NJ Medical School Global Tuberculosis Institute
December 7, 2012
1:00 p.m. ET

Slide 1

Bill Bower: Good afternoon everyone and welcome to our series of web-based seminars on Best Practices in TB Control. Today's seminar will focus on practical uses of epidemiology for tuberculosis control. My name is Bill Bower and I'm the Director of Education and Training at the Charles P. Felton National Tuberculosis Center, a component of the Northeastern Regional Training and Medical Consultation Center.

Slide 2 Our faculty today are myself, Dr. Marian Passannante, Epidemiologist at the New Jersey Medical School Global TB Institute

Slide 3 Mark Wolman, Program Manager Tuberculosis Control at the New Jersey Medical School Global Tuberculosis Institute. Patricia High, Supervising Program Analyst at the Ocean County Health Department, Toms River, New Jersey. And Lynn Sosa, Deputy State Epidemiologist, Connecticut Department of Public Health, Tuberculosis Control Program, Hartford Connecticut.

Slide 4 I'd like to ask each of you to let us know if your job requires that you use epidemiology never, once or twice a year, once or twice a month, every week, everyday, or all the time. So there's nobody who is in the never category, there are a few people in the you know, once a month or once or twice a year category, but there's a lot of people here who are using it, everyday or all the time. I mean you put those three together, that's sixty percent, so that really shows we've got an experienced audience, or a very interested one.

Slide 5 Let us know now the area in which you use epidemiology. It looks like program planning and evaluation is coming out to be the area in which most of you apply epidemiology. That certainly makes sense, but it's really heartening to see how much in contact investigation and case management, people are also using this information because it can relate to decision making about how you proceed, in both of those areas. This gives us a better

understanding of who you are and what we're currently doing about using epi in our everyday work.

Slide 6 Now let's get started with an overview of what epidemiology is. Dr. Marian Passannante is an Associate Professor at the University of Medicine and Dentistry of New Jersey in the Department of Preventive Medicine and Community Health and the Department of Quantitative Methods, Epidemiology and Biostatistics. She is also the epidemiologist at the Global Tuberculosis Institute and she's received more awards and more published articles than I have time to tell you about today. So really there's no one better to get us started on today's topic. Marian…

Marian Passannante:

Thank you Bill, today I've been asked to talk about how you can use epidemiology to enhance TB prevention and control activities, and since many of you are already doing this, some of this will be very recognizable to you.

Slide 7 I'm going to start by providing a few reasons why you should learn about epidemiology. First, simple epidemiologic methods can be used to assist TB program staff to analyze and make practical use of data. This data may come from your individual programs or from state or national sources. Second, epidemiology can help to assess current and evolving trends in TB disease to identify high risk groups in a program area, and help to determine where limited resources should best be allocated.

Finally the results of epidemiologic investigation can help TB program staff to work towards effective TB control. For example, results from studies that reveal barriers to completion of therapy can be used to implement changes in a TB program structure or procedures that can improve completion of therapy.

Slide 8 I'm going to start by talking about providing some of the basics of epidemiology. Let's start with a definition, study of the distribution in determining of health-related states in specified populations, and the application of this study to control health problems. To simplify this a bit, we can say that epidemiology can help us to see who's getting the disease, and

where, when and why diseases occurring, so that we can use this information to control the health problem.

Slide 9 There are two broad types of epidemiology, descriptive and analytic. In descriptive epidemiology, we simply describe the distribution of diseases in terms of three elements, person, place, and time. We want to know who is getting the disease, where the disease is occurring, and when people are getting the disease. This type of information is very important when figuring out which groups are most heavily burdened with disease, and to figure out where to allocate resources.

In analytic epidemiologic studies, we go even further and try to study the relationship between possible risk factors and disease occurrence. This type of information can help to identify groups that are at greatest risk of developing TB. Very specific types of analytic epidemiologic studies help to identify the most exceptional drugs that are being used to treat TB once infection or disease have occurred. Now TB programs can use both of these types of epidemiologic studies to enhance their programs activities.

Slide 10 The major source of descriptive data for TB disease is through our national TB surveillance system. In general, public health surveillance is defined as the systematic, ongoing collection, analysis, interpretation, and I think one of the most important steps is the dissemination of the health data. The purpose of public health surveillance is to gain knowledge of the patterns of disease, injury and other health problems in a community, so that we can work towards controlling and preventing them.

Slide 11 Now many of you are probably responsible for some aspect of the collection of public health surveillance data. In the United States, requirements for reporting diseases are mandated by state laws or regulations. When such laws or regulations exist, health care providers, laboratories, and public health personnel report the occurrence of these notifiable diseases to state and local health departments. CDC has been collecting information on new cases of TB disease in the United States since 1953. Data on TB cases are collected using the report of verified cases of tuberculosis or RVCT form, or a similar form

developed by a state or big city TB program. These data are then de-identified and transmitted to CDC using a variety of electronic data collection and transmission system. The state TB programs are the primary source of this TB surveillance data.

Slide 12 Now so far I've been talking about descriptive epidemiologic data and where it comes from. However, we can study risk factors for developing TB infection or TB disease by using analytic approaches. The three most common analytic study designs that epidemiologists use are cross sectional studies, case control studies, and cohort studies. And you'll hear a little bit more about these when the other presenters present today.

Slide 13 The simplest type of analytic epidemiologic study is the cross sectional design. Sometimes cross sectional studies are fairly descriptive in that they describe the disease or condition in a population at a given time in terms of person, place or time, but cross sectional studies can also provide information on possible risk factors and disease outcomes at the same point in time.

For example, a cross sectional study to determine risk factors for latent TB infection among employees at a healthcare setting might be conducted by asking employees to answer questions about possible risk factors, and then testing them for latent TB infection. This study would be limited in that it could not provide information on the causes of infection since it would be unclear whether the infection or the risk factor occurred first.

But the study could provide hints regarding the most likely risk factors associated with infection, and these findings could be studied further using other epidemiologic study design. The epidemiologic measure that is most commonly calculated from a cross sectional study is called prevalence, and this is a measure of how often something occurs in a population.

