REDUCING INCIDENTS OF TUBERCULOSIS IN CAMBODIA: A FIRST STEP

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It is important to advance humanity by utilizing one's expertise. As a pre-medical student, I knew I could do just that after I learned that Cambodian doctors had expressed a need for information on tuberculosis. In response to this community need, I chose to develop a pamphlet of information on tuberculosis for the rural public. Included in my project was translation of the brochure into Khmer. My concept for the pamphlet was to emphasize the prevention of tuberculosis, identification of the signs and symptoms, and appropriate treatments. In addition, I chose to create an annotated bibliography of academic journal articles for physicians and trained medical staff, with a focus on information about new vaccines and the latest methods of detection.

I designed my project to answer the following research questions. 1) How is tuberculosis prevented, diagnosed, and treated in the United States versus in Cambodia? 2) What is the cause of tuberculosis in rural areas and why is it continuing to spread? 3) Is health care available? 4) What information is available to physicians about tuberculosis? 5) How can these problems be solved?

Literature Review

Mycobacterium tuberculosis is a pathogen that infects nearly one-third of the total population of Cambodia. Currently, 14.6 million people are infected with the active form of tuberculosis, an additional 8.9 million will develop the active form each year, and an average of 1.7 million die every year due to infection (Baral, Karki, & Newell, 2007). Due to the seriousness of the disease, the World Health Organization acknowledged tuberculosis as a global emergency in 1993 (Baral, Karki, & Newell, 2007). Coastal Health Train (1994) explains how Mycobacterium tuberculosis (Mtb) enters into the lungs of a healthy individual via water droplets in the air when an infected person coughs, sneezes, speaks, or laughs (p. 3). Once in the lungs, Mtb can either become latent or develop into active pulmonary tuberculosis (TB). Those with latent infections are asymptomatic and are incapable of spreading the disease to others. Those with active TB will experience a cough lasting for at least two weeks, fever, weakness/fatigue, night sweats, and weight loss. They will also be capable of passing on the disease and will need to take medication in order to get rid of the disease (Coastal Health Train, 1994, p. 4).

Prevention, Diagnosis, and Treatment

Because TB is contagious, it is not always easy to prevent. Werner, Thuman, and Maxwell (2007) offer a few guidelines for illness prevention, such as covering the mouth while coughing, thoroughly washing hands with soap and hot water, boiling water that is used for drinking and cooking, and keeping the house clean by sweeping and wiping down surfaces. In addition, it is important not to spit on the floor. Those with tuberculosis should be isolated from others while eating and sleeping to keep from spreading the disease to others (Werner et. al, 2007, p. 133-136).

There are several methods of detecting an Mtb infection as described by Ernst, Treveto-Nunez, and Banaiee (2007). Health care workers most often use the tuberculin skin test with purified protein derivative (PPD) and x-rays of the lungs when diagnosing. A blood test known as IFN-γ release assay can be performed in two ways, T-SPOT.TB and QuantiFERON-TB Gold (Ernst et al, 2007, p. 1742). Sputum, or phlegm, from the lungs can also be tested using an acid-fast smear-positive, culture-positive, and microscopic-observation drug susceptibility (MODS) assay. Sputum tests, however, take longer to determine whether there is an Mtb infection because the bacterium is slow growing (Ernst et. al, 2007, p. 1743).

In the 1900s, doctors were limited on treatments for TB and would prescribe healthy food, rest, increased sun exposure, and clean air to those infected with Mtb. The first antibiotics were created in 1943 and promised a cure for pulmonary TB (Everett, 1995). However, Mtb has a thick, waxy coat of lipids on its surface that tends to prevent antibiotics from penetrating and killing the bacteria. Streptomycin was the first antibiotic created against Mtb; however, its side effects included ulcerations of the mouth, throat, and lips. Since the introduction of Streptomycin, several strains of drug resistant Mtb have surfaced, thus making it imperative to use several drugs to treat the infection (Everett, 1995). Treatment may take as long as nine months before the infection is cleared, and pills must be taken every day. However, after two weeks of treatment, the infected person is no longer capable of spreading the disease to others (Baral, Karki, & Newell, 2007). Some of the drugs available in Cambodia include Isoniazid, Rifampicin, Ethambutol or Myambutol, and Pyrazinamide (Tuberculosis Awareness, 1994). Most governments, including Cambodia, distribute anti-TB medication free of charge (Werner, Thuman, & Maxwell, 2007, p. 180).

Rural Areas and Health Care

If treatment and diagnosis are readily available, why are so many people dying from pulmonary TB? Baral, Karki, & Newell (2007) have found that

many individuals who notice that they have symptoms of TB will not seek medical attention out of fear of being socially isolated. Others stop treatment because of self-discrimination, such as depression, and self-isolation (Baral, Karki, & Newell, 2007). In rural areas, such as in Cambodia, patients have to travel long distances to medical clinics daily in order to receive their medication. This also deters people from treatment because of the travel time that takes away from time spent working (Everett, 1995).

