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PROPOSED TUBERCULOSIS MASS TESTING PROGRAM FOR THE THIRD-COUNTRY NATIONAL INDIGENT WORKFORCE OF THE COUNTRY OF PALAU

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Socioeconomic poverty makes the people of Palau at a near-critical risk for vulnerability to both natural disasters and to diseases. Chronic diseases, such as heart disease, cancer, and diabetes, top the list of diseases that negatively impact the health of Palauans, and infectious diseases, such as leprosy and tuberculosis (TB), are also quite a problem. Per capita, $881 a year is spent on the health care needs of the citizens of Palau. However, no money has been set aside for the management and treatment of health problems in the indigent people who work temporarily on this island-nation. These temporary migrant workers are often quite poor, have little or no access to medical care while they are in Palau, and are not currently tested for *Mycobacterium tuberculosis* (MTB) or other diseases when they immigrate to Palau. The prevalence of latent tuberculosis infection (LTBI) and active MTB in this population is currently unknown, and these individuals could pose a great risk to the native Palauan population due to the presence of infectious diseases, including tuberculosis. This report describes a proposed program to test these migrant workers upon entry to Palau for TB and the human immunodeficiency virus (HIV), since it can affect testing results and can change the therapy recommendations for those patients with MTB. If this proposed TB testing program is adopted, the epidemiology of these diseases could be better described. Those identified as having LTBI, active MTB, and HIV could be treated, which could prevent the spread of these diseases to the native Palauan population. If identified early, they could be treated using far fewer funds than would be required should they be identified late in the course of their disease.

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1.0 SUMMARY

Socioeconomic poverty makes the people of Palau at a near-critical risk for vulnerability to both natural disasters and to diseases. Chronic diseases, such as heart disease, cancer, and diabetes, top the list of diseases that negatively impact the health of Palauans, and infectious diseases, such as leprosy and tuberculosis (TB), are also quite a problem. Per capita, $881 a year is spent on the health care needs of the citizens of Palau. However, no money has been set aside for the management and treatment of health problems in the indigent people who work temporarily on this island-nation. These temporary migrant workers are often quite poor, have little or no access to medical care while they are in Palau, and are not currently tested for *Mycobacterium tuberculosis* (MTB) or other diseases when they immigrate to Palau. The prevalence of latent tuberculosis infection (LTBI) and active MTB in this population is currently unknown, and these individuals could pose a great risk to the native Palauan population due to the presence of infectious diseases, including tuberculosis.

The proposed TB testing program would begin at the international airport, where either the tuberculin skin test (TST) or the QuantiFERON-TB Gold (QFT-G) test would be administered to migrant workers. Individuals who have obvious symptoms of MTB upon arrival or test positive would have further testing at follow-up visits to Palau National Hospital. Appropriate treatment would then be initiated. Since the presence of human immunodeficiency virus (HIV) can affect testing results and can change the therapy recommendations for those patients with MTB, HIV testing would also be done upon entry into the country by the standard methods (enzyme-linked immunosorbent assay and a second confirmatory test by Western Blot). A database would be created on these indigent workers, with their names, addresses, and points of contact and results of their TSTs or QFT-G tests, HIV test, and chest radiographs, so that the epidemiology of TB and HIV can be described accurately in this population, especially as to prevalence of disease. This database would make it easier to seek out those who require treatment.

If this proposed TB testing program is adopted, the epidemiology of these diseases could be better described. Those identified as having LTBI, active MTB, and HIV could be treated, which could prevent the spread of these diseases to the native Palauan population. If identified early, they could be treated using far fewer funds than would be required should they be identified late in the course of their disease.

2.0 BACKGROUND

The island-nation of Palau is a series of over 300 different islands, mostly unpopulated, in the western Pacific Ocean, more specifically, in the Philippine Sea, and is located at lat. 7°30' N. and long. 133°30' E. (Ref 1). Because of the location (latitude and longitude), Palau enjoys a tropical climate year round, with an average temperature of 82 °F or 27 °C. The average rainfall is 150 inches a year; while rain can fall year round, most falls from July through October. Typhoons are rare in Palau but may occasionally occur. The country is lush with tropical vegetation, and bananas and coconuts abound, as do other tropical plants. The currency is the U.S. dollar, which underscores the close ties that this country has with the United States (Ref 1).