Slide 14 Case control studies are done when cases, who are people with disease or infection, are selected to be part of a study. Then controls, who do not have the disease or infection are identified, both are questioned about potential risk factors which occurred in the past. An example of a case control study would be a study where people who had TB, the cases, were identified and compared

to those who did not have TB, these would be the controls. We'd ask them about their possible risk factors for disease like their travel history, their cigarette smoking history, and their employment history.

Through this type of study we can estimate the amount of disease risk associated with each of these risk factors. This is done by calculating measurements called odd ratios for each risk factor. In general, the larger the odds ratio the stronger the risk factor is for that disease outcome.

Slide 15 The third type of study that I will describe is a cohort study. In a cohort study epidemiologists collect information on a group of exposed and unexposed individuals and follow them over time. By exposure we mean exposure to a risk factor. We then follow this group over time and calculate the risk of developing a disease in both exposure groups. We can use these risk measurements to calculate a relative risk, which tells us how much more likely someone who has been exposed to a risk factor is to get a disease outcome compared to those who have not been exposed. Just like the odds ratio in general, the larger the relative risk, the stronger the risk factor is for that disease outcome.

A good example of a cohort study might be, once a case of TB is identified in a nursing home, following up a group of healthcare workers who were exposed to that patient, that's the exposed group, along with a group of healthcare workers who did not work with that patient, the unexposed group. And then calculating and comparing the rate of new TB infection in both of these groups.

Slide 16 Now there's a very special kind of analytic study that's called a clinical trial. Clinical trials are used to assess the effectiveness of clinical therapies, for example, a new TB drug. In these trials, individuals are assigned to different therapies and then followed over time to measure the outcome of the therapy.

Slide 17 For all three types of study outcome measures that I mentioned today, prevalence, odds ratios, and relative risks, we often calculate something called a confidence interval around these measures. Usually, 95 percent confidence

intervals are reported in the medical literature. A confidence interval tells the reader how confident we are that the measure that we calculated in our study is a good representation of what is actually happening in the population. When confidence intervals are calculated, they take into account the size of the sample and the amount of variability there is around the measurement.

At the end of this webinar I'm going to provide you with some good references for learning more about epidemiology, and they will include references that explain exactly how to calculate and interpret the epidemiologic measures that I just introduced. But for now we just want to be sure that everyone's aware of the terms because some of them will be used in our presentations today.

Slide 18 Now there's one more thing I want to go through that's going to be presented by one our presenter's, Mark Wolman, and it's a two by two table. This is probably going to be a review for many of you, but this is a way that much of our epidemiologic data are displayed, in cross sectional studies, case control studies, and cohort studies.

It's called a two by two table because the data collected in the study can be put into two rows and two columns with four cells, identified by A, B, C and D.

Slide 19 Risk factors for a disease are usually presented in the rows, in the first row we have people who have the risk factor. I've indicated by the risk factor positive sign. In the second row, people who don't have the risk factor are indicated by the risk factor negative sign.

Slide 20 Outcome data are usually presented in the columns. The first column includes those people who have the disease outcome, that's outcome positive, and the second column includes those who do not have the disease outcome, or outcome negative.

Slide 21 People in cell A have both the risk factor and the disease, so risk factor positive, outcome positive. And people in cell D have neither the risk factor nor the disease, they are risk factor negative, outcome negative.

Slide 22 People in cell C do not have the risk factor, but do have the disease, and people in cell B have the risk factor but do not have the disease outcome.

Slide 23 Sometimes when we want to compare the results of two different tests administered to the same person, for example we might want to compare two different types of tests for latent TB infection. Or even the same test taken by different labs, we use a two by two table to do this. We just need to change the labels so that the results from one test are in a column and the results from the other test are in the row.

When the results are the same for both tests, positive for test one and positive for test two, that appear in cell A, and negative for test two, and negative for test one, that appears in cell D. We describe these results as concordant results, because the results are the same regardless of the test, positive, positive or negative, negative.

Slide 24 When the results are different for each test, for example, a negative test result for test one, but a positive test result for test two, which would appear in cell C or a positive test one, and a negative for test two, which would be in cell B, we describe these results as discordant, because the test results are not the same at both testing times. In the next presentation you will see an example of how a TB program looked at data using a two by two table, and the conclusions that they were able to draw from this information.

Bill Bower: Thank you Marian for this practical overview of epidemiology and what it can do for us. I really appreciate that you spoke a bit about the statistical methods that are behind the science of epidemiology, because it's good for everyone to see that epi does not have to be difficult and that it really can point the way to learning a lot about who are clients are, what risk factors are important and how we can change our practice to better control disease.

Slide 25 Some of you may be asking, 'Can I really do this?' 'Why should I do this?' Well now we're going to have some examples of programs at different levels that are using epidemiology to make a difference. We will start with the clinic level. I'll be turning the program over to Mark Wolman. Mark has a Master's in Public Health from Hunter's College in New York City, and he has a long history working with the New Jersey Department of Health and Senior Services. For some time now, he has been the Program Manager for Tuberculosis Control at the New Jersey Medical School Global Tuberculosis Institute, where his people skills, practical experience and persistent questioning make him a most valuable contributor. Mark…

Mark Wolman: Thank you Bill. So I'm going to report on my 2010 findings regarding the routine record review and subsequent completion of the CDC TB follow-up worksheet as it relates to the final medical dispositions of Class B2 immigrants arriving in our clinic area.

Slide 26

As most of you may be aware, according to CDC tuberculosis classifications for immigrants are described by the following categories. Class A TB are applicants with infections and potential infections of TB disease, typically are not permitted to travel, however waivers may be granted to immigrants prior to treatment. Some of the reasons for granting a waiver may be that an older child may need to come to the United States for any reason, there may be religious or political persecution, or a lack of availability of appropriate treatment. Those are typical reasons for waivers. Although I understand now that really if you're Class A, you're not permitted to travel.

Class B1 TB pulmonary, there's really three subcategories, no treatment, completed treatment, and extra pulmonary. For no treatment, applicants present with findings, typically x-ray findings suggestive of pulmonary TB, they are AFB smear and culture negative, and treatment generally is postponed until after immigration.

Slide 27 These are applicants who have completed treatment in their country of origin through DOT prior to immigration, and they're obviously permitted to immigrate. And Class B1 extra pulmonary obviously is patients who provide

evidence of extra pulmonary disease and again treatment is generally postponed until after immigration.

