So, looking quickly at some of the differences that we just discussed between TB infection and TB disease, we can see that in both conditions we have TB bacteria in the body, both conditions the tuberculin skin test or blood test is positive. But the differences are that the chest X-ray is usually normal when a person has TB infection, whereas it's usually abnormal when a person has TB disease. Sputum specimens are negative if collected when a person is silently infected. Whereas, if a person has pulmonary active tuberculosis disease, sputum specimens would be positive.

A person with latent TB, or silent infection, would have no symptoms and be considered noninfectious. Whereas a person with actual TB disease would have the symptoms that we discussed and may very well be infectious. And it's considered a case of TB.

Slide: TB Infection to TB Disease

So, what happens when a person goes from TB infection to TB disease? And what are the percentages? Well, for healthy people--healthy adults--if you have TB infection, like a positive TB skin test and normal chest X-ray, and again one-third of the world's population falls in this category, your highest risk of going from infection to disease is in the first two years after you got exposed and infected with the organism. After the first two years, the risk goes down and the lifetime risk thereafter is about five percent total. So, you have a 10 percent total lifetime risk of developing TB disease, unless of course,

you take the medication that's given to you for TB infection to prevent you from going on to active TB disease.

Now, the risk of developing TB disease is higher for people who have weakened immune systems, like the conditions we've listed here: children under five; people with diabetes, which we're going to discuss; and other forms of immunosuppression, like cancer, HIV, or kidney disease.

Slide: TB Infection to TB Disease (Schematic)

So, here's a schematic describing just what we said-- that the first two years you may have a five percent risk of going on to TB disease. That's the highest risk period. And then after the first two years, you have a lifetime risk of, again, approximately five percent.

Slide: TB Pathogenesis Progression to TB Disease

Here's another schematic that kind of gives an idea of the differences in your risk of progressing to TB disease, depending on your underlying risk factors, medical risk factors. If you have no risk factors, we just said you have about a 10 percent lifetime risk. However, you can see if you have HIV infection disease with TB infections, you actually have a risk of 7 to 10 percent per year, meaning that within a 10-year, 0 to 12-year period, you will definitely go on to getting TB disease if HIV infected and not on treatment for HIV. Treating HIV definitely significantly decreases this risk of progressing to TB disease.

And diabetes, recent studies--and there have been many now--suggest that there is a 3 to 4 times increased risk of progressing to TB disease if you're a diabetic. The hypothesis is that if you're poorly controlled, this is probably even more likely to be the case. And there is some data to suggest that. But there is definitely more research needed in this

area. Definitely a 3 to 4 times increased risk of going from TB infection to TB disease over time.

We do have a question: *Can you be re-infected after you're cured?* In other words, whether you have a silent infection or you actually had TB, you could definitely be re-infected, if once again exposed to somebody with active TB, you breathe in the TB bacteria. Those in the field of TB think it's less likely, because your body has innate immunity at that point, having once been infected or once had TB disease. However, we do see re-infection, and it has been reported and shown with data looking at the genotypes, the genetic types of TB organisms showing that people can be re-infected. And, in fact, if HIV infected, you're much more likely to be re-infected with different strains due to the immune-compromised state.

Slides: Poll 1 and How Familiar Are You With the Risk of TB Disease in Your DM Population? And Poll Results

So let's go to our first polling question, and it really sort of looks to your program and where you are and ask how familiar are you with the risk of TB disease in your diabetic population wherever you work, whether it be clinic, hospital, you know, outpatient, inpatient setting, public health department? Please do weigh in. And the choices are *never heard of interaction, you're somewhat familiar with the risk of TB disease in your diabetes population, or very familiar*. Looks like the majority of people, close to 50 percent, are somewhat familiar with the risk of TB disease in their population. About one-third of you who responded are very familiar. And a good close to 20 percent never heard of the interaction. Very interesting. Thank you for your responses.

Slide: TB-DM: Opportunities for Collaboration

So, let's see, we have a couple of more questions. Let's see, we have Dr. Brostrom on the line. Dick, do you want to respond to the question *is the risk of progressing to TB disease higher among diabetics as compared to HIV?*

RM: Sure. The data is pretty clear that the risk for progression from latent disease to active TB is stronger among people with HIV disease. There's probably there's very little doubt about that. But there are a couple of studies that showed, particularly for younger diabetics who are newly infected, and poorly controlled, their risk almost comes close to approaching that of HIV in one study I know that was done in southern Mexico.

SM: Great, thanks. One other question: *Where is TB bacteria most commonly found?* Well, in the lungs of people who have TB disease. That's where TB bacteria are most commonly found. I think that might be the question. In other words, TB bacteria just don't live in the environment. But we do have some zoonotic hosts as well. I mean, we see TB in cows, we see TB in badgers, we see TB in elephants. Different animal species.

Slide: Epidemiology

In the interest of time, I'm going to go through the epidemiology fairly quickly. Just want to note that it's really important to study epidemiology because, you know, you really want to see where the pockets of TB infection disease are so you know how to target your efforts to the right populations.

Slides: Worldwide Diabetes Prevalence and the Global Burden of TB-2012

Looking at world-wide diabetes problems, this slide really just shows that since 1995, we've had a huge increase in the estimated prevalence of diabetes worldwide affecting, really, every continent. And you can see monumental increases all over the world. Now and these are projected, projected to 2025. And it looks like it's definitely on the rise. So, if you look at the global burden of TB, this is a slide from 7/12, approximately nine

million new cases, reported WHO, of all forms of TB annually. You can see about half a million are occurring in children. And it's about 1.3, even up to maybe 1.6 million deaths attributable to TB. And 74,000 of which are estimated in children. HIV-associated TB has accounted for approximately 13 percent or a million cases and approximately 320,000 deaths. And you can see drug-resistant TB is a big problem as well.

Slides: Reported TB Cases United States, 1982-2014, TB Morbidity United States, 2009-2014, TB Case Rates, United States, 2014

In the United States, we've been very fortunate with our strong TB control program, since 1993, to have a downward trend in our TB cases that has been tapering off, but we've had a decrease in cases every single year, 2014 with the lowest number of cases of 9,421, which actually translates into about a rate of 3 per 100,000. It's very low compared to some other parts of the world. And, as you might imagine, California, Texas, the Northeast, Alaska, and the Pacific Islands have the highest TB case rates-- greater than national average of 3 per 100,000. And we'll see some reasons for that.

Slide: Map of U.S.-Affiliated Pacific Islands by TB Case Rates, 2014 (Guam, and Map of U.S.-Affiliated Pacific Islands by TB Case Rates, 2014, (United States Overall at top of slide)

I just want to quickly note that where Dr. Brostrom works, in the U.S. Affiliated Pacific Islands, we have some of our highest TB case rates, as evidenced by this slide, showing that in the United States overall, we have a rate, as we just said, of 3 per 100,000. However, you can see in the Marshall Islands, that rate is in excess of 200 per 100,000. And you can see the different percentages, with actually, Hawaii being about close to 10 per 100,000.

Slide: TB Case Rates by Race/Ethnicity United States, 2003-2014

If you look at TB case rates by race/ethnicity, we do see that TB rates are lowest in white population and then sequentially higher, as you can see, going from American Indian or

Alaska Native, but highest in the Asian population. I just want to note that this probably reflects the TB rates found in the countries of origin from which our patients are coming.

Slide: Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States -1993-2014

And this slide I put in mainly just to show that the number of TB cases has been decreasing every single year in U.S.-born populations, as evidenced by the blue bars, but have been pretty consistent in terms of the number of cases in our foreign-born populations. And as of the early 2000s, our foreign-born case numbers increased over U.S. born, and that trend has been increasing.