Over 70% of the people of Palau or Micronesia are located in the State of Koror. There are, as of the last census, 20,044 people in Palau, and there are two official languages: native Palauan and English. The ethnic makeup of this island-nation is 69.9% native Palauan or

Micronesian, 15.3% Filipino, 4.9% Chinese, 2.4% other Asian ethnicity, 1.9% Caucasian or white, 1.4% Carolinian, and 4.2% unspecified (Ref 2). The ethnicity of the native population of Palauans is thought to be of the Malays of Indonesia, the Melanesians of New Guinea, and the Polynesians, which is why the Palauan people are also called Micronesians.

It is unknown when the ancestors of the modern Palauans actually migrated to this island-nation, but it is thought to have occurred several thousand years ago. Artifacts have been discovered that have been carbon dated back to at least 1000 B.C. Palau was controlled by Spain from the mid-1800s until 1899, when it was sold to Germany. After Germany lost the first World War, the island-nation was transferred to Japan, which owned Palau until it lost the second World War in 1945. Throughout colonial times, while under the influence of the various foreign governments, many natural resources owned by the Palauans, such as bauxite and phosphate, were plundered by these governments.

Palau became a U.S. protectorate in 1947 and was such until it became an independent nation in 1994. However, Palauans and Americans still enjoy a mutually beneficial relationship, and this tiny nation is protected by the U.S. military under the Commander, U.S. Pacific Fleet (Joint Region Marianas). The Compact of Free Association is the contract by which the Palauan Government and the U.S. Government enjoy trade and other benefits with each other. There are 16 states in the Country of Palau, with Koror being the most inhabited or populous (Ref 2).

Traditionally, the economy of the Palauans was based on fishing and agriculture. The men would collect their bounty from the sea. In fact, the sea holds a special place in the history and lore of these proud people. The women would grow and harvest taro, a starchy, potato-like, tuber-growing plant with broad leaves. Interestingly, because of tourism dollars due to intense interest in sport fishing, scuba diving, boating, and other activities, the island-nation has enjoyed some good economic growth. However, the annual income of most Palauan citizens is less than $10,000, and poverty is a real concern for many of the inhabitants. This socioeconomic poverty makes the people of Palau at a near-critical risk for vulnerability to both natural disasters and to diseases. Chronic diseases, such as heart disease, cancer, and diabetes, top the list of diseases that negatively impact the health of Palauans, and infectious diseases, such as leprosy and tuberculosis, are also quite a problem. The negative impact of chronic and infectious diseases is also a real concern of the Palauan Ministry of Health due to the concept of geospatial vulnerability. As an island-nation, any disaster, either natural or an act of terrorism, could affect the supply route of medical supplies, since shipping is the major arrival route of these supplies, with a lesser amount of health supplies arriving by air. Should the shipping ports or the only airport be affected by such a disaster, the effect would be far-reaching and immediate (Ref 3).

The Palau (or Belau) National Hospital (PNH) was built in 1992 and is run by the Ministry of Health under the Minister of Health, an elected health professional. Per capita, $881 a year is spent on the health care needs of the citizens of Palau. However, no money has been set aside for the management and treatment of health problems in the indigent people who work temporarily on this island-nation. The annual budget of the Ministry of Health is $14 million. Almost 10% of the gross domestic product of this nation is spent on health care; over 90% of these funds are from the government and grants, while only 10% is from private sources. At PNH there are approximately 25 physicians, 3 dentists, and 117 nurses, as well as 1 pharmacist on staff. PNH enjoys partnerships with many different organizations that make it possible for care to be rendered to the population of this nation, including the United States (U.S. Army, U.S. Air Force, U.S. Navy medics), Republic of China (Taiwan), Fiji School of Medicine, and over a hundred other organizations. Despite these wonderful partnerships, the budget is inadequate to

provide the necessary preventive, interventional health care modalities, and infrastructure to care for the citizens of Palau. In addition, the health information management facilities are inadequate for the population served. One of the leading concerns of the Ministry of Health (MOH) is its national health priorities list, of which number five is to "control communicable and non-communicable diseases" (Ref 3,4). In speaking with the talented and dedicated professional staff of the hospital, there was a palpable concern about tuberculosis (TB) and, especially, multiple-drug-resistant TB, which is often referred to as MDR-TB (Lalabalavu S. Personal communication; 5 Aug 2008).