Slide 28 Class B2, LTBI evaluation, these are applicants, with TST, ten millimeters or greater or positive IGRAs, disease is typically ruled out in the country of origin through immigration film, and treatment is again generally postponed until after immigration. And this will be the topic of our discussion for the next few minutes.

Class B3, contact evaluation, not as common as the other B1's and B2's. These are applicants with documented recent exposure overseas, to a known TB case, LTBI may or may not be done in those countries. However, what we're looking for on the immigration forms is information about the index case, particularly smear and culture results, and sensitivities.

Slide 29 In 1991, CDC initially published the technical instructions, commonly called TI for overseas screening for TB. At that time, the instructions were felt to be pretty thorough and complete. However in 2007, they were revised requiring panel physicians overseas to administer TST's or IGRA to children, age 2 to 14, who are applying for US immigration. These were children living in countries with TB incidence of equal to or greater than 20 cases per 100,000 population.

If you compare that to the United States 2011, our case rate was 3.4. So these children coming from countries where the case rate is 6 to 7 times of the United States. These are asymptomatic children with a positive TST or IGRA, their films are negative and as such they are characterized as Class B2.

Slide 30 Now in New Jersey we have a policy that requests the following recommendations for B2 that present to the health department or clinic. A review of current medical history is provided by a parent or adult of the child or a guardian, assessment of both current and overseas medical information as provided through the immigration papers, a current symptom assessment, and regardless of TST or IGRA results overseas New Jersey recommends re-administering TST and recollecting the IGRA for confirmation purposes.

Slide 31 In 2010, despite IGRAs being phased into both our clinic practice as well as overseas screening for B2 immigrants, the TST did remain the predominant method to identify LTBI. So completing the TB follow-up worksheet with the final domestic disposition required cross checking foreign TST results as reported on the immigration forms and comparing the domestic TST results.

Slide 32 As I did this, I noticed a notable discordance in the results and this captured our attention and we decided to further explore this event of interest. So in an effort to collect, analyze and interpret this health-related data, we initiated a retrospective record review of Class B2 immigrants arriving in three New Jersey counties between September 1, 2009 and March 25, 2010.
The numbers are small. We decided to include another county but the numbers still remained small. The review consisted of comparing foreign and domestic results. We took a look at the proportion of discordant TST results and they were calculated both overall and by country of origin.

Slide 33 69 Class B2 immigrants reported for evaluations during the time period that I mentioned earlier. However, unfortunately 23 immigrants were excluded from the review for the following reasons. Several moved out of the jurisdiction, some to a different county in New Jersey, some out of state, several we were unable to locate, a few had no documented record of initial TST results from their country of origin, and few were retested with QFT.

Slide 34 We were left with 46 immigrants comparing foreign and domestic TST results. 32 of the 46 or 70 percent were from the Dominican Republic, about a ¼ were found Philippines, and 7 percent from other countries, namely Haiti, Thailand and Vietnam. Gender breakdown, 2/3 females, 1/3 males, median age 11.

Slide 35 According to immigration records, the majority of foreign TST results clustered between 10 and 12 millimeters.

Slide 36 Figure 1 on the left is the overseas results and you can see from the cluster of 10 to 12 millimeters, this is where the majority of the immigrant results

landed. On the right hand side, the domestic TST, you can see where the clusters just dissipated and the majority of the patients now were zero millimeters.

Slide 37 Overall, it's 27 of 45, which is 60 percent of Class B2 immigrants with a foreign TST result of greater than 10 or equal to 10 had a repeat result of zero millimeters.

Slide 38 A total of 45 individuals had greater than 10 millimeters TST's. Of those domestically tested, 18 remained greater than 10 but 27 now were zero millimeters for the 60 percent.

The less than 10 millimeter on the foreign TST was zero millimeters, but when it was repeated in a clinic in the other county it was read as greater than 10. There's discordance on both ends but for purpose of discussion today, the 27 of 45 which is 60 percent overall discordance in TST results from foreign to domestic.

Slide 39 This is a look at all countries. The blue is positive foreign TST, the red discordant domestic TST. We took a look at which countries these children were coming from, whether there was discordance, and again Dominican Republic and Philippines showed the most discordance. The other countries were Nepal and India, which showed no discordance.

Slide 40 93 percent of immigrants reviewed originated from Dominican Republic and Philippines and unfortunately, this limitation did not allow for analysis of data from a wider variety of countries. However, the striking discordance between foreign and domestic TST results among B2 immigrants from the two countries raises questions about the validity of the results in those countries.

Slide 41 Some of the causes that we came up with were proper and improper administration of TST and or misinterpretation of TST results, reading the redness verses induration. Two other causes may be storage of the solution and the thought may be a revival perhaps of the controversy of tubersol verses aplesol. However, that controversy was between 11 and 18 years ago so we don't think it has bearing on these discordant results. My feeling is that it's

probably most likely a misinterpretation. Even in New Jersey, even in our counties that we oversee, we still hear about private doctors, outpatient medical clinics, hospitals who are reading redness verses induration. It wouldn't surprise me if this was the issue in those two countries.
The inaccuracy of these results has various and far reaching implications including unnecessary increased workload at local health departments and clinics, unnecessary x-ray films, doctor visits, medical treatment and use of limited resources.

Slide 42 As a result of this review, a comprehensive study was recommended to address the root cause of this potentially widespread phenomenon. So representatives from the CDC recognized this discordance and initiated appropriate discussions with their global partners from the two countries in order to implement steps of quality assurance regarding the administering and reading of the TST. I'd like to mention in closing that the introduction of QSTs in our clinics were no longer allowed for the demonstration of TST to TST discordance, but rather will show and is showing TST to QFT discordance.

So despite the fact that two years later, 2012, IGRAs may be slowly replacing the TST in the screening of immigrants, it is important to say that this project in retrospect was not so much about TST, so much as it was about illustrating an awareness and questioning of unexpected and frequent occurrence, and the subsequent interest, data collection, analysis and interpretation of the data in order to gain an understanding and explanation of the occurrence.

Slide 43 I would like to acknowledge the following people for their work in this project and I thank you all for your time and your attention.

Bill Bower: Mark, thanks very much for sharing that clinic level perspective. OK, often it's the little things that are noticed day to day like that in a clinic that point the way towards something underlying that's more important, and you guys tracked it down here. Epidemiological methods are definitely the way to bring science to bear and detect deeper patterns when something like this comes up, so thanks.