Slides: Trends in TB Cases in Foreign-born Persons, United States, 1993-2014, Percentage of TB Cases among Foreign-born Persons, United States 204, 2014

And this slide shows pretty much the same thing--that the number of cases that are foreign born, as a percentage of the total number, has been sort of steadily increasing over time, as you can see here. And now, almost two-thirds of our cases this last year are occurring in foreign-born individuals, suggesting that we need to redouble our TB control efforts in that population. This slide shows the difference in the map in terms of the states that are reporting greater than 50 percent of their cases occurring in foreign-born individuals. You can see that in 2004, about half the states reported greater than 50 percent occurring in foreign born, 2014 closer to 80 percent of our states are reporting greater than 50 percent of cases occurring in foreign-born individuals.

Interestingly enough, if you looked at risk factors for TB in the United States from 2012, and keep in mind these are self-reported TB risk factors, in other words, people aren't being tested for diabetes or tested for HIV or renal disease. It's self-reports. Even given that, over and above the other risk factors, diabetes stands out with just under 1,500

cases out of those total number of cases of approximately 10,000 that we saw self-reporting diabetes, suggesting it's a big risk factor.

And if you look at the number and percentage of the U.S. population with diagnosed diabetes, this is really epidemic. I mean, you can see how both the percentage of our population with diabetes as well as the actual numbers are rapidly increasing, and that rate of increase has gotten much steeper over the course of the last 15 years.

Slide: Adult TB Cases

As you take a look at the adult TB cases of diabetes in different parts of the world and then in the United States, you'll see that about a little over 20 percent of TB cases had diabetes in India, much higher here in neighboring Mexico, about 36 percent. The U.S., overall, somewhat around 14 percent. But look at some other regions of the U.S., for example, south Texas is exceeding the percentage of cases with DM, exceeding Mexico in that statistic. And you can see our own Pacific Islander population, over 50 percent of TB cases also have diabetes. I would say that diabetes is really driving TB in in the Pacific Islands.

Slide: TB and Diabetes in Kiribati

We performed a study in the non-U.S.-affiliated Pacific Island, Kiribati, about three or four years ago. The setting was in the capital of Kiribati, South Tarawa, where the TB rate is estimated in 2013 to be 378 per 100,000. That's over 100 times the rate here in the U.S. mainland. And the rate of diabetes is extremely high as well, with approximately 30 percent of people aged 20 to 79 having diabetes. So, we thought it was a good place to study both diseases. So, we enrolled patients prospectively who developed TB in the community over the course of about a year and a half and ended up

enrolling 275 TB patients. And we had age, sex, and other demographics, as well as a geographically matched control from the community and were able to get 499 controls.

Slide: Impact of Diabetes on TB in Kiribati: Summary

And what we found was TB was diabetes was much more common in the people who developed TB prospectively the island of Kiribati than in those that did not develop TB. We calculated the additional burden of TB attributable to diabetes was 25 percent. Additionally, the burden of infectious TB, that would be patients with positive smears among people with diabetes, was significantly higher, impacting TB transmission in the community. And we found that a lot of undiagnosed diabetes simply by testing people with a point of care test for diabetes.

Slide: TB and Diabetes in Kiribati

So, in summary, although there were 275 cases, 100 of them had diabetes. There were approximately 500 controls and about the same number had diabetes. So, about so, diabetes was twice as more likely in the patients who developed tuberculosis over the year and a half. And, more, most importantly, lots of diabetes was diagnosed by the screening.

Slide: TB Treatment Outcomes

Outcomes in terms of chest X-rays, findings in sputum conversion, in other words looking at response to treatment, were not much different at two months. But other studies have found big differences with diabetic patients, lagging nondiabetic patients in terms of TB response. Response to TB treatment and eventual outcome, that is. And we felt that our sample size was rather small to detect these differences.

Slide: Pacific Bi-directional Screening for TB and DM

So, quickly to mention bi-directional screening--in other words, the screening of patients in TB clinics for diabetes and the screening of patients in diabetes clinics for TB. I want to note what the impact is in the countries that are noted here: Kiribati, Fiji, Marshall Islands, and the Federated States of Micronesia. You can see when tested or asked, the proportion of TB patients with diabetes is quite high, as high as 45 percent in the Marshall Islands. And of note, if you remember from my previous slide, the Marshall Islands also had a TB case rate of 200 per 100,000. You can see that similarly, these other countries have very high proportions of TB patients that have diabetes.

And in the screening of patients in diabetes clinics for TB is actually very yields quite a bit of TB as well. In the Marshall Islands, and Dr. Brostrom will speak to this more, five percent of asymptomatic patients sitting in diabetes clinics tested for TB were newly diagnosed with TB disease. It's incredible the amount of case findings by just simply testing patients in diabetes clinics for TB with a tuberculin skin test and then an X-ray. So, this is something that we will be highlighted more by Dr. Brostrom.

And then in the Federated States of Micronesia, you can see that three percent of patients were diagnosed with TB disease, but a further 25 percent had evidence of latent or silent infection.

Slide: Impacts of DM on TB Control

So, you know, we need to be really aware of the sort of syndemic of diabetes and TB and note that diabetes is driving TB and TB outcomes, poorer outcomes all over the world. And this high increase in diabetes prevalence is really going to have a negative impact on TB control efforts. So, we need to really focus our efforts in controlling both TB and diabetes, as they both affect each other. In 2013, an estimated 15 percent, or nearly one out of every six TB cases of the disease, were attributed to diabetes, which corresponds to over a million cases of diabetes associated with TB per year.

Slide: 2010: WHO Collaborative Framework for Care and Control of TB and Diabetes

And so, WHO, of course, has also been very interested in having impact in this area. And there's a collaborative framework for care and control of TB and diabetes that was put out in 2009. It called for to establish mechanisms for collaboration, to detect and manage TB in patients with diabetes, and conversely, to detect and manage diabetes in patients with tuberculosis.

I'm going to turn this over to Dr. Brostrom to continue from here.

Slide: TB-DM: Opportunities for Collaboration

RB: Well, before I start, I just want to say that since 2006, we've sort of been pushing TB programs to manage and help with the diabetes issues, but this is really one of our first chances to speak to U.S. diabetes experts. So, we're really grateful for this opportunity to reach into diabetes clinics, primary care clinics, and we hope that this is valuable for you all.

Slide: Real People

Okay, the third bullet there is a brief research update. And we'll fly through some of these slides. Here is another representation of the current TB or the diabetes epidemic. This is from the International Diabetes Federation Atlas. That's a great resource for us. And what stands out for us in TB control is India, which has long been our TB capital of the world, with over two million TB cases every year. And it was the diabetes capital of the world as well until last year, when China redid their numbers and has eclipsed them.

Two more things I want to say about this is, first of all, the dark lines there are people who are currently living with diabetes who are not yet diagnosed. And so, you guys in the diabetes world certainly have no shortage of cases. And it's important to remember that these rates will double by 2030, and 70 percent of those new cases will be in low

and middle income countries, where TB is often poorly controlled. Areas where there's lots of immigration to the United States.

Slide: Table 2.3 Undiagnosed Diabetes (20-79 years) by IDF Region and Income Group 2013

The not-yet-diagnosed patients are also a problem, even for us here with advanced health care systems in North America, where in nearly 30 percent of people with diabetes remained undiagnosed by WHO estimates.