3.0 SIGNIFICANCE OF TUBERCULOSIS

In humans, TB is caused by the acid-fast bacilli or bacterium *Mycobacterium tuberculosis* (MTB); in cattle it is caused by *Mycobacterium bovis*. This disease can affect virtually any organ or organ system but primarily affects the pulmonary system. It has been a scourge of man since the Neolithic period and is the most important of the infectious diseases to negatively impact the health of man. In fact, it is estimated that 33% (one-third) of the world's population is infected with tuberculosis, and the amount of morbidity and mortality that it has caused is almost incalculable. Along with malaria and the human immunodeficiency virus (HIV), TB is in the top three causes of death worldwide for an infectious agent (Ref 5).

Despite our advances in dealing with infectious diseases, tuberculosis has remained a major cause of disability, morbidity, and mortality. In fact, in 1993 the World Health Organization (WHO) declared the disease a "global emergency" (Ref 6). Moreover, TB is on the rise throughout the world; thus, the U.S. no longer enjoys the distinction that our modern medical practices have resulted in lessening the spread of this disease. The incidence or number of new cases of TB is on an upward trend in the U.S. (Ref 7). It has been said that tuberculosis has a physical, social, and mental impact on those infected. One study of 980 patients revealed that 50% of the participants constantly worried about what this disease was doing to their health. Indeed, 9% had suicidal ideations at the onset of their diagnosis (Ref 8). Another study of how TB might negatively impact the health of sufferers looked at how it might affect the quality of life of those diagnosed. The researchers noted that those diagnosed tended to be "worried, frustrated, and disappointed" with the diagnosis and that these negative emotions might negatively influence treatment outcomes. They observed, during the course of the study, that those individuals infected with MTB were less likely to find employment, were less able to pursue employment activities, and were less able to provide for their families, which constituted a great financial burden (Ref 9).

One group of investigators found that, upon diagnosis of TB in the parents, 11% of the children dropped out of school and 20% began working to help provide for their stricken parents. They found that the majority of infected individuals were from poor families and that, even at the completion of treatment, over 47% of patients still had respiratory symptoms. They further noted that the costs to the patient were enormous, which definitely impacted the poor (Ref 10). It was estimated in one study that 15% of annual household incomes was spent on the care of a infected family member and that 5% of the income of a family was reduced due to "illness-related effects" (Ref 11).

Regarding MTB, the concepts of years of potential life lost (YPLL) and disability adjusted life years (DALY) bear mentioning. YPLL is a concept that estimates the length of time a person would have lived had he/she not been diagnosed with a particular disease from an

arbitrary age value of 65 years old (Ref 12). The authors indicate it is a measure of premature mortality or disease burden. The disease burden would be higher for a younger patient than for a more elderly patient by convention. For example, if a patient were to die of TB at 45 years old, he/she would have 20 years of potential life lost. The concept of DALY refers to the sum of all the years a patient might lose due to death (years of life lost or YLL) or disability (years of life with a disability or YLD) (Ref 13). Tuberculosis is a major killer throughout the world and accounts for 2 million deaths annually, often in the younger population, which significantly and negatively impacts the YPLL and the DALY of those infected (Ref 5).

One study in Thailand revealed that, by using effective treatment recommendations, infected patients were less likely to contribute to the number of existing cases by being no longer contagious. This decreased the number of new cases by 45% and saved that country an estimated $2.4 billion in the form of indirect costs (Ref 14). Tuberculosis is a major threat to the health of the citizens of the United States and was identified as one of the nationally notifiable infectious diseases in 2003. The authors also noted that this threat was not just a threat to the health of people in the U.S. but throughout the world (Ref 15).

4.0 PROPOSED TESTING PROGRAM FOR TUBERCULOSIS

4.1 Background on TB Testing

The concept of secondary prevention is important when considering the problem of TB. The term refers to the testing of individuals with a disease so that one can intervene in the hope that the intervention can prevent that individual from developing the disease. In other words, the testing of asymptomatic individuals can identify those who are positive for the disease. Those identified can be treated or some other intervention can occur and can prevent them from suffering the full effects of the disease (Ref 16). Another author notes that this form of prevention prevents the disease from progressing even before it is apparent that it exists, i.e., in the asymptomatic phase (Ref 17). Those individuals testing positive for MTB can be treated with antitubercular antibiotics, and the disease should not develop in those treated. The various testing modalities for this disease will be discussed shortly.

