COCA Conference Call
XDR TB: Summary of Clinical Guidance
Theresa Harrington, MD
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Coordinator: Welcome and thank you for standing by.

At this time, all participants are in a listen-only mode. During the question and answer session, please press star-1 on your touchtone phone.

Today's conference is being recorded. If you have any objections, please disconnect at this time.

Now, I will turn the meeting over to Mr. Jim Schwendinger. You may begin.

Jim Schwendinger: Great. Thank you, Sue.

Thank you everyone for calling in today. This is a really interesting and important clinical subject that we're going to cover.

We're lucky enough to have Dr. Theresa Harrington here who's going to present today really more about the guidance for evaluation and management of individuals who were exposed or potentially exposed to this XDR-TB individual.

I want to emphasize that the purpose of this call is not to review the actual case itself and any of the intricacies involved with the XDR-TB patient himself, but really to go over the clinical guidance of persons exposed or potentially exposed, as I mentioned, with this and any other TB situation.

So please, if folks think that we're going to cover the actual event, I may be wasting your time. I think it's going to be a valuable call for the clinical guidance of evaluation and management.

So, we're lucky enough to have Dr. Theresa Harrington. She's a mMedical Officer with the Commission Corps of the US Public Health Service here at CDC. She's a medical epidemiologist with the CDC's Division of TB Elimination on the Outbreak Investigation team.

She serves as a field supervisor for domestic and international TB outbreak investigations and mentors EIS offices -- and those Epidemic Intelligence Service officers -- and CDC-experienced fellows throughout their training.

She joined the Division of Tuberculosis Elimination in July 2004 after completing her two-year EIS Fellowship, during which time she was assigned to the Mississippi State Department of Health, and also served as a short-term consultant to the World Health Organization Stop Transmission of Polio team, or STOP team, in Laos.

Dr. Harrington is a clinical assistant professor of medicine at Emory University School of Medicine. In addition to her CDC duties, she volunteers part-time at a community clinic here in Atlanta and at the Fulton County TB clinic. We're very honored and grateful to have Dr. Harrington here today to talk about this clinical situation.

And without ado, I turn it over to Dr. Harrington.

Theresa Harrington: Thank you Jim. And again, welcome to everybody that has taken the time out of their very busy schedule to listen to this conference. We hope to keep it

brief so you can return to your work, but this is a very timely topic and we hope that this information will be helpful to all of you.

Next slide please.

As you know, the CDC is currently investigating a case of extensively-drug resistant TB also known as XDR-TB. The case involves a US citizen with potentially infectious XDR-TB who traveled to and from Europe on commercial flights between May 12 and May 24, 2007, and then reentered the US at the Canadian-US border via automobile.

Since May 25, the index patient has been hospitalized under airborne isolation precautions or has been wearing an appropriate mask and is now receiving medical therapy for XDR-TB.

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The timeline here just shows that back in January 2007, it was an incidental finding on a chest radiograph -- the chest radiograph was taken for a reason other than a tuberculosis evaluation -- that the patient was found to have an unexplained upper-lobe, non-cavitary infiltrate on chest radiograph. Over the subsequent weeks to months he received further medical evaluation. In May, he was diagnosed with XDR-TB, after first-line and second-line drug susceptibility testings were performed on the isolate.

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Once this patient came back to the United States and a TB contact investigation was started for airline passengers, health care workers, family, friends, close social and work

contacts. We wanted to provide information to health care providers who might be asked to perform TB evaluation and testing on any of these potential contacts .

We put together a letter that you can see here. It's a letter - "Dear Health Care Professional" that provided basic information about which flights were involved, and also what XDR-TB was. We wanted to provide that information in a timely fashion to you.

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So basically, the point of this call is to review with you the principles of TB evaluation and testing.

And certainly, that involves signs and symptoms screening and also placement and reading of the Tuberculin Skin Test or QuantiFERON®-TB Gold blood test, which is approved in the United States.

And oftentimes, two-step testing is needed. It's not two-step as in hospital infection control program, but just a preliminary skin test that's placed early after exposure, and then a follow-up TST that's performed eight to ten weeks later.

And the reason we often have to do a follow-up skin testing or QuantiFERON®-TB Gold test eight to ten weeks later is because it takes approximately two to ten weeks for somebody who's been infected with the *Mycobacterium tuberculosis* organism to form an immune response that we can detect either through the skin test or through the measurement of gamma interferon produced after the white blood cells have been exposed to the TB antigen.

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So, for purposes of contact investigation, a tuberculosis skin test result of greater than or equal to 5 millimeters induration (≥5mm) is positive for any contact.

Persons with a documented prior positive tuberculosis skin test or QuantiFERON®-TB Gold result, or those who've been previously diagnosed with TB disease, don't need to be retested via the TST or QuantiFERON®-TB Gold test, but it is important to note that these persons should still undergo a TB evaluation, which can include a signs and symptoms screening and may also include a chest radiograph.

Next slide please.

So now, we're going to go through many of the algorithms that you can see here that have been put up on the COCA link. And the first one is Figure 1.

And this is an evaluation algorithm for how you would approach TB evaluation and testing in a non-immunocompromised contact. And it really is up to the clinician to decide, is this person a contact or not?