Information Available to Physicians

How does Mtb cause infection in the lungs? And what is the body's response against the infection? When Mtb enters the lungs via a water droplet, certain proteins on the bacterium's surface interact with Toll-like receptors (membranous receptors that activate immune cell responses) on a macrophage, a certain type of white blood cell. This interaction causes the release of cytokines, a signaling molecule important to the development and functioning of both the innate and adaptive immune system responses (Bhatt & Salgame, 2007). Once Mtb is recognized as foreign, it is phagocytized (ingested and destroyed) by the macrophage. However, Mtb has a way of avoiding its own destruction by inhibiting the lysosome (sub-cell that digests viruses and bacteria) from fusing with its own vacuole, or cavity within a cell (Bhatt & Salgame, 2007). If, however, the lysosome is fused with the vacuole, the macrophage will degrade the bacterium into peptides and display them on its surface with major histocompatibility complexes (MHC) class II (Chaplin, 2003, S448). The purpose of displaying the peptide bound to MHC is to show T cells that a bacterial infection is taking place (Chaplin, 2003, S448-9).

T cells bind to the MHC peptide complex, become activated, and differentiate into Th1 cells or Th2 cells. Activation is achieved by a signal transduction cascade that phosphorylates from one step to the next (Delgado et.al, 2002). Th1 cells recruit other cells and antibodies to fight the infection by secreting cytokines like IFN-γ which stimulates more macrophages (Chaplin, 2003, S450). Th2 cells bind the target and induce phagocytosis of the bacterium by macrophages or neutralize the bacterium by binding to it (Chaplin, 2003, S448-9).

Problem Solving

Not only is lack of treatment causing the rise of TB infected individuals in Cambodia, genetic polymorphisms in the immune response contribute to tuberculosis susceptibility. Delgado et. al (2002) discovered T cell anergy, or inactivation, among the Cambodian population. Twenty-five of the 364 Cambodians diagnosed with pulmonary TB and involved in a controlled

study demonstrated T cell anergy to the PPD skin test (p. 7577-8). These individuals did not show a PPD-positive skin test even though they had been exposed to Mtb. Further studies by Delgado and colleagues showed defective phosphorylation of the signal transduction needed to activate T cells. The error was found during phosphorylation of TCRξ, ZAP-70, and MAPK (Delgado et. al, 2002, p. 7578). So what does this mean? It appears that PPD skin testing is not always an accurate test for tuberculosis in Cambodia. A negative result should be followed by an x-ray or sputum culture. An IFN-γ release assay should not be relied upon, because it tests the same components as the PPD skin test.

Although some Cambodians have the problem described above, others may be secreting cytokines or chemicals that may also cause inactivation of T cells. Boussiotis, Tsai, Yunis, Thim, Delgado and Dasher (2000) investigated IL-10 and discovered it directly causes anergy in T cells. They also found that IL-10 is present only after the addition of Mtb or PPD in patients whose immune systems respond normally. However, IL-10 was found to be present before and after Mtb and the PPD addition in anergic patients. Anergic patients also show a lack of IFN-γ (Boussiotis et. al, 2000, pp. 1320-1322). Goldfeld (2004) agrees and believes patients treated with an anti-IL-10 monoclonal antibody will re-establish their T cells' capacity to respond to a PPD skin test (Goldfied, 2004, p. 79). She also found an MHC relationship to Mtb susceptibility. Evidence shows the allele HLA-DQB1*0503 translates to an aspartic acid at beta 57 of the HLA-DQB molecule that decreases its ability

to bind and display Mtb peptides resulting in a reduced immune response (Goldfied, 2004, p. 78).

There are several strategies that could be used to address the tuberculosis crisis in Cambodia. Simple prevention measures can be used, along with seeking available treatment despite stigma and discrimination factors. Treatment may also be improved by bringing medications to villages rather than requiring villagers to travel to clinics. However, scientists have found that genetic factors contribute significantly to the problem. Medical professionals must be diligent when testing for active tuberculosis, as a simple PPD skin test has proven ineffective for anergic patients. The research indicates that genetic polymorphisms, such as defective phosphorylation during signal transduction, ineffective MHC binding, and secretion of IL-10 have rendered a significant minority of Cambodians more susceptible to tuberculosis.

Project Description

I developed two projects that focused on tuberculosis. First, I developed a booklet that described prevention measures, signs and symptoms, and basic knowledge about tuberculosis. This booklet was designed to train teachers so they might use the information in their classrooms to educate students. It was my hope that students would then pass the information on to their families. The booklet was also intended to be used to train staff members of the Cambodian Women's Crisis Center. These employees, while traveling to rural areas, could educate villagers about the effects and prevention of tuberculosis.