Live, attenuated mycobacterium was used to develop a vaccine to prevent tuberculosis. The vaccine, called bacille Calmette-Guerin (BCG), was named for its developers. This vaccine, developed from live but attenuated strains of a close cousin of MTB, *Mycobacterium bovis*, varies in terms of efficacy in preventing disease, most likely due to varying antigenicity of the various strains of *M. bovis* used in the production of the vaccine (Ref 18). This vaccine, administered to infants and children, caused these children to produce circulating antibodies against *Mycobacterium tuberculosis* called cell mediated immunity. When exposed to the pathogen, the antibodies helped prevent the disease from occurring. The BCG vaccine caused 90% of those vaccinated to form antibodies (which last for approximately 20 years) against MTB and was primarily used to protect children against tuberculous meningitis and disseminated disease (Ref 19). This form of prevention (vaccination) is called primary prevention, which is defined as the prevention of a disease in a nondiseased individual (Ref 17). Vaccination is used in nations with high rates of TB, such as in the Far East, and is rarely used in the United States (Ref 18). It is quite inexpensive, but its efficacy is debated.

The primary method of testing asymptomatic individuals for TB in the United States is with the tuberculin skin test or TST. The so-called diagnosis of LTBI or latent tuberculosis

infection is based on the results of this test, which is based on the administration of five international units of the purified protein derivative standard (PPD-S) obtained from the bacterium. It is also called the Mantoux skin test or the latent tuberculosis infection test (Ref 20). This small injection is given through the very top layers of the skin or intradermally, thus delivering the five international units of PPD into the forearm using a very small 27-gauge needle. A small wheal is made and the patient is released. After 48-72 hours, the area is examined for appearance. A patient who has not been exposed to MTB should have no raised, indurated, erythematous area. However, should a patient have been exposed to MTB, even 2 to 12 weeks prior to the test, the result could be positive. A positive result will reveal a certain amount of this red, swollen, edematous reaction, which is caused by sensitized t-cells being recruited to the area and releasing cytokines (Ref 19). The reaction is read perpendicularly in millimeters from the long axis of the forearm and is defined in terms of whether the induration is 5 mm, 10 mm, or 15 mm. A 5-mm induration in a high-risk individual (e.g., someone who has had close contact with an MTB patient or a patient with HIV) is positive. A patient with certain risk factors, such as alcohol abuse, diabetes mellitus, having worked in a tuberculosis laboratory or hospital, having been incarcerated, or being from an area with a high prevalence of MTB, is considered positive with a 10-mm induration. For everyone else, a 15-mm induration is considered a positive result. Unfortunately, children and adults who have recently received the BCG vaccination can test positive (Ref 20).

The sensitivity and specificity of the TST are better than 90%, making it a very good test (Ref 21). However, the BCG vaccination can "muddy the waters" some and lessen the positive predictive value of the test by causing false positive results (Ref 19,20). Also, there can be false negative results for patients who have some form of immunodeficiency, chronic renal failure, or malnutrition; who have received systemic steroids; or for other causes (Ref 19,20). HIV can decrease the sensitivity of the TST to almost 64% (Ref 22). Recent advances in laboratory testing procedures have improved the sensitivity and specificity of MTB testing, especially in the immunocompromised population. A test using interferon-gamma responses to MTB-specific antigens is called the QuantiFERON-TB Gold (QFT-G) test; this indirect test for exposure to MTB is almost 90% sensitive even in HIV or other immunocompromised individuals (Ref 23). Also, the QFT-G test can improve the specificity and sensitivity and decrease the false positive rate among those individuals who have received the BCG vaccination. One study found the sensitivity and specificity of this test to be 93% and 91-100%, respectively (Ref 24). The QFT-G test may soon replace the TST due to this increased ability to detect LTBI (Ref 25).

4.2 Proposed Testing Program

As previously stated, there is a large workforce of third-country national indigent laborers in Palau. These workers are from the Philippines, China, Japan, and a variety of other countries in that region of the world. These temporary migrant workers are often quite poor, have little or no access to medical care while they are in Palau, and are not currently tested for MTB or other diseases when they immigrate to Palau. The prevalence of LTBI and active MTB in this population is currently unknown, and these individuals could pose a great risk to the native Palauan population due to the presence of infectious diseases, including tuberculosis.