Slide: Double Trouble: TB-DM Lit Review

So, when I discuss TB/diabetes literature, I like to divide the research, really, into three main areas. First, I should say that there's kind of an exploding literature volume for those first two questions. *Does diabetes cause TB* and *does diabetes affect TB treatment?* For question number three, there's actually almost nothing, and we're working to improve the literature basis for that one.

Slide: Risk Factors among Foreign-born With TB infection in CA (2012)

Let's take a look for the first question. Here's a slide I stole from California, from Pennan Barry and from Jenny Flood and this this shows risk factors among the foreign-born with TB infection. And the classic TB risk factors are the ones up in the upper right-hand column, with HIV, ESRD, folks with rheumatoid arthritis that may or not be on TNF Alpha Inhibitors. And we can see, though, that all of those risk factors amongst in our foreign-born folks are, are eclipsed by a very large pool of people with diabetes. If we added smoking to this, which, which is also a TB-risk factor, we would also see further eclipse of the traditional medical risk factors for TB.

Slide: TB-DM: Diabetes Control

In the past, we've sort of ignored diabetes as a risk factor in the TB world, but it's clear that it affects our TB world now. But the question is: *Is there really an association?* And I think this next study provided us with a great example to clarify that for us. This is for 40,000 people who live in Hong Kong. And what it showed us that on the X-axis you can see time is about seven years of follow-up. And then there's the cumulative hazard of getting TB on the Y-axis.

Slide: TB-DM Diabetes Control A1c>7

So, we can see that for diabetes, there's a there's an elevated risk of TB versus people without diabetes. But the author then looked more closely. And what we found was something that you folks in the diabetes world will not be surprised by. And that is when you look at the level of glucose control, there is a remarkable variation, very clear, in TB risk among those who were poorly controlled, with an A1c greater than 7, and those who were very well controlled, with an A1c of less than 7. And it's pretty clear to us that it's actually not diabetes that's related to the risk of TB, but poorly controlled diabetes that is related to the risk of getting TB.

Slide: National Estimates of TB and Diabetes, 2013 (Sierra Leone, top left)

Now, there's various studies that show this linkage is not consistent around the world. So, here is a graph I put together of national estimates of TB and diabetes. And again, the left axis shows the estimated TB prevalence and the right axis shows adults over age 20 with diabetes. And you plot every country in the world and it looks like this, and I would call that an epidemiologic dog's breakfast. Don't worry, you shouldn't really get anything from this slide, except maybe to take a peek at our little islands out there at in the high-risk zones.

Slide: National Estimates of TB and Diabetes, 2013 (Marshall Islands, top right)

But, if we, if we subtract those countries that have less than five percent of diabetes and the countries with less than 30 per 100,000 of TB, and we plot this on a log scale, then it starts to make a little bit of sense. And we can see some areas where the TB-diabetes mix is strong. For us in the U.S., this highlights the high-risk countries for TB and diabetes that immigrate commonly to the U.S., both the Marshall Islands and other Pacific islands, Philippines, India, other Southeast Asian countries, you can begin to find on a graph like this.

Slide: Hawaii Adult TB Cases with Diabetes

For TB cases, it's not required to be tested for diabetes. We like to ask them, but the national requirement is not to test, at least not yet. But in the Pacific, we routinely test all TB cases for diabetes. And you can see before 2012, we simply asked the question, a few people got tested. But we instituted a universal testing with an A1c, and then we actually uncovered what our actual diabetes rate is, and it's much closer to 40 percent among our adults. That reminds me to say that for TB programs, the question should never be, "Do you have diabetes?" The question really should be, "Would you please hold your hand out so I can test you for diabetes?" because there's so much silent disease.

Slide: Adult TB Cases with DM in Hawaii; 2014

And when we do this, we also find that the rates of diabetes are quite different among TB patients, depending on where they were born. For U.S. born, it's around 20 percent, and I venture to say we would find this result with universal testing in the U.S. I think it would be close to that number, not just in Hawaii but also across the U.S., if we indeed did testing.

For other Asian countries, we find around 38 percent. In the Philippines, which is a major source for TB/diabetes and about 90 percent of our TB cases or 70 percent of our

TB cases in Hawaii. That's close to 40 percent. And in the Pacific Islands, it's well over 50 percent.

Slide: TB as the “Diabetes Defining Illness”

As you mentioned, there's lots of diabetes that's poorly diagnosed, and when we test all of our TB patients, we find that those TB patients under age 50, almost half of them did not know that they had diabetes in the past.

Also, you should know in our population, the average A1c is about 8.7, which I know is terrible. And, of course, TB recruits from a population with, with in general poor access to care we do understand that the semi-acute nature and the delayed diagnosis and the prolonged infectious periods may cause an artificial elevation of A1c in these patients who are sick.

Slide: Double Trouble: TB-DM Lit Review

So, there are many studies that confirm Question 1. And it's sufficient to say, the answer is yes. Diabetes triples the rate of going from a positive skin test to full-blown TB disease.

Slide: TB and Diabetes: Case Management

What about diabetes affecting TB treatment? Does diabetes affect our ability to cure TB? Does diabetes increase the risk of relapse? Well, before we get to that question, I do want to say that these cases are harder to treat. We see that people with TB and diabetes together have more atypical TB presentations. That means we find the pneumonias in various places, lower lung disease, and not typically the classic atypical disease that we see in a non-diabetic. There are a multitude of medication interactions, especially with sulphonylureas. Metformin seems to be not such a serious issue with our TB meds. There are longer periods of infectiousness and they're slower to respond. And

we know that at least one study has shown that Rifampin is only about half as strong in people with diabetes. Circulating metabolites were much less. And some programs are actually routinely checking levels of TB meds in their patients that have diabetes.

There's also higher risk of medical complications, including hepatitis from the TB meds.

Slide: TB-DM Outcomes: Relapse

But in the TB world, we look at outcomes. We really look at two major outcomes of interest. And one is relapse. This is important to us because when you have to retreat a patient, the risk of a drug-resistant TB is so much higher. So, here's a 2012 study from Megan Baker and her group at Harvard. And she published a meta-analysis that verified sort of what we kind of all suspected, and that is the risk of...the overall risk of relapse is significantly higher; they're four times more likely to have to come back for a second treatment. I got a call actually two days ago from the island of Kiribati, where there's a patient that's being treated for the third time and now has MDR disease.

Slide: History of Prior TB

In the Pacific, our rates of having prior TB, which is sort of a surrogate for a relapse, are elevated about to 2 to 2 ½ times amongst patients with TB and diabetes.

Slides: TB-DM Outcomes: Death During TB Tx and All-Cause Mortality During TB Treatment

What about the most important outcome? And that is survival. Well, the news isn't very good. The age-adjusted, all-cause mortality is five times higher for patients with TB and diabetes versus TB alone. In the Pacific, we note the same risk of about five times more. And these patients are fragile. They've often got nephropathy or macro- or micro-vascular disease, and they need improved attention and care during the time of TB treatment. It's unknown whether we can impact this, but the initial data actually looks pretty good.

Slide: More DM Complications: More TB Risk

We also know that as there are more diabetic complications--if you just start to count the number of heart attacks and strokes, amputations, etcetera--we find the risk of TB rises in that patient with each complication of diabetes, an interesting surrogate to look at TB risk.

Slide: Higher A1c: Worsening TB Presentation

And we know that if we look at A1c, that individuals that have a higher A1c have a much higher likelihood—2 to 4 times higher--of having cavitary disease, high burden disease. And these are the patients that are the hardest, hardest to cure.