Slide 44 We've got time now to take one question.

Participant: Mr. Wolman, this is Houston. BCG was not mentioned in your study.

Mark Wolman: Dominican Republic and the Philippines do use a BCG. The question about BCG is or the controversy surrounding it is, as we know, does not give life-long protection. So if the TSTs were being read inappropriately in those countries, for instance if redness was being recorded as opposed to induration, and by the time we did the TST perhaps the TST was not influenced by the BCG because they were already over 11 years of age. And the protection of BCG was not evident in the TST results.

Bill Bower: Mark, usually the TST done overseas is probably done within a year of when you would have repeated it here in the US, isn't that true?

Mark Wolman: It probably is, I would say a couple months to a year.

Bill Bower: You're both testing under similar conditions of BCG being a factor. Dr. Lardizabal…

Alfred Lardizabal: All these countries have it in their policy to administer BCG and they're usually done around birth. The discordance, using the same test are, I don't think BCG would have been a factor there. And again as Mark had said, perhaps it's in the administration of the test or interpretation of the test or perhaps even the storage of the antigen could have been a factor.

Slide 45

Bill Bower: Thank you very much. Let's move onto the next speaker. I'll be turning the webinar over to Patricia High. Patty has a background in global disease epidemiology and control and she's worked domestically and internationally on a range of health issues with USAID and Medical Care Development Incorporated. She currently supervises ambulatory care clinic operations in compliance with federal and state guidelines at the Ocean County Health Department. Patty?

Patty High: Thank you so much Bill for the introduction and I'm excited just even for the opportunity to be able to share today some of the lessons that we learned at the county level in using epidemiology to discover and unveil some TB in places where it's not typically identified.

Slide 46 In New Jersey, in 2011 we saw approximately 3.8 cases per 100,000 which continues to exceed the national average of 3.4. So New Jersey is one of the higher burdened states in the US. In Ocean County, however, we're considered a low incidence county with only 2.6 cases, falling below the national average, as well as below the average for the state of New Jersey.

While cases of TB among US born are typically known as decreasing over the last 10 and 20 years, what we are seeing in Ocean County is that US born cases are actually on the rise and because of that, we look at whether or not the index of suspicion was appropriate among the clinicians in our county that are diagnosing TB. So for example, in 2008, Ocean County saw that 16.7 percent of all of our cases were US born, that increased to over 30 percent in 2010 and is now in excess of 2/3 or 66 percent in 2012. It does remain important for us to continue to look for TB in populations that may not be the traditional risk factors as most clinicians are thinking of them, the younger immigrant populations that present with very clear illness. It does sort of underscore the importance of making sure we have high levels of suspicion even in low incidence counties like Ocean County.

Slide 47 One of the unique things about Ocean County, however, is that we have a very, aged population. 21.1 percent of county residents here are 65 years of age or older, compared to much smaller percentages in both the State of New Jersey as well as in the US as a whole. The thing that makes that very unique is that older residents may be more likely to have things that make it more difficult to diagnose TB. Other than being naturally overlooked as an at risk population, they're more likely to be on immunosuppressive medications, that may help initiate the replication of TB bacilli or bacteria.

For example, TNF alpha inhibitors or immune suppressing drugs like prednisone or Humira, those types of things will actually lower the immune

system in such a way that that bacteria can then escape from the encapsulation from a latent TB infection and allow active TB disease to occur. And I always think of watching TV at night and seeing those commercials saying, 'Before you start this medication please ask your physician whether or not you should be tested for TB disease.' And this is exactly why.

The other thing that makes older residents potentially more likely to see active TB diseases, to be undiagnosed for that disease, is that they may have underlying respiratory or chronic conditions, like COPD or community acquired pneumonia that would mask TB or cause a clinician to diagnose something else without including TB in the differential. Those are one of the things that you really want to keep in mind as a clinician not only in the US but also in those low incidence areas.

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Basically what can happen then if you don't test for TB? This is the very thing that we saw happen in Ocean County in early 2011. We received a phone call from a short term rehabilitation facility that had recently identified four skin test converters working near the same skilled nursing unit.

The nuance though is that no patient or employee had been diagnosed with active TB disease. If you think back to Dr. Passanante's presentation, we weren't able to do a cohort study because we could not determine the difference between who was exposed and who wasn't since no diagnosis had been made. What we ended up doing was testing facility staff for TB infection and disease, and then also looking at the clinical presentation and medical records for patients with pulmonary disease at that facility for the last two years to see if we could identify those that may have symptoms compatible with TB and to see whether or not additional skin test conversions had happened.

The unique thing though was that because this facility received the majority of their clients from an acute care facility located next door, there was a lot of concern that the hospital had missed a diagnosis. Based on the levels of finger pointing and the shrugging of responsibility for a missed case, looking at other patients that may not have had similar presentation with symptoms, we

actually utilized epidemiology to sort of support, strengthen and bolster our argument for identifying cases or potential cases that may have been there.

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By using epidemiology and the statistical analysis that we looked at, we tested all the facility staff and administration and identified through a case control study that housekeepers and nursing administrators on one particular unit were at greater risk of having been infected with TB disease.

And as you can see here the odds ratio, which is what OR stands for, were greater among those housekeepers and administrators at statistically significant levels. What you can see here is a basic outline floor plan of the facility in question. When we talk about Unit C, where the greater number of individuals were positive, it's the upper right hand corner, and what we found was these two x's mark where the housekeepers were, which is if you're looking at the screen on the right hand arrow, and the nursing administrators in Unit C, which is the left hand arrow. Those two x's, utilizing our epidemiology, allowed us to look into this region to say something we believe happened over here, and it kind of helped us look at the patients that were symptomatic and at greatest risk of having TB and begin to ask additional questions.

And sure enough, of the three clients and three patients at the facility that were brought to us, the client of greatest risk was this x right here marking the second room in on this unit, directly across from the nursing station and immediately across from both the housekeeper storage unit and point of congregation as well as the offices for the nursing administrators.