The proposed testing program for migrant workers would begin at Koror International Airport in Airai, where medical personnel would administer the TST to the workers. Their names and contact information (how they can be located and where they are to be housed while

in Palau) would be obtained upon entry through customs. In 48-72 hours, these individuals would then be seen at PNH or its satellite clinics for the reading of their TST. Those who have a positive skin test according to the Centers for Disease Control and Prevention (CDC) current guidelines should have a chest x-ray or radiograph performed at that time. If an individual received the BCG it should be ignored per current CDC recommendations (Ref 26). In those individuals who test positive, by current CDC guidelines, treatment for LTBI should be initiated (Ref 19,26). See Appendix A for a table classifying the TST reactions (Ref 26). Alternatively, the QFT-G test could be administered, which would require a blood draw, but the advantages would be decreased time to obtain a positive or negative result (approximately 24 hours), increased sensitivity, increased specificity, and decreased false positive results even among those who have received the BCG vaccination. Another advantage would be lessened likelihood of loss to follow-up, since workers would not need to return in 48-72 hours to have their test read by health care workers.

Obviously, for those immigrant workers who have obvious symptoms of MTB upon processing through customs [cough, fever, night sweats, weight loss, hemoptysis, the common symptoms of active MTB (Ref 19)], further testing would be required at the follow-up visit at PNH. Not only should such individuals be tested for MTB by the TST or QFT-G, but other confirmatory testing is recommended. The current thinking is that such individuals should provide a sputum sample to test for the presence of acid-fast bacilli (Ref 6). The sputum sample should also be cultured to grow out *Mycobacterium tuberculosis* so that sensitivities can be obtained. A positive smear or culture would be grounds to immediately initiate therapy (Ref 20).

Since the presence of HIV can affect testing results and can change the therapy recommendations for those patients with MTB, HIV testing should also be done upon entry into the country by the standard methods (enzyme-linked immunosorbent assay and a second confirmatory test by Western Blot).

A database should be created on these indigent workers visiting Palau so that the epidemiology of tuberculosis and HIV can be described accurately in this population, especially as to prevalence of disease. Their names, addresses, and points of contact; results of their TSTs or QFT-G tests; HIV results; and chest radiographs (if appropriate) should be obtained and updated in this database so that the epidemiology of these diseases can be ascertained. This database would make it easier to seek out those who require treatment. The database could also contain the results of sputum stains and cultures, if obtained, for those individuals who have symptoms of active MTB. It could also record baseline and, for those who require it due to age or other medical condition, monthly liver function test results for all patients treated for either LTBI or active MTB, if the treating physician deems these necessary. This paper is primarily concerned with screening and treating those workers with LTBI. Appendix B is a data entry page for the initial screening of the visiting indigent worker. Should a worker actually have LTBI, then any of the numerous LTBI treatment records or calendars could be used. As an example, I included a copy of the Tacoma/Pierce County (Washington) LTBI Treatment Record (Appendix C). This treatment record could be modified if needed to suit the needs of the investigators in Palau.

Regarding treatment of LTBI or active MTB, health care workers from the Ministry of Health should initiate treatment of these indigent workforce members either at PNH or one of its satellite clinics. Alternatively, a health care paraprofessional (nurse or physician assistant) could visit groups of these workers at their worksites on a monthly basis to give them their medications, monitor them for side effects, and draw laboratory samples, such as liver function

tests, if needed. If compliance issues might be a problem, the MOH should send someone out to the workplace to directly observe workers taking their medications. Directly observed therapy (DOT) is recommended as a means to increase compliance and may decrease the odds or risk of MDR-TB from developing (Ref 27).

The cost of the testing materials is minimal: according to a research scientist at the CDC, the TST is only $3 and the QFT-G is only $6-$10 (Mazurek J. Personal communication; Aug 2008). The latter may be a better test for the reasons stated previously, most notably that a higher percentage of these people may have been vaccinated with BCG. This, as has already been stated, may cause some false positives on TST.

5.0 TREATMENT OF THOSE WORKERS WITH LTBI AND ACTIVE MTB

The BCG vaccine has not proven to be a very effective vaccination method. The search continues for an effective method of vaccination. However, until such a method is discovered, the best prevention strategy to prevent the spread of MTB is the treatment of active MTB cases (Ref 28). The literature suggests that close contacts of active MTB patients be treated (chemoprophylaxis) regardless of their TST results, and this has been known for quite some time (Ref 29). In addition, treatment of LTBI patients can prevent them from developing active MTB (a form of secondary prevention) and can prevent their close contacts from being at risk of exposure to the MTB bacillus and, consequently, the disease (a form of primary prevention) (Ref 17).