Some people are the "worried well" and they think that if they were in a supermarket and perhaps this person was in the same supermarket with them, then perhaps they should be tested. Your clinical judgment is really what will come into play as to whether or not you will consider this person as a legitimate contact if they present to your office.

But should somebody present and you consider them a contact, either because they were a passenger on this plane, or because they worked with the index

patient, or because they were a client of the index patient, or because they were a health care worker who might have performed a procedure when taking care of the index patient, then those people would be legitimately included among persons to be considered as TB contacts.

So let's go through the first step.

The first box at the top shows that there's a medical evaluation, and we see in Figure 5 that the medical evaluation would involve taking the past medical history. You want to document any illnesses that could increase the risk of latent TB infection progressing to TB disease, such as HIV infection; use of immunosuppressive medication such as rheumatoid arthritis medication; prolonged use of prednisone (at 15 milligrams per day for 30 days or more); certain cancers; end-stage renal disease, or even uncontrolled diabetes mellitus.

In addition, it is recommended that if the patient has not been tested for HIV, one thing you could do is offer HIV counseling and testing to somebody who presents and thinks that they're a contact, because that might affect how you would interpret further evaluations down the line and the other algorithms.

So certainly a medical evaluation would begin with your past medical history; then, you would document any history of TB disease or latent TB infection; any history of prior treatment for TB disease or LTBI; the location that treatment took place, the dates, and medications used (if that information is available). We would recommend documenting any past TST results.

Oftentimes, these TST results are provided from memory (not officially documented). A person will remember that, " I had a negative -- I used to be a schoolteacher". You can certainly document that information and note that it was provided from the person's memory.

But written documentation would be most helpful--dates and locations of TST's and the reason that a TST was performed in the past (i.e., Was this person part of a prior clinical or contact investigation?) That will be information that will be useful to have.

A commonly asked question has to do with persons who have immigrated to the United States from TB-endemic countries and who have received BCG vaccination(s). We want to have as much information about a person's medical history as possible, so we will document in the history if a person states or has documentation of a past history of BCG vaccination(s); however, we do not change our cutoff for a positive. We use the ≥5 millimeter (transverse induration) as the cutoff for a positive TST during a TB contact investigation, whether or not a person has a past history of having been BCG-vaccinated.

We would like to know about any history of social or behavioral risk factors that could have increased a person's risk of acquiring LTBI or progressing from LTBI to TB disease such as a history of incarceration(s), illicit drug use, homelessness, excessive alcohol use, etc.

And then, as we mentioned before, you would do a signs and symptoms screening. You're going to look for fever, chills, cough, night sweats, unexplained weight loss, things like that.

In addition, you will perform a physical exam, noting body habitus (Is the person losing weight or appears emaciated; do they look healthy?), whether they are coughing, things like that.

And then you would place a tuberculin skin test or perform QuantiFERON®-Gold TB test. It would be helpful to note the location where the TST was placed (i.e. left forearm), the date it was placed, the antigen that you used, the

lot number, and the expiration date to ensure that you're not using the expired antigen.

The result and the date that you read the TST would be documented 48 to 72 hours later (if it's tuberculin skin test). Of course, if it's a QuantiFERON®-TB Gold whole blood test, it's one test -- three tubes are taken at one time on a specific date, and then that is further run by the laboratory.

If a tuberculin skin test or QuantiFERON®-TB Gold test comes back positive on either Round 1 or Round 2 of testing, then chest radiograph evaluation would be indicated.

In addition, anybody who has signs or symptoms or TB, whether or not they have a positive TST or QuantiFERON®-TB Gold result, you would also refer for a chest radiograph.

If the person has a cough or other symptoms (or a positive chest X-ray), collecting sputum for for AFB smear and culture would be indicated.

So again, going back to Figure 1. If we've just completed what would be the medical evaluation and we've placed the tuberculin skin test (or performed the QuantiFERON®-TB Gold testing), and let's say that if on our medical evaluation and TST or QuantiFERON Gold (on the left side of the algorithm), test we find no evidence to suggest active tuberculosis disease then - and the results of initial tuberculin skin test or QuantiFERON®-TB Gold testing is negative, then, as we mentioned before, we will repeat the tuberculin skin test or QuantiFERON®-TB Gold eight to ten weeks after the known last exposure to the index patient. And if that again is negative and the person is a non-immunocompromised host, we will not recommend that further evaluation needs to be done.

Now, if the person, through their, you know, we've ruled out active disease and now we're looking for infection - latent TB infection, and if their results of the initial tuberculin skin test or QuantiFERON®-TB Gold testing is 5 millimeters or greater, we consider that a positive for the point of this contact investigation. Then we would consider the person infected, and we would then go to Figure 2.

If on Round 2 of tuberculin skin testing the person converts from a negative skin test to a positive, or from a negative QuantiFERON®-TB Gold test to a positive, we would also then consider that a new conversion, and we would also go then to Figure 2.

Over on the right part of Figure 1, if upon initial medical evaluation there are any signs or symptoms to suggest active TB disease, then we get a chest radiograph. Again, we always want to rule out disease first and we want to rule out infections second.