Slide: TB and Diabetes Summary 2-3-4-5

I can go on, but I won't. We'll just stop here and say that people with diabetes and TB have twice the risk of remaining culture positive. They're three times the risk of progression to TB disease, as Sundari pointed out. They have four times the risk of relapse and five times the risk of death. So, when I'm talking to my TB doctors, I like to say, "2, 3, 4, 5--so simple, even a doctor can remember it."

Slide: Double Trouble: TB-DM Lit Review

So, let's go to the third question. We do know now that diabetes makes TB harder to find, harder to treat, affects our TB outcomes. And in the Pacific, where 60 percent of our island patients also have diabetes, I can confidently say that diabetes is the HIV of the Pacific. The question is can we make a difference?

Slide: TB-DM: Opportunities for Collaboration

So, although diabetes in our TB clinics are making things more difficult for us, we want to know if we can affect the outcomes for people with TB and diabetes. Can we make a

difference for their TB, and can we make a difference for their diabetes? Well, in 2005, we set out to try to do better with this, with these patients. And we're still implementing these, but here are some of the results of our collaboration so far.

Slide: Pacific Standards for Management of TB and Diabetes

First of all, we need some guidelines. In the TB world, we love our guidelines. And having directed our National Diabetes Programs in Saipan for 10 years, I can say that we do things a little differently. We drafted a set of guidelines for TB-diabetes cases, and these were later modified and peer reviewed with our friends at the F.J. Curry Center and adopted in 2010. Now, the standards 1, 2, and 3 are standards that follow a bidirectional screening model that was purported by WHO in the framework. And it tells our TB programs to screen for diabetes. We've been pretty successful at that. And it tells our diabetes programs to screen for TB. We've not done so well for that, and we're hopeful that an audience like what we have today is going to bring us better success. The fourth standard guides clinicians to treat these TB patients, and the fifth standard, fifth and sixth relate to our ability to manage diabetes in TB clinic for persons that have TB.

Slide: Best Practices: RMI Diabetes Clinic

In the Pacific, we've had great partners with people like Andy Heetderks and Gwen Hosey and Dawn Satterfield. They've helped us to implement these, and we have some real successes. Here's one of our best clinics in the Republic of the Marshall Islands, where we know the rates are very high for both TB and diabetes. And you can see diabetes screening going on in TB clinic and TB screening going on in diabetes clinic.

Slide: TB Screening in Diabetes Clinic: Finding TB

So, what happens when you do this bidirectional screening? Well, as Sundari mentioned, we were surprised to see the rate of TB among asymptomatic adults just

sitting in diabetes clinics waiting for their Metformin refills. And it was over five percent. That's more than 20 times higher than the rest of the country. I don't know what the rates are going to be in the U.S. I'm quite sure they won't be five percent. They probably won't be one percent, but we're going to find a lot of TB, subclinical or latent TB, amongst foreign-born individuals in certain pockets in the United States. I'm sure of that.

Slide: Death during TB Treatment in Ebeye (2010-2012, n=23)

More than this slide though, I think what happened afterwards was, was really amazing. And that is this: for diabetes and TB patients who were not screened in diabetes clinics-- in other words, the TB program got a call from the ER because there was a new TB patient that also had diabetes, the rate of survival was very poor; 45 percent died before they were cured of their TB. They had very complicated patients, and I think they sort of had a bad strain. We went over this with the program several times. But I think it's interesting that during the same time, if the diabetes clinic was a source for screening, if the TB patients were found because they went in with diabetes and screened them and found them earlier, the death rate was so much less than it was after the patient showed up in the ER. And you have to ask does this mean that screening for TB amongst high-risk, foreign-born patients with diabetes, can it save lives? Well, I think the answer is yes. Early diagnosis in TB is always a good thing.

Slide: What Happens after Bi-directional Screening (Cartoon)

So, that's sort of bidirectional screening. And I like to show this slide, because I think initially we're all really tied up with bidirectional screening. We love it. We want to make sure that people are checking for diabetes in TB clinic and checking for TB in diabetes clinic. But I think it's important that after we're done with that to go further. Otherwise, we're just sort of counting, right? And you can see here there's no Nobel Prize for accounting.

Slide: Diabetes for Dummies

So, to begin this process of doing more, I think we have to educate ourselves in the TB world. And this is actually a real book, apparently, published in England, *Diabetes for Dummies*. And this is sort of our approach in the TB land. Our goal is to blur the lines between infectious disease and chronic disease between our public health siloes.

Slide: Battle Creek Sanitarium: Exercises, 1911

So, let's start in TB clinic. First, we had to re-educate ourselves about diabetes. Now, we have a proud and talented group of senior public health nurses in Hawaii--really, really impressive, very good at their jobs, very talented. But, we also have to motivate them for change. So, I like this slide from 1911 and I use it because it reminds me that before the mid-1940s, TB docs and nurses did not have any medications to treat TB. We were forced to improve TB outcomes by focusing on a diet and exercise and improving immune status with every other means we could. And some of those outcomes were actually pretty good, pretty impressive.

Slide: Basic DM Management for TB Clinic

So, in the Pacific, we started a TB clinic by making sure that we address the clinical complications of diabetes, and we extend the treatment for many for nine months to prevent relapse. And this is Standard 4. This is actually easy enough to, to implement. Some patients do not get nine months, but in the Pacific most of our patients are treated a little bit longer in an attempt to prevent relapse.

Slide: Enhanced DM Management for TB Clinic

But then we get to the hard stuff. This is Standards 5 and 6, and these are the platinum standards. Standard 5 is where the TB clinic measures glucose and A1cs. The TB nurses are doing this. And they even provide limited diabetes education. And Standard 6 is the

hardest part, but it's really my favorite one, and that's where diabetes education is taking place by the TB community worker during daily TB treatment. So, for those of you in the diabetes world, you might not know this, but we give most of our patients treatment by directly observed therapy. That is, no patient with TB disease leaves our clinic with any pills. We show up at the house every day for six months, and while we are watching them swallow their pills and checking for complications, we're standing at their doorway or in their kitchen. We think this is a great opportunity to provide a teachable moment for diabetes and actually may be their best chance ever for solid diabetes education.

Slide: Key Messages for TB and Diabetes

So, how do we do diabetes education in the midst of getting treatment for TB? Well, we partnered with the Australian Respiratory Council to create this teaching tool for diabetes. The messages are simple. They are repeated, so in the brief intervention model, there's two minutes or less really. Do it a couple of times per week with the DOT visits or with the nursing visits. Now, for those of you professional diabetes educators out there, you might be insulted by this document. There's no carbohydrate counts. There's no discussion of glycemic index. We're just talking about the low-hanging fruit and diabetes education, you know, portion size, food substitutions, regular exercise. And actually, there's no discussion of diabetes medications even other than a reminder for patients to take the meds that their doctors are giving them. That's sort of where we've drawn the line.

Slides: DOT Helps Cure TB and Week 58 (Day 1) You Have Also Been Diagnosed with Diabetes

Here's a page from week two, day one, and you can see the, the flipchart has something for the patient. And then on the other side of the flipchart is the health care worker's reminders and things we want them to go over with the patient. And we spend the first

month focusing on tuberculosis. But by the second month, when they're starting to feel better, we begin to go after them about their diabetes, and the most of the rest of the messages are about diabetes, although we continue to talk about TB as well.

Slide: Hawaii TB Nurse's Training

Implementation of this in Hawaii proved to be helpful, and here's our Hawaiian TB nurses learning to use that flipchart. We brought in a certified diabetes educator, but the best teacher, I think, was the role playing that we did, where nurses talked to each other. One was a patient, one was a nurse. They'd go through one page and then turn it around and the other was the patient and the other was the nurse.