It is estimated that approximately 10% of individuals with LTBI go on to develop active MTB at some time in their life if left untreated. Of those LTBI patients who develop active MTB, most will progress from LTBI to active MTB in the first 2 years (Ref 26). It is for this reason that that such individuals need to be treated with chemoprophylactic medications. There are four methods to manage LTBI patients. In the first method, patients receive 300 mg of isoniazid (INH), an antitubercular antibiotic, for 9 months. Most sources recommend that these patients also receive pyridoxine or vitamin B6 to lessen the likelihood of peripheral neuropathy, a side effect of INH therapy. In the second method, patients receive INH therapy for 6 months at 300 mg daily; this is less efficacious but also less prone to toxicity. In the third method, LTBI patients receive rifampin (RIF) at 10 mg/kg/day and pyrazinamide (PZA) (at a dosage of 20-25 mg/kg/day) for 2 months. In the fourth method, LTBI patients receive RIF (at the dosage listed above) alone for 4 months. Other variations of these four methods are acceptable [e.g., twice a week versus daily therapy (for the first three methods)] to lessen the likelihood of toxicity, but if variations are used then DOT is recommended (Ref 30).

In treating active MTB patients, there are four preferred methods currently acceptable. Each method requires the administration of four drugs for 2 months as a preliminary treatment period. These drugs include INH, RIF, PZA, and ethambutal. Following this 2-month period, once culture and sensitivity tests are known, the patient is then treated for another 4 to 7 months. For a full description of these methods, see the *Morbidity and Mortality Weekly Report* article from the CDC on this subject, specifically, Table 2: Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms; for a description of first-line and second-line agents, see Table 3: Doses of Antituberculous Drugs for Adults and Children (Ref 31).

In treating the indigent, third-country national population of Palau, it is highly suggested that these methods be used, as they have been effective in managing these separate clinical

entities (LTBI and active MTB). The immigrant workers could have a host of different factors that would demand, as always, individual tailoring of medical treatment. For LTBI patients, these factors include history or close contact with an INH-resistant active disease, a history of liver disease, renal insufficiency, a history of alcoholism, and compliance issues. For those patients with active MTB, antibiotic regimens would need to be individually tailored due to similar conditions, i.e., a history of liver or renal disease, alcoholism, extrapulmonary disease, pregnancy and breastfeeding conditions, compliance, relapse or treatment failure situations, and drug resistance, which will be discussed more fully in the next section (Ref 30,31).

6.0 DISCUSSION AND FURTHER RECOMMENDATIONS

The country of Palau (with only 20,044 people in the last census), from the years 2003 through 2004, had an increased rate of tuberculosis infection from five to nine people, with new infections within the island, and the case rate increased from 25.0 to 45.6 people per 100,000 population. In nearby Guam, during the same period, there was an increase from 51 to 61 patients, and the case rate increased from 20.7 to 37.3 patients per 100,000 population (Ref 32). For 2006, WHO estimates the incidence of new cases of tuberculosis in Palau to be 10, with a case rate of 62 per 100,000 population (Ref 33). This can be compared to the United States as a whole, where from 2003 to 2004 there was an increase from 14,517 to 14,852 people with tuberculosis, but the case rate went from only 4.9 to 5.1 people per 100,000 population (Ref 32).

An official media release (Ref 34) from the U.S. Embassy in Kolonia, Micronesia, concerning the 5th Annual Pacific Island Tuberculosis Controllers Association Meeting, which was held in 2007, included the following:

- There were 138 cases of confirmed tuberculosis in 2006 throughout the Pacific Islands including Palau and with the exception of American Samoa.
- The U.S. Affiliated Pacific Islands had a case rate of 27.58 new cases per 100,000 people.
- This case rate was six times greater than the case rate per 100,000 in the United States.
- Three cases, or 2% of the new cases identified, were multiple-drug-resistant tuberculosis cases.

Another press release from the State of Hawaii Health Department in August 2008 brought to light that multiple-drug-resistant tuberculosis had been found in the Micronesian island of Chuuk. Five patients with MDR-TB had been diagnosed, with four of the patients succumbing to the disease – a case fatality rate of 80%. This problem was so distressing to the Minister of Health of Chuuk that he immediately requested aid from the CDC in Atlanta. The CDC, in partnership with a number of other governmental and nongovernmental organizations, will form a task force to study the problem and prevent the spread of MDR-TB to other island nations in the Federated State of Micronesia, including Palau, and to other countries such as the United States (Ref 35).