So we get a chest x-ray immediately, and if there's no evidence of active TB disease, that's when we go down the algorithm towards infection. If there is evidence of active TB disease, then that needs a much more thorough workup for active TB, which would include the person being placed in airborne isolation precautions, evaluated with sputum smears and cultures for acid-fast bacilli, and any for other considerations you have in your differential diagnosis.

I think we'll - we can go to Figure 2 then.

Next slide.

So for those persons on Figure 2, again,this is for management of a non-immunocompromised contact with a positive tuberculin skin test or QuantiFERON®-TB Gold result.

So this is for people that are infected. And this could be past infection or recent infection. And I think that that's going to be a question that most people are going to be concerned about.

But a TST positive of 5 millimeters or greater or a QuantiFERON®-TB Gold positive either on the first round or on the second round, you would do the chest -x-ray; you want to make sure that there's no evidence of active disease.

And if there's no evidence of active TB disease and you go through all the other factors in the past -- their past medical history; their BCG; birth in a country of high TB burden; history of no prior TB or LTBI -- if you had any of those considerations, we would consider standard LTBI treatment. This is often nine months of isoniazid therapy, and if that is if they were not previously treated and if we do not think that they would have been infected by the index patient (with XDR TB).

If the person has a new positive TST but doesn't have any other exposure that we could document, anything that would lead us to suspect that they were already infected in the past or infected from a recent travel other than just being on a plane or being a healthcare worker who was working with them, then at this point, you want to consult with a TB expert.

But in this case (of new latent TB infection that you suspect is due to XDR TB), the person would have to undergo repeated symptom screenings and chest radiographs (to follow them closely).

And so we would recommend that there be follow-up symptoms screening and chest radiographs performed at 3, 6, 12, 18 and 24 months at a minimum because we know that in the first two years following becoming infected (developing latent TB infection),, that that's your highest risk, in the first two years (about 5% risk) of developing TB (disease).

Next figure.

The next figure is Figure 3. And this is the evaluation algorithm for contacts who are immunocompromised. These are persons who have HIV infection or AIDS; persons who have poorly-controlled diabetes; end-state renal disease; certain cancers; persons who've been on prolonged course of prednisone (≥15 mg/day for 30 days); and persons who are on a tumor necrosis factor-alpha medication such as the rheumatoid arthritis medications, or some medications for Crohn's Disease--just to give you an idea of some of the people included in this group.

So again, we would start with a medical evaluation. We would often do a chest x-ray right off the bat because, as we know, persons who are immunocompromised don't always present with as many symptoms as somebody who has an intact immune system. So we will want to do a medical evaluation and perform a chest radiograph right away.

And we will place a TST or get a QuantiFERON®-TB Gold test done. We'll have to always be thinking that these persons possibly have a compromised immune system, so we can't expect that everything will be the same as with a person who has a normal immune system.

Now, on the left on Figure 3, we can see that the contact that you're evaluating has no evidence suggestive of active TB disease-- i.e., no infiltrate, no cough, no fever, no sweats, things like that.

Then you look at the results of your initial tuberculin skin test or QuantiFERON®-TB Gold testing. If it's negative, meaning a tuberculin skin test of 0 to 4 millimeters of induration, or negative QuantiFERON®-TB Gold testing, you would repeat the testing eight to ten weeks post-exposure (post-last known exposure) to the index patient.

If everything remains negative on the second round of testing, then we would still recommend follow-up of immunocompromised contacts at 3, 6, 12, 18 and 24 months with a symptoms screening and chest radiograph.

If, however, on the initial evaluation or on the second round of testing, either the TST or QuantiFERON®-TB Gold test comes up positive, we will refer to Figure 4 and we will go through management of this - of a TST- or QuantiFERON®-TB Gold -positive immunocompromised contact.

To finish up with Figure 3, however, on the right side, if we have immediate evidence on our medical evaluation or chest radiograph or initial TST to suggest active TB disease, these persons must be placed into airborne isolation precautions and evaluated with AFB smears and cultures and any additional testing for active TB, and appropriate therapy provided. And that will be done in consultation with a tuberculosis expert.

Let's go on to Figure 4 now.

Figure 4 refers to management of immunocompromised contacts with a positive tuberculin skin test or QuantiFERON®-TB Gold test result. Again, if

an immunocompromised contact has a tuberculin skin test that's 5 millimeters or more of induration, or has a QuantiFERON®-TB Gold positive test result, then we would also want to go back to the information we collected in their past medical history.

We want to know if there were other risk factors that put them at risk in the past for TB before this contact investigation. Had they even been in an environment where TB exposure was a possibility? Where they born in a country of moderate or high TB endemicity (high TB burden) with greater than or equal to 20 cases per 100,000 population? Did they have a history of previous TB disease or LTBI? Were they ever previously exposed in the past to a TB patient but weren't evaluated as part of a TB contact investigation in the past, so this is their first time?

If the answer to any of those past medical history questions is yes and the person has a positive tuberculin skin test or QuantiFERON®-TB Gold test, we would probably suggest that they were infected in the past and not as a result of exposure to this index patient, the XDR index patient. We would recommend considering standard latent TB infection treatment with nine months or more of isoniazid if this person has not been previously treated (Sometimes immunocompromised patients will be re-treated if it appears that they have been recently infected, even if they were treated for LTBI sometime in the past.).