That began to allow us to feel more confident that an undiagnosed case of TB that had since passed away, may have been the source or the index for our outbreak of conversions. Of note as well, this arrow here identifies the air exchange pattern that we believed was a part of the risk for seeing even more individuals within the facility being exposed inadequately and infected with TB. Because the client had significant pulmonary disease, he had received regular respiratory therapy, routine sputum induction, as well as active

respiratory procedures to try to continue to clear this individual's throat, lungs and larynx.

As a result of the air exchange within the building, the air within his room was intentionally pushed outward directly into that nursing station and across from the housekeepers' closet, and into the vent at the end of that hallway, which happened to be the main intake and a source for ventilation for four different units. So it impacted that green, red, purple and yellow unit in such a way that it allowed the air to travel further than maybe at another portion in the building.

Slide 50 The patient that we had identified, the symptoms included worsening chest x-rays with cavitation and infiltrates, rapid unexplained weight loss, hemoptysis, increased cough and sputum production for an extended period of time. As well as hoarseness, loss of voice and vocal cord paralysis, that we believe may potentially have been indicative of laryngeal TB, which is known to involve the larynx producing some of the vocal cord and laryngeal mucosa, as well as the hoarseness and the vocal cord paralysis that we saw.

He was a US born individual, a 77 year old white male. And despite numerous tracheal and pulmonary procedures over the course of the two years prior, unfortunately acid fast bacilli smears and cultures were never ordered and TB was never considered in a differential, despite the fact that the individual was very healthy in the years prior to developing symptoms and had no other significant issues other than the respiratory conditions he presented with. The individual ultimately passed away and the cause of death was listed as tracheal bronchitis, which for the most part is an unusual source of death. Of note, looking back at some of the biopsies and procedures that were performed, it was noted that clinicians did identify predominately granulation tissue in some of the procedures they did and yet still never considered TB.

Slide 51 What we began to do and to again continue to bolster our case that because we couldn't identify an index case because our assumption was that the individual that served as the index case had passed away. We began to look at testing other individuals. We first tested the patients sole household contacts, who

tested skin test and Quanti-FERON positive, had a recent history of bronchitis, and an abnormal chest x-ray, and as we utilized some of the clinicians at the National Global TB Institute in Newark, believed to be potentially suggestive of past healed TB, despite the fact that sputum and smear cultures had remained negative.

We continued to test facility staff for TB infection and disease. We found a total of 59 of 318 previously negative employees were found to have had conversions and 38 of those went on to test positive for Quanti-FERON. We did test the facility residents on Unit C that indicated unit, believing that if we offered the opportunity to test those first, and the rates of conversion came back significant we would continue to test the remaining residents at the facility. However, of those that tested on that unit, no one came back positive for latent TB infection and based on the nature of the facility being a short term facility, we didn't believe it was necessary to carry that testing on any further.

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This is just a quick basic overview of the results of our testing. It sort of presents that picture of a cross-sectional epidemiology study. Looking at the prevalence of infection through the building, again 318 employees were susceptible for testing. Of those that came back with a positive skin test, we went onto look at newly documented reactors as well as Quanti-FERON positives to identify those that we consider true converters.

There had been a little bit of a lapse in the infection control protocol, such that not all the healthcare workers had been tested annually. And so we defined a new conversion or a conversion that we counted as a conversion as individuals with a test that was previously negative in the last two years and had since become positive. Any greater than that, we couldn't confirm that happened the time that we felt confident we could say was based solely on this exposure. Of those true converters, we saw two facility staff members that had evidence of TB disease. They both had abnormal chest x-rays and symptoms of concern, persistent coughing that wouldn't go away, rapid weight loss, unexplained for another reason. TB was ruled out in the one based on a primary care physician's diagnosis of sarcoidosis. It was difficult to change

that perception and so that was left for what it was. The second facility staff member was both smear and culture negative and was treated for TB disease empirically based on the situation.

Slide 53 Of the 38 Quanti-FERON positive employees, they were all initiated on treatment and actually 100 percent of them completed their treatment course, which was predominantly a 6 month course of rifampin. Rifampin had been recommended because it is a shorter course, typically 6 months as opposed to 9 months, which was preferred by most of the individuals offered the treatment.

100 percent is unusual for treatment completion, especially among healthcare workers. However, we did find that the facility administration was quite adamant that their healthcare workers involved in this outbreak were treated, and adequately so, in order to avoid anything like this from happening in the future, or to avoid the development of active TB disease that would go under the radar and cause, another such sort of scenario.

Slide 54 How did this reflect the gaps in the TB response in Ocean County? Our biggest concern was that no one at any point in the chain had suspected TB for an individual that presented with symptoms, clearly possible of having been TB and it's because the level of suspicion for TB in a low incidence county was too low.

It really unveiled different areas where Ocean County has the ability to respond and improve at every level the opportunities to screen for TB and therefore to rule it out. Some of the missed opportunities that we identified was that the patient was seen, both at the onset of a TNF alpha inhibiter that daily administration of prednisone, and was failed to be tested for TB at that time, which is the recommendation for any of those drugs. Additionally, when they presented for symptoms compatible with active TB disease, the individual was never tested for TB disease, not a skin test, not a Quanti-FERON, not a sputum test, not a culture, nothing.

Finally, it kind of highlighted an opportunity for sub acute care admissions policies to sort of be reassessed for the nurse liaisons that work between long

term care, assistant living, sub acute care, and the hospitals that refer them. It highlighted an opportunity to be able to utilize symptom assessments and medical history to ensure that they're actually not receiving an active case of TB without having adequately ruled it out or at least gone through a level of steps to ensure that individuals that may require a TB differential diagnosis should have that TB ruled out prior to actually being received in a facility incapable of providing the isolation or the care that would be needed if they did indeed turn out to be TB.

Finally, reinforcing the importance of annual TB testing for healthcare workers; it remains such a pertinent and important part of ensuring that our health care workers that may be at greatest risk are protected. And it serves to show you that they can also serve as a sort of sentinel event for identifying an undiagnosed case of active TB disease.

Slide 55

The implications that we see, low incidence counties, you've got to keep the level of suspicion for TB high. Continue to keep screening and diagnosis of TB a part of your hospital infection prevention program even in low risk counties, and utilize administrative controls, develop the policies that are needed in order to get TB diagnosed.

We actually saw as a result of this outbreak and other TB cases identified late in the course of care, that two of our hospitals have since changed their policies ensuring that any individual presenting with cavitation is tested for TB and beginning to look at symptom screening, such that if you have a cough of two week duration or longer, as well as another symptom of concern that you are going to be screened.