Regarding the above information, it can be seen that tuberculosis is a real problem in the Pacific Islands and especially Micronesia or Palau. Also, the rates and population numbers mentioned in this paper refer to the official population of Palau and do not necessarily accurately reflect the indigent third-country nationals who have come there temporarily to work. The prevalence and incidence of new cases of tuberculosis including extensively drug-resistant or multiple-drug-resistant tuberculosis cases are not accurately known. Again, even one case of

MDR-TB could prove disastrous to Palau due to the infectious nature of this organism and the financial cost to the people of Palau of treating such a case. As stated earlier, the average Palauan earns less than $10,000 a year, and that the Palauan Government through the Ministry of Health spends less than $810 per person on health care matters. An article from the CDC states that even one case of drug-resistant tuberculosis can cost almost $100,000 (Ref 36). The occurrence of even one extensively drug-resistant or MDR-TB case would quickly exhaust the health care dollars available in Palau. In fact, one case of MDR-TB would use up what would normally be spent on other health care concerns for 123 Palauans. Another source stated that it is from 10 to 100 times more expensive to treat a drug-resistant form of tuberculosis than it is to treat nondrug-resistant tuberculosis (Ref 37). Of note, it costs only about $200 to treat latent tuberculosis in the United States; so from a cost benefit ratio standing, it is obviously better to treat LTBI before these patients develop overt MTB infections, especially if cases of drug-resistant MTB can be prevented in doing so (Ref 38).

Another important factor to consider in dealing with a tuberculosis prevention program is HIV. Although the disease was first described in the San Francisco area in the early 1980s, the Pacific Island Countries and Territories (PICTs) have not escaped the spread of this disease. Currently, all Pacific Island countries have seen cases of HIV except Niue, Tokelau, and Pitcairn Islands. The majority of the cases have been found in New Caledonia, French Polynesia, Fiji, Guam, and Indonesia, of which all have at least 150 cases each. Unfortunately, health professionals from the region believe that these numbers vastly underestimate the true prevalence of this disease and do so by 90%. They also have discovered that transmission of this disease in the PICTs is mainly by heterosexual contact. Homosexual behavior and intravenous drug abuse are thought to be low in the native Palauan population. Fortunately, since testing for HIV began in Palau in 1989, only seven cases of HIV have been discovered, all of which were in Koror. However, there may be many more cases than this since only 10%, on average, of HIV-infected people get tested (Ref 39). The prevalence of HIV in the indigent workforce of Palau, the numbers of these transient workers who engage in homosexual behavior, and the prevalence of intravenous drug abuse are completely unknown.

The enhanced susceptibility of HIV-infected people to pulmonary tuberculosis is well described and is a very serious problem throughout the world. It is thought that 8% of tuberculosis patients are also infected with HIV (Ref 6). Some authors note that tuberculosis infections are on the rise, and one of the most important contributing factors is coinfection of MTB with HIV (Ref 7). It is recognized that the immunologic challenges facing those with HIV cause an increased propensity for those with tuberculosis to develop drug-resistant forms of the disease (Ref 5). It is necessary to aggressively treat patients with tuberculosis who also have HIV. To treat these patients in the best manner, antitubercular therapy (ATT) is combined with antiretroviral therapy (ART). Unfortunately, poor compliance with ATT and ART can cause MDR-TB to develop, as well as allow the HIV to mutate to more resistant forms. Poor compliance may occur in these patients due to expense of agents, behavioral factors, and incidence of side effects such a diarrhea or nausea. In addition, certain agents used in ART, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, may lessen the efficacy of certain ATT agents. These factors may contribute to poor response of MTB-affected people and allow for the change of natural to drug-resistant forms of the bacteria (Ref 6).

Unfortunately, the “monitoring and evaluation environment” of the HIV status of the native Palauan population has been fairly weak and has been noted as an area that needs improvement (Ref 39). In addition, the HIV status of those migrant or indigent workers

temporarily visiting the island nation of Palau for work purposes is entirely unknown. If this proposed TB testing program was adopted by the Ministry of Health of Palau, the epidemiology of MTB status as well as HIV status could be better described in this population. Secondary prevention methods such as screening could identify those with LTBI or active MTB, as well as those with HIV. Proper treatment of those so infected with LTBI and active MTB could restore their health and prevent them from developing more extensive disease. Directly observed therapy could improve patient compliance with taking the ATT agents and prevent drug-resistant forms of the disease from developing. Patients identified with HIV could be treated at PNH by the hospital's skilled physicians to prevent Acquired Immunodeficiency Syndrome from developing. In skillfully treating patients who are infected with both agents (MTB and HIV), resistance to both ATT and ART agents could be minimized.