If a contact has a positive tuberculin skin test or QuantiFERON®-TB Gold test, but we do not know if this contact had a positive result due to this exposure (to an XDR TB patient) or not, there are two options to consider. And again, this should be done in consultation with a TB expert.

One option is that this immunocompromised contact whom you are evaluating could have been exposed to somebody else (with TB) and we just haven't identified that source TB patient. The source probably had pan-susceptible (pan-sensitive) TB, and so we would consider using standard LTBI treatment if the contact wasn't previously treated, because the risk of progressing to TB disease is so high in an immunocompromised contact. So certainly, treatment would be recommended in this case.

And then, the other option is to weigh the risks and benefits of possibly offering no LTBI treatment versus a highly individualized, but potentially toxic LTBI regimen. This would have to be considered if we really felt that exposure to the XDR patient was what resulted in their (the contact's) skin test (or QuantiFERON®-TB Gold) positivity. And in that situation, you must contact a TB expert because there's no standard regimen that's recommended in this specific case.

And so, that would take a consultation and really individualized therapy if therapy is to be offered. And that would also require intense follow-up with symptoms screening and chest radiograph at 3, 6, 12, 18 and 24 months (at a minimum).

We can talk about questions about this. I know that this is complicated and making a decision as to whether or not you think this person is positive based on recent exposure to the index patient versus past or other exposure based on travel history, country of origin or other possible exposures, that's where people, I think, will have the most questions.

Next.

And footnotes for the algorithms are all listed at the bottom,but the most important point to understand is that management of contacts to XDR TB patients is extremely complex, and it's largely based on expert opinion.

Individual patient decisions may need to vary from these algorithms based on individual circumstances. Consultation with a TB expert, especially one with experience in managing MDR- or XDR-TB, is strongly recommended, especially for any contact suspected of having TB disease who has a positive TST or QuantiFERON®-TB Gold result, or who is immunocompromised regardless of TST or QuantiFERON®-TB Gold result.

And there are some Web links that you can go through. We're happy to answer any questions based on these algorithms, but the notes are there at the bottom of the COCA page for you to go through.

And we also have many links here. There are links to TB diagnostic standards; links to state and large-city TB control officers; links to many of our United States TB experts or MDR-TB who are spread out throughout the country. They (the experts) work in consultation with the Regional Training and Medical Consultation Centers, the RTMCCs, funded by the CDC. These are excellent resources for clinicians.

And Francis J. Curry (in San Francisco) is the center (RTMCC) for the western states and the Pacific; the Heartland TB Center in San Antonio takes care of Texas, Arizona, New Mexico and all the way up through the Midwest; the Southeastern National TB Center takes care of the Southeast, and that's in Gainesville, Florida; and then we have the Northeastern Regional Training and Medical Consultation Center, in Newark, New Jersey.

So I just wanted to let you know that those links are all available to you and those people are happy to consult on that whenever you need it. That's what they're there for.

So, with that, I think we've covered some of the basic information, and we're happy to answer your questions.

And there are other persons on the line who are experts who can also answer some of your questions.

Thank you.

Coordinator: Thank you.

We will now begin the question and answer session.

If you would like to ask a question, please press star-1. Please un-mute your phone; you will need to record your name and organization at the prompt. Your name is required to introduce your question.

To withdraw your request, press star-2.

One moment please as we wait for the first question.

Question: Yeah, hi. I thought I need to ask a question.

I have two questions related to Figure 1.

First question is, for exposed folks who have no previous PPD test results, should we not do a booster PPD to establish a good baseline?

Theresa Harrington: Well…

Question cont'd: Second question is for exposed folks who have had PPDs in the past and they're non-immunocompromised and their PPD reading was 6 millimeter, should the positive on the P testing at ten weeks be considered as increases in duration size by 5 millimeter?

Thanks.

Theresa Harrington: Oh. Thank you.

I think that the point - were not recommending two-step testing in answer to your first question. Two step-testing is recommended for health care workers and for other persons who are going through annual testing or periodic testing because of their job.

In this situation, unless the person was tested right at the beginning as a baseline, we really are not recommending two-step testing and then an initial testing to see whether or not a booster phenomenon is causing a positive tuberculin skin test.

But I think that's something to mention. The US passengers might not have been tested (for TB) since they were a child. Back then, perhaps they were tested with the tine test that we used to get when we were students back in grade school.

So, at this point, we're not recommending other than the first round or - and/or second round (of TB evaluation and testing) depending on how long it has been since the person might have been exposed to the index patient.

And then you're saying with somebody that already have a 6 or greater than a 5 who has a baseline that you know is greater, then we'd want to see that there was an increase.

But I think the point would be to do a signs and symptoms screening and do a chest radiograph because I think that at this point, if you truly think that they're a contact, I can't say that it's going to boost by 5 millimeters. I think that that's a difficult decision to make.

So, if there are others on the line, especially Lauren (Lambert) or somebody who wants to chime in, (or Tim Holtz), I'm happy to have them also contribute to the discussion.

Does that help you?

Question cont'd: Yeah, thanks. That did answer. Thanks.

Theresa Harrington: Thank you.

Question: Hi. Thank you again for allowing me to talk.