My second project focused on developing a PowerPoint presentation for Cambodian medical professionals. The presentation addressed the genetic polymorphisms present among the Cambodian population that renders them more susceptible to infections from *Mycobacterium tuberculosis.* In addition, I researched and collected seven journal articles that addressed the immunological background behind tuberculosis and relevant genetic anomalies. Using these articles, I created a reference guide with an introductory paragraph, an annotated bibliography, and copies of the journal articles.

In-Country Activities

While in Cambodia, I presented my research to physicians at Sihanouk Hospital in Phnom Penh. My presentation used data from the World Health Organization to set tuberculosis in a global context. I also provided a brief overview of the immune system, discussed the mechanisms of

how mycobacterium evades the human immune system, and explained the genetic defects that impair many Cambodians and the resultant consequences. My first attempt to work through our translator, Sophal Stagg, was unsuccessful. She had difficulties translating the medical terminology and concepts. She explained to me that English to Khmer is not a word-for-word translation. Rather, a whole idea is translated.

With the help of Dr. Nathan Griggs, I revised my presentation and made the points simple and clear. After explaining to Sophal the basic concepts of my presentation, she successfully translated the information to the doctors. The pulmonary physician was most interested with the results of my research. At each hospital I handed out the reference guide of medical journals to the physicians. I also toured the pulmonary clinic, out-patient clinic, and laboratory of the hospital.

When we traveled to rural Prey Sadeah, I presented my research to another group of medical professionals. Although they were very interested, they explained to me that they were unable to test any of their patients for tuberculosis due to the lack of medical supplies. I also gave them the tuberculosis booklets containing information on signs and symptoms for their patients.

Results

I had the unique opportunity to interact with doctors in Cambodia on a more professional level than previous McMaster Scholars. In order for my project to be most effective, it was important that the doctors had some background in immunology. It appeared that Cambodian physicians are not as well trained as the physicians I am used to in the United States. However, it was difficult to distinguish a lack of knowledge from mistranslation during the presentation.

While presenting, I had to be flexible and willing to present basic information in order to make my research understood. Eventually, I began to understand that each doctor seemed to have attained a different level of training and education. The variation in their backgrounds became apparent when the TB specialist at one hospital asked, "After giving the PPD skin test, how large does the bump need to be before I can diagnose the patient with TB?" I realized then that this doctor had been diagnosing patients without knowing the most basic information required to read a PPD skin test. After one presentation, I learned from the physicians that many Cambodians are plagued by miliary tuberculosis, which attacks the joints or lymph nodes. The doctors were also struggling to understand how to test and treat this type of TB.

In addition, I discovered that medical professionals are working with significant technological inadequacies in the hospitals of Phnom Penh. The doctors have no choice but to make do with the equipment they have. When I toured the labs, I learned that everything was manually tested and entered into the computer system. The technicians had very few machines and one computer that required manual typing to enter the results.

Although the hospitals in Phnom Penh were challenging, the hospital in the rural area was a different story. A doctor in rural Baah Prey told me that the clinic did not have the means to test for tuberculosis. He estimated that 40% of his patients were TB cases that were sent to Phnom Penh for diagnosis. It was difficult to discern how I could be of service to them. However, they did appreciate the TB booklets that could be passed out to their patients.

REFLECTION

Initially, my project was to research and collect medical journals on vaccine development and other general tuberculosis articles to be given to the Cambodian doctors. However, while researching, I came across an article in which the authors hypothesized that a large percentage of Cambodians are more susceptible to tuberculosis due to genetic defects in their immune system (Goldfeld, 2004). Because I was enrolled in an immunology course at the time, I was excited about understanding all of the concepts. I continued my research and discovered that Goldfeld has not been the only scientist to study the Cambodian population.

After collecting all of the materials and creating a presentation, I found that it was more difficult to explain this information to Cambodian doctors than I had imagined. Not only was I working through a translator, I was also unsure about both the doctors' immunology background and my own. I was intrigued while listening to the doctors' questions after my presentation. I felt like an expert and really enjoyed fielding questions. I had to gauge the doctors' medical knowledge and be careful not to judge them based on American standards.

Despite the differences in education, the doctors were receptive to the research I presented. In the future, I hope that the doctors will have better access to research and medical journals to help them more accurately diagnose and treat pulmonary tuberculosis. And because the doctors explained that they have just as many miliary cases as they do pulmonary, a possible project for future scholars might be to address the need for information on miliary tuberculosis. With proper information and control, Southeast Asia could decrease the incidence of cases of TB in the future.

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