And what's more they've also determined that if you present with a positive smear and symptoms compatible with TB, they will now automatically issue a NAT test, the nucleic acid amplification test, to either rule in or rule out mycobacterium tuberculosis specifically, which we believe is in their benefit, such as they do not have to isolate non MTB cases for as long as they would if they were solely based on symptom presentation.

Slide 56 So this is just one flow chart that had started to be developed in conjunction with the department of health to just consider for either long term care or sub acute care units, as well as our infection preventionist to say, 'It's just and overview, use it or change it as you like, but these may be the things that you want to consider as you're moving forward to identify and screen individuals compatible with TB.'

Down below, the box that was just highlighted are things that must specifically happen, usually at an acute care facility that NAAT testing is usually offered through hospitals, in the labs that perform those sputums, and then again chest x-rays, especially if there's evidence of opacities, hilar lympadenopathy, cavitation. We're really trying to get our clinicians that are diagnosing cavitary community acquired pneumonia to at least consider TB in a differential diagnosis as well, if the other symptoms are compatible.

Slide 57 In conclusion, what we basically saw was that epidemiology could be used to really strengthen and bolster our response to those naysayers that were afraid to accept that a diagnosis of TB had been missed. It was used to identify and quantify TB exposure and risk within a facility and helped us to limit and identify a possible index case. It also identify the possibility of missed diagnosis and it's impact on the community at large.

What happens when we don't diagnose TB and that individual is allowed to go into a facility where the exposure could be great. It also helps us to support some of the new recommendations that we were making at a county level response, being able to say based on what we've seen, and that the statistics behind it. There are things that can be done across the spectrum of healthcare to really minimize TB within the county. Looking at acute care facilities, administrative controls, the policies and procedures they put in place to screen for TB, different triggers like the initiation of a TNF alpha inhibiter or the presentation of symptoms, cavitary lesions within a chest x-ray, that may really kind of change how TB's handled at that level. Sub acute and long term care admissions policies with the nurse liaisons trying to use symptom assessments to rule out possibly accepting an active case of TB.

Continuing to screen TB workers for TB annually, not missing that, not allowing those gaps to occur. And then also being very intentional about educating individuals that work in the healthcare facilities that may not be healthcare workers themselves, like the housekeepers, like the administrators, that may have greater levels of fear if exposure does happen, making sure they're continuing to educate them about the risks, about the options, about the treatment, and ensuring that everybody's on the same page.

Overall, very honestly fun investigation but very much highlighting the importance within any incidence county of making sure that TB continues to remain at the forefront of our minds if we're looking to indeed reduce the total levels of what we see in the United States.

Slide 58 Just a special thanks to everybody that took part in this investigation both from the county and the state level as well as some of the facilities that participated as well, so thank you very much.

Bill Bower: Thank you Patty. I'm glad you were able to show the way your study design and numbers actually bolstered the arguments.

Slide 59 Right now I'd like to turn the program over to Lynn Sosa, she's an Assistant Clinical Professor of Medicine at Yale University School of Medicine, Department of Epidemiology and Public Health. And as the Deputy State Epidemiologist for the Connecticut Department of Public Health, she provides medical and epidemiological oversight to the TB and STD programs, and therefore she's really well suited to tell us about using Epi at the state level. Lynn?

Lynn Sosa: Thank you Bill for the introduction and today I'll be talking about analysis of tuberculosis deaths in Connecticut that we undertook, and before I start I would like to recognize our EIS officer, Jessica Kattan who was with us from 2009 to 2011, who performed this project for us.

Slide 60 This data everyone is familiar with. It shows TB incidence in the United States over the last six years, which has really dramatically decreased. In

2011, there was just over 10,500 cases of TB in the United States, which equals a rate of 3.4 per 100,000, which is the lowest rate ever seen in the United States.

Slide 61 So in Connecticut we also saw our lowest numbers ever reported in 2011 with 83 cases. Almost 80 percent of our cases were among foreign born persons, who were from 23 different nations. About half of our cases were among males and cases were reported from all over the state. Last year we had 7 cases that were co-infected with HIV and one case with multi drug resistant TB.

Slide 62 Every year in the United States about 550 people with TB die. In Connecticut from 2001 to 2010, 80 people or approximately 7 people per year with TB were either dead at diagnosis or died during treatment. CDC recommends that all deaths and persons with TB be reviewed to determine if they could have been prevented and to help guide policies to reduce these deaths. However, there's no standardized method for this review and few programs actually perform these reviews, including in our programs.

Slide 63 We decided to do an analysis of TB deaths with these three questions in mind, first, 'Were the deaths TB related?' meaning did people with TB actually die from TB or TB treatment? Second, 'Were there missed opportunities in the diagnosis and treatment among the patients with TB related deaths?' and third, 'Are there certain factors associated with death of TB patients in our state?'

Slide 64 All of the deaths during 2007 to 2009 were symptomatically reviewed, which included review of TB program records and all available medical charts. A tool developed by the California Department of Public Health for systematic mortality review of their TB deaths was modified for this particular project to assess both for TB relatedness of deaths as well as missed opportunities.

Slide 65 So the TB relatedness of deaths was determined using an algorithm in this data tool which I mentioned, which was based on several factors including severity of TB disease, TB related complications, anatomical site of TB disease, as well as cause of death documentations, which included death

certificates. The algorithm then incorporated the information to categorized deaths as TB related or not.

Slide 66 The categories of missed opportunities assessed in diagnosis of medical treatment using the data tool are shown here. They included patient delay in seeking care, provider delay in performing a TB diagnostic evaluation, delay in reporting by the provider to the health department, treatment errors and delays by the lab in processing specimens. It is important that I note that missed opportunities were only assessed among deaths determined to be TB related.

Slide 67 For this analysis, we used just surveillance data from TB patients who survived during the study period for comparison. A limited subset of demographic and clinical variables were analyzed since extensive chart review was not performed on survivors, only on the decedents, and statistical tests were used to assess differences between proportions.

Slide 68 In all, there were 301 cases of TB reported during the study period 2007 to 2009 and of these there were 21 decedents. One decedent was eventually excluded from the analysis because they had left the state several months before death and records could not be obtained. So in the end there were 20 decedents included in the analysis.