If you look at Figure 2 and go to the right-hand side, no evidence of active TB disease and the patient has a past history of BCG, does that affect what you do?

Theresa Harrington: Thank you for this question. And I have a good friend in Montana. So you're lucky to live in such a beautiful place.

Question cont'd: Okay.

Theresa Harrington: But I do want to let you know, when we are doing a contact investigation, though we take into account the past history that this person might have had BCG vaccination(s), we do not use that in our decision making for interpreting tuberculin skin testing results of contacts.

So, despite the fact that the person had a BCG vaccination in the past, if their tuberculin skin test is 5 millimeters or greater, we actually do consider that a positive because oftentimes in somebody who was vaccinated as a child, that immunity will wane. Many people, despite the fact that they were vaccinated as a child, when you re-challenge them with tuberculin skin testing antigen, they will have a negative.

And so we won't usually have a true baseline for most U.S. passengers or other contacts in this case--we can't say whether you have a negative or not if you haven't gone through repeated skin testing (unless they were a health care professional or a teacher or something like that).

So again, for any contact investigation in the United States, we do not make the decision (of interpreting a positive TST) based on whether or not they (the contact) had a BCG vaccination in the past. We still use that ≥5 millimeter cutoff. And then, at that point, there will be additional evaluation (symptoms screening and chest radiograph).

Does that answer your question?

Question cont'd: It does. Thank you very much.

Theresa Harrington: Thank you.

Question : Am I live?

Coordinator: You are live.

Question cont'd: Okay. We really don't know whether the individual that we're dealing with today is an index patient at all or simply an isolated event, and we don't know whether this individual, at least I don't, is a HIV-positive or not.

However, we do have with extreme tuberculosis the first focal epidemic that we've seen in Southern Africa, and I'm wondering whether anyone has current statistics on this epidemic -- the mortality, the epidemiology, who is getting this infection and how rapidly is it spreading.

Does anybody know what we know about the epidemic of extreme tuberculosis in Southern Africa where we have many more than one index case -- we've got a whole heck of a lot of sick people?

Theresa Harrington: Thank you, I wanted to let you know that certainly, the CDC is very much involved in what's been going on in South Africa, in Kwazulu-Natal, as well as many investigators from universities and public heath schools as well as the Ministry of Public Health in South Africa.

We also have Dr. Tim Holtz on the line who is an XDR-TB expert. He was also involved in the original discussions in South Africa about how to make the definition of extensively drug resistance-tuberculosis.

And this patient had not traveled to South Africa. So I just want to make it clear that this is not related to that specific - the outbreak of extensively drug resistant-TB and the Kwazulu-Natal region of South Africa.

Question cont'd: Obviously not. Extreme TB has been found throughout the world.

Theresa Harrington: Correct.

Question cont'd: However, the South African situation is the first focus that we have.

Theresa Harrington: Correct. Because there (in South Africa) was the convergence of HIV and TB that we find in many regions of the world. And it's just that at that point in time, many of these persons (the XDR TB patients in KZN) were also receiving HAART (highly active antiretroviral therapy) yet, were succumbing to disease. And it turned out to be that this was the organism that they had--disease caused by this extensively drug resistant-TB.

And as you know, we do not know the extent of XDR-TB in the world because many countries only have the resources to check smear status; they have no resources to be able to to perform (TB) culture and drug susceptibility testing.

And I think that that is definitely a priority of the Centers for Disease Control and Prevention as well as the World Health Organization. They are pouring many resources into trying to improve (TB) diagnostic capabilities throughout the world.

Question cont'd: So we don't actually know anything about what's happening in South Africa?

Theresa Harrington: I'm not sure that I…

Tim Holtz: I'd be happy to try to…

Theresa Harrington: I think we do.

Tim Holtz: …answer the question.

Theresa Harrington: Go ahead, Tim.

Tim Holtz: Thanks, for the question.

As you noted, XDR-TB had been found in almost all continents in the world. I think it would be hard to say that the focus is in Southern Africa as this would - as it would be difficult to say that MDR started in one place.

We think that occurrence of XDR-TB in many different countries around the world is sort of a natural progression of drug-resistant bacteria as they get exposed to second-line drugs, sort of inappropriate use of second-line drugs.

So I think focusing on Southern Africa because they may certainly have a higher number of cases probably because of the confluence of many factors including HIV, including a poorly-performing TB control programs, difficulties with adherence to therapy, et cetera.

But I think there are many other places in the world, such as even in Latin America and Southeast Asia, where we know that there are XDR-TB cases.

Your question points out a very good salient point about XDR-TB epidemiology in that we really do not have very good surveillance for this, and points to the need for improved drug susceptibility testing on isolates of patients who are at risk for drug-resistant TB as well as improved surveillance systems that will be able to report on this problem. And CDC is working with WHO right now to try to improve surveillance for drug resistance around the world.

Question cont'd: I can find absolutely no current information on what is going on in South Africa, and it is the very first focus of extreme TB. I'm not talking about extreme TB - 50 cases here or 50 cases there.

I'm talking about a focus that it's very clear that we are getting person-to-person communication of extreme TB, and there are no statistics coming out of South Africa to say what the heck is happening. This is an epidemic.