Slide: Hawaii TB Nurse's Documentation

Of course, to help with implementation, we added a form for reminders and data collection, which should eventually help us to see if we're actually making a difference with the glucose control. And we're getting some early data in now.

Slides: Can the TB Clinic Help with Glucose Control? and Average A1c During TB Treatment in Hawaii

Last year, we put the first round of results together to see if we could you know this new effort could reduce the A1c of our TB patients, checking A1cs every three months during TB care. And initial results are actually quite good. Our program is really proud of this trend. As the average patient dropped their A1c by 1 ½ points during the course of TB treatment. I think this is really remarkable.

Slide: Mean Hemoglobin A1c During TB Treatment: 2013-2014

This year we just started to get an updated data set, and we've uncovered sort of another trend, and that is the patients who benefit the most are the ones who, not surprisingly, had the worst A1cs. But that's where we want the most benefit. This slide is

put together by Ally Pyan. She's my CSTE Fellow and should get credit for this. And, by the way, her fellowship ends in June and if you're looking for a crackerjack epidemiologist, send me a note.

Slide: Can Our Programs Take Credit for This?

But before we get too excited about this data, I think we have to stop and say can our programs really take credit for this A1c improvement? A1c should drop during treatment, because infections elevate blood glucose, we know, and patients may use this as sort of a wake-up call to address their diabetes. On the other hand, though, there are some things that make this improvement very impressive. For example, we know Rifampin and INH, actually, will elevate blood glucose throughout treatment, which would make A1c rise. And almost all of our patients gain weight, usually 10 pounds or so, during TB treatment. And to obtain a percentage and a half point of A1c drop while gaining 10 pounds is got to be pretty much unheard of in the diabetes world.

Slides: 1% of A1c Change and Retinopathy, 1% of A1c Change and Nephropathy, 1% A1c Change and All-Cause Mortality, and the 1% Solution

What does one percent mean? For us in the TB world, we like to see 99 percent or 98 percent cures, etcetera, but 1 percent we know in the diabetes world means a lot. You, you understand this better than we do in the TB world. And that a one percent decrease in A1c can decrease the retinopathy progression, it can decrease nephropathy progression. There's a 24 percent relative drop in mortality. And according to the CDC Web site, for every one percent reduction in A1c, the risk of developing eye, kidney, and nerve disease is reduced by 40 percent. We are really proud of our initial results so far.

Slide: Double Trouble: TB-DM Lit Review

So, to answer that third question, *Can we make a difference?* Yes, we can. We can diagnose TB with active case-finding and improve outcomes, and we can identify high-

risk individuals in diabetes clinics for TB prevention. And this is where we really need you guys.

So, let's go to the next and last topic, which is TB and diabetes opportunities for partnership.

Slides: TB-DM: Evolution of Man and TB Screening in DM Clinic (Where was my Patient Born?)

So, I think the thought of screening or treating latent TB in every person with diabetes across the United States is daunting and, quite frankly, probably pretty dangerous. I don't think we want to do that. I don't know anyone who thinks that every diabetic person ought to have a skin test. I think we need to sharpen our tools and our focus a little bit before we start preventing TB in diabetes clinics. So, is there a way to do that? And I think the answer is not entirely clear. The epidemiology is forming up and the, and the evidence is forming up, but I think we are starting to get something that begins to make some sense.

Slide: TB-DM: TB Screening in DM Clinic (Maps)

The first question you have to ask yourself is where was my patient born? Sundari went over this slide, which shows even more darkened states now in 2014. Most states have most TB cases that are foreign-born.

Slide: Poll 2:

Time for a poll question. Okay. What percent of your patients with diabetes are foreign-born in your diabetes clinics? If you're seeing diabetes patients, we'd love for you to click one of those boxes.

Slide: Approximately What % of Your DM Patients are Foreign-Born?

It looks like we could not have divided that up more evenly if we tried. It looks to me like about 40 percent have over half of the diabetes patients are foreign- born, about 60 percent have half that are not foreign-born. Let's move on. Thank you for that result. That's very interesting.

Slides: TB Screening in DM Clinic, TB-DM: Diabetes Control, and % of DM with A1c<8%

So, the second question then is for your patient sitting in diabetes clinic: What's the current level of glucose control? Now, we saw this graph earlier and we know that TB triples the rate of going from latent disease to active disease and as diabetes complications increase so does the risk of TB. The good news is this--and that is about 60 percent of high-risk patients with diabetes in the U.S. have an A1c of less than 8. So, I would focus, at least to start, on those patients who have an A1c of greater than eight. Now, unfortunately for us in the Pacific, probably less than 40 percent of our diabetes cases have an A1c of less than 8. In a recent study I did in the Navy--with the Navy in the Marshall Islands three years ago, we found that 70 percent of adults with diabetes had an A1c greater than 8. There was poor control overall. But this helps us to really focus on which patients should be screened for TB. And brings us to the next poll question.

Slides: Poll 3, Approximately What % of your DM Patients Currently Have an A1c<8.5?, TB Screening in DM Clinic, TB-DM: Younger DM Cases at Highest Risk

This is a tougher one. If you're not sure, we'll accept your best guess. Yeah. Still coming in pretty fast and furious. I'll let this go for a little bit longer. Nobody gets an A-plus with more than 90 percent, huh? Well, I guess there's two. Alright, thirdly, the question is *What's the age of my patient?* Now this one's a little bit upside down. You might be surprised by this. But what we're showing is that the younger patients with diabetes actually have the highest relative risk of having TB. This is relative risk, mind you. But you can see that the green bars, which are those that have TB and diabetes, versus the red bar, which is the TB and no diabetes, that's where most of the patients are on the

bottom. But the risk is higher in the top. So, I think it makes sense for us to focus on our younger patients. The association of TB is strongest in younger patients with diabetes and that's good news for us who want to try to prevent TB in diabetes clinic.

Slide: Summary: TB Infection in DM Cases

Younger patients have a higher risk. They may be closer to their initial TB exposure. They may be in poor control, we don't know, but something is happening there. But, we also know that younger diabetic cases, they tolerate preventive treatment better. Younger people with diabetes--younger people in general tolerate preventive treatment better, and they also realize more long-term benefit from giving this preventive treatment. They've got more years to enjoy the, the, the fact that they've taken their 3HP or their INH or their Rifampin.

Slide: Possible Risk Profile for TB Screening in Persons with DM

So, we can tie questions one and two and three together in a chart like this, which I have to be careful about putting up because this is I'm calling this my completely untested, unproven draft, interim, temporary, potential, possible paradigm for risk ratification for an individual from a high-risk country. The point here is that we're more worried about an A1c of 8 in a 30-year-old than we are in a 60-year-old.

Slide: Summary: TB Screening Cornucopia

Finally, when I talk to diabetes programs, the next question invariably comes up: *What screening test should I use?* Now, in keeping with the Thanksgiving theme here, I have to say that we have plenty of screening tests in TB: the skin test, the IGRA, the symptom screen, the chest X-ray, sputum smears, new test called the GeneXpert. And TB docs will happily argue for several hours or maybe even days about which test you should use. Just go see your local TB program for help on this one. And I think what's really

important is to make sure that decisional analysis about testing doesn't become decisional paralysis and not testing.

Slides: TST and IGRA, IGRA or TST Diabetes

Here's a side-by-side listing of the benefits of TST versus IGRA. That's Interferon Gamma Release Assay that we use more and more commonly in TB control. And in diabetes, I think the TST, the old skin test works pretty well with for diabetes cases that have fairly good control. If they're very young, there may be more false positives because of BCG vaccination. And for older individuals with advanced sequela of long-term diabetes, probably not a great test and can miss lots of TB-infected individuals. I think for these folks, the IGRA seems to perform better in this population.