Slide 69 Of the 20 decedents, 14 died during treatment, one died after diagnosis but before starting treatment, and 5 were diagnosed with TB after death.

Slide 70 This chart shows some demographic features and risk factors of the decedents. A little more than half were 65 years of age and older, male and foreign born. Excessive alcohol use in the previous year was the most common social risk factor among this particular group.

Slide 71 This chart shows some of the clinical features of the decedents. 14 or 70 percent of decedents had at least one medical co-morbidity, three quarters had pulmonary TB only, importantly no patients had MDR TB, and only 1 patient was HIV positive.

Slide 72 Of the 20 deaths, 17 were determined to be TB related and 3 were not TB related. An example of a TB related death was a patient with pulmonary TB and no other active medical problems, who died in the setting of massive hemoptisis. And an example of a death not TB related was a patient with TB who died in a motor vehicle accident.

Slide 73 The 17 TB related deaths were used to analyze missed prevention opportunities.

Slide 74 Overall, 94 percent of cases with TB related deaths had at least one missed opportunity. So now I will present the most common missed opportunities in diagnosis and medical treatment.

Slide 75 So this chart shows missed opportunities related to case detection or diagnosis. Delay in reporting the case to the health department was the most common missed opportunity in case detection, 67 percent or 10 cases having this missed opportunity. And certainly just to point out it was possible for there to be more than one missed opportunity for a particular case.

Slide 76 This chart shows the missed opportunities related to medical treatment, and the most common missed opportunity in this category was laboratory delay in processing initial drug susceptibility results.

Slide 77 And lastly, I will present demographic and clinical factors with their associated risk of death. All patients reported with TB during the study period were used for this analysis and patients with risk factors were compared to those without. Because all patients reported with TB during the study period were included, a cohort analysis was performed. This analysis showed that age greater than or equal to 65 years and excessive alcohol use were the two factors that significantly associated with death.

Slide 78 There were a few limitations to this analysis. Missed opportunities among survivors were not assessed, since medical chart review was only done on decedents. Also, missed opportunity does not mean that a death was indeed

preventable. And finally, the small cohort size limited power to detect significant differences.

Slide 79 So in conclusion, the majority of deaths in the study were determined to be TB related and missed opportunities were common. Factors associated with death included older age and excessive alcohol use, and certainly these, similar, other studies have shown these factors to be involved with TB related deaths as well. And the value of doing this type of analysis, even a small state like ours, I think this shows that was really important and allows for situational awareness of TB mortality trends and can guide death prevention interventions.

Slide 80 This was actually a really important project for us and has led to several actions. First, the Connecticut TB Control Program has now instituted regular review of TB patient deaths. Also, factors associated with death, including age, comorbitities and alcohol use are reviewed for living patients discussed during case management meetings. These findings have been disseminated widely to healthcare providers and public health partners through educational sessions, including a state TB conference that was held in October 2012, national scientific meetings, and the findings were recently published in the International Journal of Tuberculosis and Lung Disease.

Slide 81 So thank you very much. There were a lot of people that contributed to this project, and again this was one of the main projects of our EIS Officer Jessica Kattan.

Slide 82

Bill Bower: Thank you Lynn, it seems like there were only a few cases but I think the research really did yield important findings in terms of the risk factors and missed opportunities.

Let me throw it open now to have some questions. Patty the question to you is, ‘Is it possible that older US born TB patients represent a cohort that was infected when they were younger and TB was more prevalent and not easily treated?’

Patty High: To answer Alice's question, absolutely, that is possible. We know that once an individual is infected with TB, you have approximately a 10 percent lifetime risk of going on to develop active TB disease, usually 5 percent in the first year after infection, and then 5 percent over the course of the rest of your life. And so, you would think that if you were exposed as a child, the older and older you got, it is potential the more likely you would actually go on to develop the disease based on the number of years that your body has failed to continue to encapsulate that bacteria, and again the additional risk factors for limiting the immune system in order to reduce your overall immune response to be able to prevent that. So I would say, yes certainly, older US born patients could represent a group that was exposed as children and infected as children and not treated for LTBI.

Bill Bower: OK thanks Patty.

Slide 83 In the interest of time I want to make sure that we still have a chance for Marianne to help wrap it up.

Marian Passanante: Sure Bill, so I'm going to describe some data and educational resources that can be used to assist in TB control programs.

Slide 84 The first resource that I want to mention is a general epidemiology reference. It's a CDC Web site called EXCITE and it stands for Excellence in Curriculum Innovation through Teaching Epidemiology and the Science of Public Health. It provides easy to understand materials that describes the basics of epidemiology.

It's actually written for, materials that are written for people from kindergarten to 12th grade. Now most of the materials that you'll see are really in the high school reading level, but they're pretty sophisticated, and I use them with teaching medical students and students in the school of public health. But they're at a very basic level, enough so that anybody can pick it up and learn a little bit about epidemiology.

So for people who are interested, I would recommend that you take a closer look at the Web site.

Slide 85 The next set of resources also comes from CDC but they are TB specific. Now each year the Centers for Disease Control publishes TB surveillance reports and reproduces slide sets based on updated information. And the most recent data reports that are available are for TB cases reported in 2011.

Slide 86 Now this slide is the title slide of the CDC surveillance slide set that's available on this Web site. This is Tuberculosis in the United States from the National Tuberculosis Surveillance System, highlights in 2011.

Slide 87 Now the next slide will illustrate the epidemiologic data that are presented in the TB slide set, just some of them, by person place and time. So I just wanted to show you the types of information that are presented initially. In the top left corner is an example of descriptive epidemiology data by person. This shows the TB case rates by age group and one thing that I really like about these slide sets is that it also has a complete description of what you should get from the slide.

So for example, it tells us that the description says it shows that rates tended to increase with age, and as age increased, the case rate in men increased faster than women and the rate in men 45 years and older were approximately more than twice those in the same age women. In the right corner is a slide that presents epidemiologic data by place. We're told that 37 states reported a rate of less than 3.4 TB cases per 100,000, which is the 2011 national average.