When SARS hit China, we excoriated China because they were not being forthcoming about the statistics on SARS. There are no statistics coming out of Southern Africa on extreme tuberculosis from one person to another. We are not getting the information we need to evaluate what's going on there. And I don't understand why.

Tim Holtz: Well, I appreciate your concern. I think it's a…

Question cont'd: It's not my concern. I'm questioning this.

Tim Holtz: And I…

Question cont'd: What the heck is going on? Why aren't we getting these numbers out of South Africa?

Tim Holtz: I appreciate your question and concern. Perhaps, we could even take this discussion apart from this call. This call, I think, is trying to focus on issues about contacts of patient - contacts of this…

Question cont'd: Excuse me, sir.

Tim Holtz: Okay. So…

Question cont'd: I really am looking for information on what the heck is going on in Africa. And I don't want to take anymore time on this conference call because, as you say, I am intruding on everybody else's time. But if you have a chance to give me an email, I'd really appreciate it. I just can't find out what's going on in South Africa and I don't know why.

Thank you.

Jim Schwendinger: And actually sir - and Dr. Holtz, thank you for your answer.

For anyone else that might be on the call, for that question and certainly ones that are, you know, maybe beyond the purview of this call's intent, you know, if you'll give an email to us at CDC at coca, C-O-C-A, @cdc.gov, we will be, you know, happy to work with the subject matter experts to find the answers for that. So that's coca, C-O-C-A, @cdc.gov for, you know, that question and any others that, you know, maybe beyond the scope of this call.

And thanks again, Dr. Holtz.

I think we can move on to the next question.

Question: Thank you. Thank you very much for a very good presentation. I actually have two questions.

One, if you were evaluating an individual who was a contact with a history of a recent negative TB skin test, would you retest now at that time of the evaluation or would you wait eight to ten weeks from the first negative TB test that was the recent one?

Theresa Harrington: Only one question?

Question cont'd: I have two questions. Should I ask the other also?

Theresa Harrington: Go ahead. What's the second one.

Question cont'd: The second one is, "What was the source for your algorithm for the evaluation for this particular case?"

Theresa Harrington: I can answer the second question first. Dr. Phil LoBue, who is one of our MDR TB experts here (at the CDC), and he is the Associate Director for Science here at the Division of Tuberculosis Elimination. He and a group of experts in MDR came up with this algorithm based on the multidrug-resistant TB algorithm.

Question cont'd: Okay. So this is CDC file?

Theresa Harrington: Yes, but it was made in conjunction with world experts.

Question cont'd: Okay, thank you.

Theresa Harrington: So maybe you can give me a little more information about when somebody had a recent negative TST.

Question cont'd: Like in the last four weeks.

Theresa Harrington: Okay.

Question cont'd: Uh-huh.

Theresa Harrington: And when was the contact exposed to the index patient?

Question cont'd: So it would have been June - let's say using the example of the intercontinental flight exposure…

Theresa Harrington: Uh-huh.

Question cont'd: …so you have somebody who, you know, had a routine negative test May 25, 26, whenever he was exposed.

Theresa Harrington: Right.

Question cont'd: Is contacted because of what is being go-and-seek-your-health-care-provider-because-of-your-exposure, and so that person presents for an evaluation.

Theresa Harrington: Right. So that person already has - what - you're saying that this person, maybe they're a health care worker or maybe - for whatever other reason, they had a negative tuberculin skin test very shortly before they traveled.

Question cont'd: Exactly.

Theresa Harrington: Okay. And so you can actually consider that a baseline.

Question cont'd: Okay. And so then, you would just do it eight to ten weeks later from the first test?

Theresa Harrington: Right, exactly.

Question cont'd: Okay, okay. Thank you very much.

Theresa Harrington: Next?

Coordinator: Thank you. Our next question comes from the VA Southern Oregon Rehabilitation Center.

Question: Yes. In a facility such as ours, if we have someone who is - has been identified with tuberculosis and we have him in isolation to start treatment, we normally release him from isolation after two to three weeks of drug therapy, negative smears, which they might have had originally, and clinical improvement.

Is there any reason to change that process and keep someone in isolation until their drug sensitivities are back?

Theresa Harrington: You know, this is a question that's being asked now. Thank you for your question. Actually, this is a question that's being asked all throughout the United States.

People are concerned as to whether or not should we be expecting a higher rate of drug-resistant tuberculosis. And if so, then do we have to change our guidelines? Should we be waiting until the drug susceptibility testing results are back?

I think that this will have to be done on an individual basis. But if your patients have not been previously treated for TB, and if they hadn't traveled to an area where you suspect that there's a lot of drug-resistant TB, then I think you can still follow those guidelines.

The other option that sometimes is offered is that there are DNA probes. There are DNA probes that can be done on the (AFB-positive) sputum just to determine whether or not there is rifampin or isoniazid resistance. That could be done on the actual sputum specimen.

And I know that Ed Desmond's lab out in Berkeley or Richmond California, the California State Department of Health Lab, does that (test). And there might be other reference laboratories that can look for the rpoB (mutation) and you can use rifampin resistance as a marker for MDR.

And so I think that if you suspect (drug-resistant TB) because of a patient's clinical history-- certainly, you're seeing in a VA hospital people who might have traveled in the past to TB-endemic areas where perhaps there was a lot of high drug resistance or the persons that are coming back now from different parts of the world--that is something to be considered on an individual basis, not a group basis.