In this brief paper, the author has attempted to identify a potential problem that could negatively impact the health of the population of Palau: the unknown health status with regards to LTBI, active MTB and HIV of the indigent workers who temporarily visit Palau for a few months to a few years. If this proposed TB testing program is adopted, the epidemiology of these diseases could be better described. Those identified as having LTBI, active MTB, and HIV could be treated, which could prevent the spread of these diseases to the native Palauan population. If identified early, they could be treated using far fewer funds than would be required should they be identified late in the course of their disease.

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APPENDIX A

Fact Sheet on the Tuberculin Skin Test
(from Ref 26)

Classification of the Tuberculin Skin Test Reaction

An **induration of 5 or more millimeters** is considered positive in	An **induration of 10 or more millimeters** is considered positive in	An **induration of 15 or more millimeters** is considered positive in any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.
-HIV-infected persons -A recent contact of a person with TB disease -Persons with fibrotic changes on chest radiograph consistent with prior TB -Patients with organ transplants -Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)	-Recent immigrants (< 5 years) from high-prevalence countries -Injection drug users -Residents and employees of high-risk congregate settings -Mycobacteriology laboratory personnel -Persons with clinical conditions that place them at high risk -Children < 4 years of age - Infants, children, and adolescents exposed to adults in high-risk categories	

APPENDIX B

Data Entry Page for the Visiting Workers of Palau

Name: Last, First and Middle_____

Age:_____ Sex: Male or Female_____

Country of Origin:_____ Visa or Passport Number:_____

Estimated duration of work:_____

Who will employ you?_____

How do we contact you?_____

Address of where you will live:_____

Any past medical history of tuberculosis or human immunodeficiency virus (HIV)?_____

Did you receive BCG as a child?_____ Estimated date:_____

Any drug allergies?_____ What drugs?_____

Any history past or current of alcoholism?_____

Result of TST in millimeters:_____ and/or
Result of QuantiFERON-TB Gold in a Tube:_____

Results of HIV tests: ELISA:_____ Western Blot:_____
(if TST, or QuantiFERON-TB Gold test, and HIV tests are negative stop here)

Results of initial liver function tests (ALT and AST): AST_____ and ALT_____

Results of screening chest x-ray or radiograph:_____

Decision to treat for LTBI (yes or no):_____

What pharmacologic agent(s) selected?_____

APPENDIX C

Latent TB Infection (LTBI) Treatment Record

LATENT TB INFECTION (LTBI)
TREATMENT RECORD

Patient Name _____ **DOB:** _____

Duration of Therapy _____

Monthly Visits

1. Date of visit												
2. Taking Rx as prescribed												
3. Jaundice/cloudy, brown urine												
4. Nausea/decreased appetite												
5. Vomiting												
6. Numbness/tingling in extremities												
7. Fatigue/weakness												
8. Rash, itching, body aches												
9. Cough, fever, nightsweats, weight loss												
10. Taking other medicines*												
11. # Meds given												
12. LABS												
13. Provider Initials												

* **<u>Rifampin may interfere with</u>: Methadone, Oral hypoglycemics, hormonal contraceptives, anticoagulants, theophylline, dilantin, cardiac glycosides.**

Legend:

0: Evaluated, no problem
NA: Not applicable
+: Problem noted; see progress notes

6/2008

LIST OF ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
ATT	antitubercular therapy
BCG	bacille Calmette-Guerin
CDC	Centers for Disease Control and Preventioin
DALY	disability adjusted life years
DOT	directly observed therapy
HIV	human immunodeficiency virus
INH	isoniazid
LTBI	latent tuberculosis infection
MDR-TB	multiple-drug-resistant TB
MOH	Ministry of Health
MTB	*Mycobacterium tuberculosis*
PICTs	Pacific Island Countries and Territories
PNH	Palau National Hospital
PPD-S	purified protein derivative standard
PZA	pyrazinamide
QFT-G	QuantiFERON-TB Gold test
RIF	rifampin
TB	tuberculosis
TST	tuberculin skin test
WHO	World Health Organization
YLD	years of life with a disability
YLL	years of life lost
YPLL	years of potential life lost