And 13 states and the District of Columbia, which are all presented in dark blue, are reported a rate above 3.4 TB cases per 100,000 population. And the figure at the bottom of the slide illustrates the presentation of epidemiologic data over time. I think everybody has seen this slide on TB cases, which shows the marked increase that occurred in the resurgence of TB in the mid 1980's, and then case counts beginning to decline in 1993. And as of 2011, the 19th year of decline in the total number of TB cases reported in the US since the resurgence.

Slide 88 TB surveillance information can be found at the following URL. The first document is the text report of the most recently available TB surveillance data. The second item listed on this slide is the slide set that accompanies the written report. And the last item on the slide is an online tuberculosis information system called OTIS.

It allows you to ask for TB surveillance summary data for the US, your region, or your state. And I find OTIS to be a very useful data source, so I'd like to just walk you through a simple data query to see how easy it is for you to use.

Slide 89 And I'm going to start by selecting current tuberculosis case reports from 1993 to 2009, by clicking on a data request. You can see that from the yellow arrow. This will bring me to the 2009 data request form.

Slide 90 You're given the option of creating tables using one or more of the items that appear on the RVCT form. In addition to getting the case counts, you can request incidence rates, completion of therapy information and drug susceptibility information. And much of this information is available by single state, groups of states and metropolitan statistical area or by years or group of year. And this actual data request form is really three screens long. So I'm just showing you what the beginning looks like, but much of the information is in the RVCT form and is available on this data request form.

Slide 91 This is an example of the type of output that you can produce with OTIS. Notice that OTIS provides the case count, the rates per 100,000 population, meaning they take the census data and calculate the rate for you, and the percent among those who are eligible who completed therapy within one year.

Slide 92 Now OTIS can also create graphics like this bar chart that can be easily cut and pasted into documents for written reports or into slides for presentation. So I would recommend that you try to access this on your own after the presentation to see just how easy it is to create useful tables and charts that you might want to use.

Slide 93 Now recently the CDC added TB data to another data query system and that's called Atlas. Atlas is an interactive tool that allows users to observe trends and patterns by creating detailed reports, maps and other graphics. And you can access Atlas system using URL at the bottom of the slide. It really is interactive; it will actually show you the changes over time for all of the years that available on the Atlas Web site. And it will go sequentially 2001, 2002, et cetera. But this is a very new system, it actually was developed not just for TB but for other infectious diseases, the TB just has recently been added.

Slide 94 There are two educational resources that we have produced at the Global TB Institute that I'd like to mention briefly. The first is the Basic Epidemiology for Tuberculosis Program Staff Manual. The manual was developed in 2005 for TB programs staff ranging from healthcare workers including public health nurses, to TB program managers working in local, county, or municipal TB programs. And it continues to be one of the most requested and downloaded GTBI educational products. We're really excited to announce that we've updated the manual and it should be available online. We have revised and updated the material in the manual based on the responses from TB control staff around the country.

Slide 95 We have divided the manual into two sections; first we present the basics that include a few of the topics that I described today but in much greater detail. We've included lots of TB examples as well as problem sets at the end of each chapter. We also added a new chapter on Presenting Program Data, because this was one topic that many TB prevention and control staff felt would be useful.

Slide 96 The second half of the manual is called Beyond the Basics for those who want to delve a little more into epidemiology. We included detailed descriptions of how to calculate and interpret indicators used to measure the usefulness of a test, things like sensitivity, specificity and predictive values, as well as indicators that measure the strength of an association between a risk factor and a disease outcome, like odds ratio and relative risks. We also included on a section on Statistical Concepts that you might see when reading an epidemiologic study. Finally, we expanded our section on Genotyping and how it can be used in TB control.

Slide 97 The last chapter of the manual is a TB Control Case Study that allows the reader to apply the epidemiologic concepts described in the manual to public health decision making. Finally, we've added six appendixes including a glossary of epidemiologic terms and solutions for sample problems in the manual, a suggested reading list, as well as information on national TB program objectives.

Slide 98 Now once you feel comfortable with some of the basics of epidemiology, you might like to get a little more practice using them, and that's the second resource I'm going to mention. To do this you can work through some exercises that the staff at the Global TB Institute created using real TB data. These exercises, which are part of our Incorporating Tuberculosis into Public Health Core Curriculum resource, can be accessed on our Web site.

Slide 99 If you click on epidemiology, it will show you that there are four epidemiology case studies that are available. Once you complete the exercises, you can click on the instructors guide key at the bottom of the page in order to access the answer key. This will allow you to assess how well you've mastered the material.

Slide 100 In closing, I hope that the presentations today have illustrated how epidemiology can be used to identify local, state, and national patterns of disease. How epidemiologic methods can be used to improve both patient care outcomes and the effectiveness of individual TB programs. And introduce you to some new TB educational and data resources.

Bill Bower: Well thank you Marian.

Slide 101 For the last time I'd like to throw it open for questions. Mark, Bruce Chandler had asked: do you retest all the immigrants with a history of TST of 10 millimeters or greater, a test that was done in their home country, before they come in here to the United States before you would consider treating them?

Mark Wolman: Any B2 immigrant that arrives in New Jersey is retested. So if someone comes in with documented 10 millimeters or more on TST, depending on the clinic, the TST is either re-administered or QFT, whatever that clinic uses, yes.

Karen Galanowsky: This is Karen Galanowsky, Nurse Consultant, with the New Jersey Department of Health, and I wanted just to thank Mark and Patty High for their presentations, and also for the work they did. Because from his study, we changed our state policy and we're still seeing it occur, so we know that we're on the right track.

Bill Bower: Thanks Karen. A typed question came in. It says, 'In Mark Wolman's presentation we talked about discordant TST results, but does anyone do research of discordance between QFT results?'

Mark Wolman: Well I can just speak on what I see in the clinic. I think while QFT's or IGRA's are being introduced overseas, we're still seeing B2 immigrants with positive TST's and they are repeated in this clinic with QFT's. And we are seeing discordance of TST positive, IGRA negative, or QFT negative here in this clinic, we are seeing discordance.

Slide 102

Bill Bower: I want to thank very much the faculty today. You really shared a lot of knowledge and experience and hard work with us, and I hope it's inspiring to people in programs to say, 'I can do that.' And actually learn more about what's going on with your cases and how to improve your programs using these epidemiological methods. For those of you who are interested in even more resources on epidemiology, here are other ones.

Slide 103 And this concludes the conference, I want to thank you all for your participation.

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