Slides: TB-DM for DB Clinics: Where to Start? Screening in DM Clinic for TB Disease and TB-DM for DB Clinics: Where to Start? Screening in DM Clinic for TB Infection

So finally, let's get to some recommendations. So, if you're in diabetes clinic and you're looking for TB disease, who are you going to target? I think we look at all persons with diabetes, especially foreign-born from a high-risk country. We use a TB symptom screen. We're happy to provide that for you. It goes to your local TB program or you can see them online. There should be probably annual symptom screening. It's free, it's easy, it's fast. There's nothing to this one. You just ask the list of TB symptoms. And then refer all the positives to the TB clinic for a chest X-ray and further work-up. Again, I don't think we're going to find a ton of active disease in your diabetes clinic. But, certainly, when you do, that's a risk for both the patients in the waiting area and the staff and it's not a good idea.

What about TB infection? This one's a little tougher, so there are no recommendations that have been approved. And in the interim in Hawaii, we're going to focus on those with an A1c of greater than 8 and those who are under age 50. And we'll use a TST, maybe with an IGRA to diagnose TB infection. And we're going to treat the people that

we find who are positive. If the person is negative, it makes sense to do to repeat this test every so often. In the Pacific, we have said every 2 to 5 years. If you're in the states, that probably should be more like five or longer, because there's less circulating TB. And then refer all your positives to a TB clinic for treatment. And 3HP, I think, has got a great place for prevention.

Slides: Poll 4, and TB Screening in DM Clinic (Poll Results)

Okay, our last polling question. For TB screening in diabetes clinic, where are you guys at? Are you going to be able to advocate for TB screening for those from high-risk countries? Or will you advocate for TB screening for all cases? Or are you still sort of unsure about whether you can do TB screening? Or the fourth is, "Sorry, Dr. B, we're not going to do any TB screening. We're too busy." Don't worry, this is anonymous, you tell me you can be honest. Fantastic, I'm seeing about 90 percent of people feel like maybe we can start doing some TB screening at diabetes clinic.

Slides: Enhanced TB-DM Program Collaboration (Image of Meg Ryan and Billy Crystal, Enhanced TB-DM Program Collaboration)

Very good. So, now what? So, what's the first way to do this? Well, I think the first thing is to call up your local TB program, you folks in diabetes clinic. I definitely recommend you take your TB nurse to lunch, okay? I want to make that clear, make it a fancy lunch and make sure you pick up the tab afterwards. And while you're sitting at lunch, here are some things to talk about. First, speak out and meet your TB program. I would recommend you choose a pilot diabetes clinic for serving high-risk areas. Decide which diabetes cases need to be screened. Who's going to perform the screening? Is TB program going to come over and do it? Who's going to pay for the TB screening? And how are you going to communicate the results back and forth? These are really important questions to get started with.

Slide: How Else Can DM Programs Help?

And then, when the main course comes, you can talk about these more advanced issues, which are sharing culturally appropriate TB education materials, providing feedback on TB materials, offer to teach basic diabetes principles to the TB nurses and the DOT workers. Teach them how to do a random blood glucose or an A1c, like we're doing in Hawaii, and provide some diabetes education. And one thing that was very successful in the Mariana Islands is that we did TB only diabetes education classes. And this was after folks, who of course, were rendered noninfectious.

Slide: Diabetes.co.uk

And then for dessert, when the dessert comes, I offer this up for your discussion. This is an interesting article that looks at Metformin and its effect on diabetes treatment. And it's interesting it seems to improve TB outcomes in mice, and possibly even improved TB severity in humans and may have worked on people that or mice, anyway, that were non-diabetic even. It seemed to make a difference in their TB outcome. This is very interesting and there's a couple of bigger studies that are going to relook at this, but who knows, maybe Metformin will be part of our of our four-drug therapy.

Slide: TB-DM Framework Summary

So, to finish, our framework for TB and diabetes is that frequent glucose and A1c testing for TB cases is helping. Our diabetes education is helping, both in clinic and directly observed therapy. We refer our, our diabetes cases to the diabetes center. For some, programs are actually treating the diabetes with a directly observed therapy. And our hope is that that's going to improve our, our TB outcomes. But we hope that the true collaboration is a shared goal of improved, lifelong diabetes control so that we can do our part in this tough battle against diabetes, one TB patient at a time.

Slides: TB-DM Clinics: Case (Hernandez, 43-year old male), and TB-DM Clinics: Case (After 4 Months)

SM: Here's a quick case scenario, because it's always good to learn through listening to cases. Mr. Hernandez, 43-year-old male from Mexico, living and working in Houston, complains of blurry vision and nocturia. His primary care clinician orders a random blood glucose, which is found to be 276. He has a referral made to diabetic clinic for care, is admitted to a diabetes clinic, and his initial A1c, as you can see, is high at 9.2. Very compliant, attends a total of six weekly group sessions for education. After three months, he gets his A1c down a little bit to 8.7 percent.

RB: Yeah--foreign born and young and an A1c of 9.2, so this is a high-risk case. Go ahead.

SM: High-risk patient, yeah. After four months, another patient notes that he's coughing in the waiting area for the past three weeks. And the clinic tells him to see his primary care doctor to manage his cold, which I'm sure many of us have heard this scenario. Four weeks later, he does see his primary care clinician who gives him of all antibiotics, Levofloxacin, a fluoroquinolone, which many of you don't know, we use to treat TB. It's not good to give out for presumed community acquired pneumonia. Helps some, of course, but the cough persists.

Slides: TB-DM for DM Clinics: Case (Image of Chest X-ray at left) and TB-DM for DM Clinics: Case (Sputum was ordered)

So, chest X-ray--we have a delay here, clearly, in diagnosis if this is TB. And here's a TB, here's a chest X-ray with a classic TB presentation with bilateral upper lobe disease with infiltrates. And you can see cavitary lesions on both sides really. And the CT scan simply confirms fairly advanced significant involvement of the lungs with TB in all likelihood. So, the sputum was ordered and he was 4+ smear positive for AFB, most likely tuberculosis. Referral was made to public health for a TB treatment. He started on our standard four-

drug regimen for tuberculosis and is then and random blood glucose is 340. So, what do you think about that, Dick?

RB: Well, it's elevated. And what we find is that after initiating therapy, the Rifampin can increase blood glucose. And we find transient elevations in glucose after initially starting a TB treatment. Again, this patient was highly infectious, and the waiting room seems to be sort of the last holdout for infectious control. So, I'm worried about the waiting room, Sundari.

SM: Exactly. And it's I think others, especially in the diabetes clinic, where he was already coughing for three weeks, who were probably at higher risk on the basis of having diabetes or being suspect for diabetes, are even more highly at risk potentially. But certainly, different exposures in different settings. So, after two weeks, the public health did inquire about the patient seen at the diabetes clinic. And a contact investigation was initiated for 23 other people. So, this is, I think, a really big message with TB, since it's communicable and airborne. This is what a lot of programs and many of you out there deal with, is contact investigation when you have delays in diagnosis that lead to exposure of others and potential transmission.