There are tests out there that can help you make that decision if you suspect (drug resistant TB). But otherwise, I don't think at this time that we're recommending any changes to the clinical guidelines that you've been following all along.

And they sound very reasonable; it sounds to me like you're following the two to three weeks (of therapy) and that they're (the patient) responding to therapy.

Question cont'd: Thank you.

Theresa Harrington: Uh-huh. Thank you.

Question: My question is regarding a client who has had four negative sputum, but his culture came back positive. And I'm wondering how infectious is he at this point.

Theresa Harrington: So do you mean how infectious the person is to close contacts?

Question cont'd: Yes.

Theresa Harrington: Okay. Well, we know from the literature that perhaps up to 15% to 20% of persons who end up developing latent TB infection have been infected by a smear-negative, culture-confirmed contact of a source case. So, certainly yes, there is a possibility. The transmission is much lower from smear-negative cases, but transmission is still possible.

But just putting the person (TB patient) on therapy as you would normally do reduces the bacterial burden immensely within days to a couple of weeks.

Question cont'd: Yeah, because he did come - the susceptibility indicated that he was resistant to INH. So he was switched to rifampin.

Theresa Harrington: Okay. No, but he's on four drugs. You said he's culture-confirmed.

Question cont'd: Yes. And then, his culture…

Theresa Harrington: Oh, okay. Originally, he just had LTBI?

Question cont'd: Yes.

Theresa Harrington: Okay, I understand, yes. But now, he'll be placed on additional medication.

Question cont'd: Okay. Thank you.

Theresa Harrington: Thank you. Next question.

Question: I think you're very clear and concise and very helpful.

I'm wondering if these algorithms exist for pan-sensitive tuberculosis.

Theresa Harrington: Yes, ma'am. In our Treatment of TB Guidelines, June 20, 2003, Volume 52, Recommendation 11, Reports and Recommendations Number 11, you can access that on the CDC Web site.

I think it's also linked at the bottom of the COCA Web site and you can just push on that and it's called Treatment of Tuberculosis. And we do have algorithms in that. They'll take you through it kind of step-by-step.

Question cont'd: Thank you.

Theresa Harrington: Sure. You're welcome. Thank you for your question.

Question: Thank you, Dr. Harrington, for the helpful algorithm. I have a question on Figure 2 on the right-hand side.

When the TST is positive and the QuantiFERON Gold is positive, but there's no history of previous TB exposure and no birth in country of high TB burden, so we have to concede then that this person is positive secondary to exposure to the XDR-TB?

And the reason why we're not treating but we are following screening of chest x-ray typically for 24 months is because we don't have any medication that we can also just treat the LTBI. Is that true?

Theresa Harrington: Hi. Thank you. I appreciate your question.

Yes, I think on this …First of all, was this person a very recent positive TST, or how far after their exposure to the index patient was the tuberculin skin test performed?

Question cont'd: It's a theoretical question, so I…

Theresa Harrington: Oh, theoretical question. Oh, okay.

So this is a hypothetical situation. Okay because I think that in this case, at least as of this point, we're not expecting that there has been a lot of transmission from this case, the XDR case.

But if you're assuming that yes, if, let's say, you did find a person and you really think that they became infected from the XDR-TB patient, then you're absolutely right.

There is no standard therapy. There is no (standard therapy)- we do not have enough world experience with extensively drug resistant-TB. And there are very few medications that could be offered to somebody for treatment of disease, and that's separate from treatment for latent TB infection.

And as you know, your risk of developing TB disease is approximately 10% over a lifetime, and that's in an immune-competent person who has a normal immune system.

And so, that person's (the contact) risk is approximately 5% from progressing from latent TB Infection to TB disease within the first two (to five) years following infection.

And that's why we want - I mean – excuse me-- in the first two years following infection. And so, that's why we want to really closely follow them, in particular for those first two years.

And so, you're absolutely right that, this would be the guidance that you would follow, --to really focus on symptoms screening and chest radiograph.

And you'd have to impress on that person that at the first sign of any respiratory cough or illness (or other TB-related symptoms), that they come in to be re-evaluated. Or, if they become diagnosed with diabetes or if they're diagnosed with Crohn's Disease and have to be put on immunosuppressive medications -- or rheumatoid arthritis -- certainly you will be following these people very closely.

Question cont'd: Thank you.

Theresa Harrington: Thank you.

Question: Hi. I was wondering what CDC has in mind as far as reviewing their worker - health care worker protections in light of the emergence of XTB. I know that you recently updated your TB guidelines, but there's a lot of recommendations there that aren't really evidenced-based here, really based on expert opinion.

A good example is the use of N-95 respirators and the need to fit-test them. And, you know, CDC's somewhat ambiguous as far as saying that this - they

should be fit-tested periodically, but we don't really know what periodic means.

And we also have questions about whether or not there is actually data to show whether or not N-95 respirators are even sufficient. We know there's institutions like Johns Hopkins that are using powered air purifying respirators for TB - or even regular TB exposures, let alone XTB.

So I guess the question is, you know, are you going to review the guidelines for health care workers? And also, are you going to look at the level of compliance that already exists against TB?