Slide: TB-DM for DM Clinics: Case (After 6 weeks culture was confirmed)

SM: So, after six weeks, TB culture was confirmed. He's sensitive to all medications, thank goodness. There's no resistance, and but there's a workplace contact investigation. Total of eight contacts were found to have a positive test for TB infection. That's a blood test; five of those had no prior test; three had positive tests in the past. And all eight individuals were active TB was excluded, and they were placed on preventative treatment with 3HP, which is our new regimen for treating latent TB infection. Twelve doses within 12 weeks, which really increases patient completion, we found from our operational research studies and is well tolerated.

Slide: TB-DM for DM Clinics: Case (After 2 months, he continued to have positive AFB

So, after two months, he continues to have positive smears and response to TB treatment is extended. And, Dick, do you want to say something about extension of TB treatment potential in diabetes?

RB: Sure. For folks who are still culture positive at two months and folks that have cavitary disease, the guidelines do recommend that we extend treatment. And this will help to obtain a cure that, and the patient won't relapse back into requiring retreatment. So, it's really important, I think. And it's the rule in the Pacific. And there are some studies that show that for diabetics, routinely nine months is, is better. That's yet to be determined as a general rule, however.

SM: If the hypothesis still needs to be confirmed and may depend, as some people already noted in questions based on diabetic control as well, as we see with HIV as well. So, the TB and diabetes clinic met to optimize his treatment and he was given better treatment for his diabetes with Metformin, increased dosage, and he returned to clinic after he was deemed noninfectious by the TB program. Lifestyle changes were reinforced. The patient received diabetic indication monitoring as part of his DOT, which is really important. I think we have to highlight the importance of case management for these patients. Simply giving medications and isolating for infectious patients isn't enough. All these other education objectives and the case management is so important to ensure the patient gets the best treatment possible in a patient-centered approach.

Slides: Case Study and Case Study (36-year old Latino Woman)

So, after nine months, the patient completes treatment and, hopefully, is cured. Okay, now I'd like to present a case study to illustrate many of the points that we've discussed today. This is a case of a 36-year-old woman, who is Mexican- born, close exposure to an infectious individual with regular drug susceptible pulmonary tuberculosis. She has a

long history of poorly controlled diabetes. And we've already learned here today that this is a big risk factor for progression to TB disease from latent TB infection.

Slides: Compared to Other Contacts to the Source Case and Linkage between Tuberculosis and Diabetes

So, compared to other contacts of this source case, is she more at risk for developing latent TB infection? In other words, once cost on by the pulmonary TB case, is she more likely to get infected with TB? Well, the answer here is "no," because having diabetes does not predispose one to actually become infected once exposed. This slide will show you that there is a linkage between tuberculosis and diabetes, but when a patient is diagnosed with diabetes, the immune response is weakened and then they're exposed to tuberculosis. There's no increased risk that they're going to become latently infected. The risk is progression to disease once latently infected, as we're going to see here in just a second.

Slide: Compared to other Contacts

So, our next question, *Compared to other contacts, is this patient more at risk of progressing to active TB disease once she has been latently infected?* And the answer here would be "yes." That is how diabetes or other immunocompromising conditions affect the individual. They're more at risk of progressing to active TB disease.

Slide: WHO 2009

You can see here the WHO statement from 7/9, which states very clearly that people with a weakened immune system as a result of chronic diseases, such as diabetes, are at higher risk of progressing from latent to active TB. In fact, people with diabetes have a 2 to 3 times higher risk of getting TB--that is, TB disease--compared to people without diabetes. About 10 percent of TB cases globally are linked to diabetes as a result.

So, once again in review, once cost upon by an infectious TB patient, diabetic patients are not at more risk for actually getting infected but are at risk of progressing to active TB disease--2 to 3 times more likely, that is--than a patient without diabetes once infected.

Slide: What Additional Evaluation or Treatment Should This Diabetes Patient Have?

The next question is: *What additional evaluation or treatment should this patient have?*

And the choices are medical history, tuberculin skin test, or Interferon Gamma Release Assay, chest X-ray, a hemoglobin A1c. Should they start Isoniazid for a latent TB infection or should they have a, a few of these things? And I'll just say there's no right or wrong answer. This just stimulates thought. Certainly, the patient should have a medical history, should have a tuberculin skin test or a blood test because they're just contact to a case. Probably does not need a chest X-ray, because we would only get a chest X-ray if the tuberculin skin test or the blood test is positive. Certainly, the patient could have a hemoglobin A1c, but it wouldn't be part right now of the initial evaluation of the contact. And you would certainly not start this person on Isoniazid for latent TB infection, because you haven't established latent TB infection at this time.

Slides: Case Study and Image of Chest X-ray

So, the patient has a 20mm tuberculin skin test, so it's positive. And she notes several weeks of dry cough but is otherwise well. Of note, her hemoglobin A1c is 8.9, suggesting that her diabetes is fairly poorly controlled. Now what do we do? Well, the next step, when a person is a contact to an infectious TB case and has a positive tuberculin skin test, is to rule out active disease by attaining a chest X-ray. So, this patient has the following chest X-ray, which at this time looking at it looks relatively good. There may be some subtle findings here in the left upper lobe. You can see that there's a few little nodules, and it looks a little bit different than the other side. Maybe just a little bit more

haziness. But it's a very subtle finding. And I think in this particular case, it was called normal at this time.

Slide: Case Study

The chest X-ray was read by normal, the exam was normal. The patient reported allergies and her dry cough was attributed to her allergies. And one sputum specimen was submitted, which is interesting because with the normal chest X-ray, the reason probably one was obtained is because of the cough. But I think most people would get three at this point and not one. But this patient had one. It was smear-negative for TB.

Slide: What Else Should Be Done?

So, what else should be done at this time? And you can choose two options. As we just said, one sputum specimen was obtained. Would you obtain more? Three sputum specimens for smear and culture? Would you perform a bronchoscopy on this patient to clinch the diagnosis? Would you start treatment for latent TB infection at this point, because the patient has a positive tuberculin skin test and a chest X-ray that's read as normal? Or would you start treatment for active TB disease at this time?

Slides: Case Study

Well, in this case, the patient is symptomatic with a cough, and in retrospect, really, the chest X-ray is slightly abnormal, but let's just say we still think it's normal. It's not at all unreasonable to get the additional sputum specimens and to empirically start treatment for TB disease, because this patient is diabetic and actually has a high risk of progressing to TB disease, as we've already seen. Again, there's a lot of gray area here, and different people would do different things.

Slides: Case Study and Image of Chest X-ray

It turns out three months later, the patient actually has fever, now has a productive cough, and is coughing up blood, has the following X-ray. So, back at that time, she was not started on treatment that you can see, where we earlier saw that there was some abnormality there in the left upper lobe. Now, there's clearly an infiltrate and some nodules. And, for example, this is a nodular process here. And it may even be like a small cavity there. But of even more concern, there's an infiltrate on the right side also. So, this patient has actually rapidly progressed on her chest X-ray to a very abnormal film.

Slides: Case Study and What Now?

At this time, a sputum specimen is obtained, and it is smear positive for AFB. And the chest X-ray we just saw--bilateral, upper lobe calcifications, infiltrate and cavitation. So what to do now? Well, at the time, that patient was not placed on the four drugs. In fact, she was placed on just Isoniazid at the time, unfortunately. At this time, probably the thing to do is to just start four-drug treatment for active tuberculosis. We would not add a fluoroquinolone, because you wouldn't want to put that one drug at risk. There's no reason to add a fluoroquinolone when a person's still a TB suspect without drug susceptibility test results. And in this case, just starting four good drugs, Isoniazid, Rifampin, Pyrazinamide, and Ethambutol, is probably the thing to do.

Slide: Case Study

The culture grows TB and later is found to be resistant to Isoniazid. So, back when that patient had the normal X-ray, she was started on INH, even though she had a cough. That chest X-ray initially was read as normal. But, again, with 20/20 hindsight, we can say that there was kind of an abnormality even to start off with. And it's probably as a result of being on Isoniazid for three months as mono-therapy, when she was actually symptomatic, that she may have developed resistance to Isoniazid. So, her culture growth is found to be resistant to Isoniazid.

Slides: Are Outcomes Different Than for Other TB Patients? Case Study

So, let's talk about outcomes. And Dr. Brostrom discussed this in detail during his TB literature update. Are outcomes different for patients who have diabetes compared to patients who do not? Are patients with diabetes at risk for slower sputum conversion, increased risk of failure, increased risk of death from tuberculosis, increased risk of relapse? Or all of the above? Well, I think we've seen from Dr. Brostrom's talk that patients with diabetes are at increased risk of all of these negative outcomes. Slow conversion of cultures and smears occurs, usually only after 2 ½ months of treatment, whereas we see smear and culture conversion often under two months in patients without diabetes, slower radiographic improvement has been noted. And this patient had very slow radiographic improvement. Hemoglobin A1c is still high at greater than nine percent, suggesting that diabetes is still very poorly controlled. She's having some nausea and some vomiting after TB meds, which is very concerning that she's not getting the medications in. And we know that there's a risk factor for further acquired drug resistance and negative outcomes.

And of note, her Rifampin level is found to be extremely low. Now, there are some studies that support the fact that TB meds may not be absorbed as well by patients with diabetes due to the abnormal function of the GI tract. There can be some gastric dumping that is commonly seen in patients with diabetes. And maybe just poor motility, leading to poor absorption.

Some studies have shown lower Rifampin levels in patients with diabetes and some have not. The jury's still out on this. But, the fact of the matter was that this patient for whatever reason, maybe because she was vomiting the medications, or maybe she was mal-absorbing the medications. Hopefully, she was getting full directly observed therapy, which I'm sure in this case she was, ensuring that at least she was taking the

meds and not spitting them out or, you know, flushing them down the toilet or anything like that.

Slides: Image of Chest X-ray Month 2 of Therapy, Case Study and Image of Chest X-ray Month 5 of Treatment

So, her Rifampin level is at trace. Chest X-ray is significantly improved after two months of treatment. You can still see the cavity right there, but the infiltrate is quite a bit less. And on the other side, the infiltrate is less as well.

So, she then achieved improved diabetic control with diet modification, exercise, and a change in medication. She had an increase in her Rifampin dosage due to her low serum level and was given some medications to prevent vomiting--nausea and vomiting. In other words, the patient was pre-medicated with an anti-emetic like Compazine or Zofran, and she didn't have nausea and vomiting from there on out. She was clinically improved and radiographically improved. Here's her end of treatment X-ray, well, month five. And she actually was extended treatment to month nine. But you can see even here at month five, she has significantly improved findings, with almost closure of cavity on the left side. And her abnormal signs on the right side have resolved.

So, this patient ended up completing treatment over a nine-month period, because she was still culture positive at two months, which is and she had a cavity at diagnosis, both being indications to extend treatment for TB to nine months from six months. We don't just extend treatment to nine months on the basis of a patient having diabetes alone. But, in any patient who has a cavity in chest X-ray at diagnosis and is still sputum positive at two months, we do extend treatments to nine months. So, this patient completed nine months of treatment and was considered cured at end of treatment.

Slide: Helicopter/Shark

And I will end there and just note this is a digitally mastered slide, but it's a great one. And I think the threat of drug resistance looms and is a big problem worldwide. We haven't really had a chance to discuss it that much in this presentation, but it is one of the greatest threats to global TB control and domestic TB control.

JM: This is Jude again, and there have been a couple questions related to poverty. One which is, *is the increase in TB related to poverty?* And then another which is a little more complicated, but considering that there are other that poverty is a risk factor, are there any messages that you can recommend on TB and diabetes in terms of people with the lowest income levels?

SM: Yeah, I'll turn that over to, to Dr. Brostrom in a second. So, I, I think that the, the link with poverty is real and probably represents lots of other factors that are associated with poverty. In other words, the lack of access to health care, that would be one. Living in more crowded situations might be another. Poor nutrition might be the other. Being potentially exposed to other social risk factors, medical risk factors, having other medical risks as a result of lifestyle or as a result of a lack of access to health care. Perhaps things like substance abuse and alcoholism, homelessness. All these things that are associated with poverty absolutely drive, I think, the problems with TB in those populations.

And for diabetes, I think we see diabetes in all socioeconomic classes. So, I don't know. Dick, do you want to speak some more to that?

RB: Sure, I love this question because I think it really is, it's not talked about enough, because it's just so hard to address it and make changes. But, you know, I think the underlying theme here, really, the tie-in theme is poverty. And it's long been known to be a TB an important TB risk factor with crowding and poor access to health care and

people staying at home with coughing out AFB to their family members and living in crowded conditions. And we see this across the Pacific as well as other places where TB rates are high.

But, I think the link with poverty and diabetes is sort of newer anyway, and, but very strong. And diabetes, which used to be a disease of food excess, is now a disease of more food security. And I think we're seeing rampant rises in diabetes from the westernization of diet and that food is cheaper than other food. So, I think the association with poverty is really bringing these two diseases into the same household and is responsible for lots of the fueling of TB that we see even in places that didn't used to have diabetes as a problem.

SM: Yeah, great question.

JM: And then some other questions that are, are kind of linked since we are the National Diabetes Education Program, I have to ask you these. Are there any educational materials that could help educate the general population or public health people or physicians about the relationship between diabetes and tuberculosis?

RB: Well, there's, there's a growing body of studies and literature, but there's also a growing body of useful tools. I know that the diabetes flipchart--I've seen there's been a couple of questions requesting the flipchart, and it's...the link that I showed was for the Pacific version. But as we hoped, it, it sort of got a little life of its own, and it's been adopted and changed. On the East Coast, I forget, I think it might be Virginia that's done this or Kentucky. I know that Diana Fortune in in New Mexico has a version that she has amended to make it sort of a Southwest flavor. One of the Northwest states is looking at it.

We're hoping that you could make this tool better. We're hoping that sort of every version of the diabetes flipchart, the TB flipchart, is going to get better as it gets amended. And although it's been looked at by professional diabetes educators, we

know that you folks can make that tool better than it currently is. So, there are more and more tools. There are in terms of educating the public health staff, a quick Google search will, will bring lots of online talks, just like this, where TB and diabetes is discussed. So, I, I think there are a, a growing number of tools available for public health folks as well. We're hoping to be able to present at some of the diabetes scientific meetings soon so that we can share this information for our national decision makers as well.

SM: Yeah, and there are 5 CDC-funded regional training and medical consultation centers for TB that are located around the country. And there is a TB regional training medical consultation center resources web page that does have plenty of education materials. And there are some specific for TB and diabetes. I believe the Heartland National TB Center has been instrumental in producing some of those. So, that's another good resource.

JM: I think what we can do at, at NDEP is to talk to Dr. Mase and Dr. Brostrom a little later and gather some of this together and, and make a list available, at least get people started. I would like to thank very much our two very expert and interesting speakers. And thank you all for attending this webinar. And please attend some of our others. Here's some information on the screen about NDEP and how you can get in touch with us. So, thank you all very much.

SM: Yes, thank you very much. Thanks for the opportunity to present, and we will definitely respond to all the questions. And you have our contact information, so if a particular question comes to mind, feel free to shoot us an email as well.

RB: Thank you all.

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