Because our members, we represent about a million health care workers, and they're not receiving the education that they should be receiving to be on the lookout for XTB.

I know that patient that came down from Montreal and moved to Atlanta stopped in New York. And it's probably one of the hospitals where our members work. And, you know, we're concerned about their exposures.

Thank you.

Theresa Harrington: Thank you for your question.

I know that at the highest levels of the CDC, in this kind of situation, we have been looking at whether our guidelines are stringent enough. And I think, though, that this is also something that's done in consultation always with NIOSH. They're really the leaders on the occupational health and safety.

So, it's, you know, I don't want to speak for NIOSH and what they're doing also in regards to this, but they've also been very much - from the very beginning, they have been involved in every conference and every consultation in this case.

I don't know, Lauren Lambert is our expert on hospital infections and she was very instrumental in putting together the most recent guidelines for preventing transmission of *Mycobacterium tuberculosis* in health care settings from December 30, 2005. And she is on the line and she might be able to further comment on this.

Lauren are you there?

Lauren Lambert: I am and thank you.

I just want to say you are correct, sir, that those guidelines are written - a lot of them on expert opinion rather than evidence-based just because the evidence was lacking especially for what you mentioned specifically the efficiency of N-95 and how often to test periodic or how what exactly periodically means. Ambiguous because of the fact that there are no data to explain what periodic should be and if it's different from every setting.

So sorry it's not a good, but I'm afraid that the reason is because there just isn't enough evidence to say one way or another the efficiency of the respirators and periodicity of the testing. So it's a very gray area.

Question cont'd: And, you know, am I still on the line? Can I still…

Theresa Harrington: Yes.

Question cont'd: So I guess really the question is, I mean, how is CDC going to kind of try to collect some evidence-based research? You know, again, it's not just XTB, it's, you know, we had the same situation with SARS and we're going to continue to have situations with other airborne agents whether pandemic flu, whatever.

And so, what is CDC doing to fund basic research on - to better characterize bio aerosols and also to validate to the level of protection for health care workers regarding respiratory protection?

Jim Schwendinger: I think maybe if you could send that question in an email? I mean, it is a very complex, you know, very good questions you're asking. But as Dr. Harrington said, really, it's kind of beyond the scope of this call, plus it involves many other agencies including the National Institute of Occupational Safety and Health as well as the Occupation Safety and Health Administration, you know NIOSH and OSHA.

So, if you can maybe email that to us, we could possibly, you know, get together with the subject matter experts that are under the CDC umbrella and possibly get some of some of that very good content question answered. And send that to coca, C-O-C-A @cdc.gov.

Question cont'd: Okay, thank you. But, you know, I'd also appreciate the NIOSH part of the CDC.
But I will get you a - and I will type up a question get it to you.

Jim Schwendinger: Sure. And I was just saying, again, it's NIOSH-OSHA -- it's a really complicated, kind of multijurisdictional issue. But it's a very good one and a very timely one.

I think we'll take two more questions. I hate to cut off folks but Dr. Harrington here has been great in giving us a lot of her time.

And I think for anyone that didn't have a chance to ask questions, please send them via email to COCA and we will do our best together with her and the other subject matter experts to get them answered.

So Sue, if - we'll take two more questions I think.

Question: Hi, Dr. Harrington. I just wanted to clarify the question of retesting someone with a recent skin test.

The follow-up test should be eight weeks after the last possibility of the exposure. So sometimes, we would look at eight weeks after two weeks of medication rather than eight weeks after the first skin test, after the first TST.

Theresa Harrington: Yes. I agree. I'm sorry if I didn't make that clear. It's eight-to-ten weeks after the last exposure. You're absolutely correct.

Question cont'd: And for people that are at home, it should be after they've completed the medication, not just when they first started on the medication?

Theresa Harrington: Thank you.

Question cont'd: Thank you.

Theresa Harrington: Thank you for qualifying that.

Question: Thank you. And thank you for the excellent presentation.

One of the early reports in the news up here in New York was that the index patients of the XDR-TB traveled to Vietnam. And I'm wondering, is there any inkling of any other areas where he may have travel where he might have acquired this thing?

Thank you.

Theresa Harrington: I'm not going to be able to comment on the index patient's case specifically; but yes, just as many of us have traveled to different parts of the world, he has traveled to different parts of the world over many years. His most recent travel, as has been reported, was for a few weeks to Vietnam last year.

Question cont'd: Thank you.

Jim Schwendinger: Great. Well, again, I'd like to thank everyone for calling in on our discussion. I'd especially like to thank Dr. Harrington and Dr. Holtz and…

Theresa Harrington: Lauren Lambert.

Jim Schwendinger: …Dr. Lambert for calling in or you're helping with the Q&As.

Sue's going to tell about the playback number for this call. And, of course, you know, we'll have the transcript and the recording on the Web site pretty soon. And then, you know, please email any questions you didn't get a chance to ask to coca@cdc.gov and we will try to get those answered.

And perhaps, we could, if there seems to be themes in the questions, we may even be able to post those on our COCA Web site.

Coordinator: Thank you.

If you would like to listen to a replay of today's conference call, you can dial in to the toll free number, 1-866-380-8119. That will be available in approximately one hour.

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