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Tuberculosis In Developing Nations:
Why New Drugs Need To Be Researched And Developed

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Abstract

Pharmacologic treatment for tuberculosis is widely available in developing nations, and is often financed by the governments of these countries. Treatment however can be highly toxic and require a lengthy duration of therapy. There are now many strains of tuberculosis that are drug resistant. People in impoverished nations frequently cannot afford to pay for transportation to and from treatment facilities. Research and development of new tuberculosis drugs is necessary given the presence of resistance and toxicity of the existing drugs. Newer agents that require shorter treatment duration with decreased toxicity and increased efficacy are most desirable and needed in developing nations.

Tuberculosis In Developing Nations:

Why New Drugs Need To Be Researched And Developed

The rate of new tuberculosis (TB) cases is on the rise, even in light of better diagnostic methods and treatment regimens. According to Alteri, Xicohténcatl-Cortes, Hess, Caballero-Olín, Girón, & Friedman, tuberculosis remains the most devastating bacterial cause of human mortality. One-third of the world's population is infected with the TB mycobacterium (Kumar, Malhotra, Goswami, & Bamezai, 2003), and two million people die from the disease every year (Salomon Lloyd-Smith, Getz, Resch, Sánchez, Porco, et al, 2006). This is a significant problem worldwide. Existing drugs have a long course of therapy, and most are hepatotoxic. In addition, drug-resistant tuberculosis cases are increasing. New TB drugs need to be developed to stop this disease from becoming an epidemic.

Bacteria *Mycobacterium tuberculosis*

— Tuberculosis (TB) is a disease caused primarily by the *Mycobacterium tuberculosis* bacterium. *M. tuberculosis* is an acid-fast mycobacterium that grows very slowly. Its cell wall consists primarily of lipids and allows the bacterium to resist disinfectants, antiseptics, drying out, and other environmental hazards. Because of its structure, *M. tuberculosis* is difficult to kill.

There are several types of TB infections, each named mainly for the location of the infection. Pulmonary TB is the most common and also the most deadly form of TB (Kumar, et al., 2003). For simplification purposes, in this paper “TB” and “tuberculosis” refer to pulmonary tuberculosis unless otherwise specified.

In pulmonary TB, the *M. tuberculosis* bacteria enter the body through the lungs by

inhalation. If an individual is healthy, the immune system initially recognizes the bacteria as intruders. However, TB bacteria have a surprise feature, one that makes TB a difficult, if not impossible, opponent for an immune system to conquer. *M. tuberculosis* possesses the ability to bypass the defense mechanisms of the human immunologic system. It has the “ability to arrest phagolysosome biogenesis, avoid direct cidal mechanisms in macrophages, and block efficient antigen processing and presentation” (Deretic Singh, Master, Harris, Roberts, Kyei, et al., 2006 p. 719).

The initial detection of *M. tuberculosis* by the immune system triggers the body’s natural defenses, including the mass migration of macrophages to the site of infection. These macrophages attempt to contain the infection by building walls of cells around the invaders, enclosing them in capsule-like lesions called tubercles (Tortora, Funke, & Case, 2004). In the rush to contain the infection, macrophages are encapsulated along with the tuberculosis bacilli. They are left to destroy all the intruders inside the capsule, but this does not occur. After the tubercles have been formed, *M. tuberculosis* acts as a parasite, evading detection by entering into and living inside the macrophages, specifically in phagosomes (immature phagolysosomes). Phagosomes normally mature into phagolysosomes, but this process does not occur in immune cells invaded by the tuberculosis mycobacterium because *M. tuberculosis* produces two substances – a lipid and an enzyme – both of which prevent the conversion of its host phagosome into a phagolysosome (Deretic et al., 2006). Since phagolysosomes are a major component of the body’s immune response, the ability of *M. tuberculosis* to evade detection in this way defeats the body’s natural defense system against TB, giving it time to multiply. When the bacilli are still encapsulated, the tuberculosis infection is said to be latent. A TST or blood test will indicate exposure, but since the

bacteria are contained within the tubercles, they are not present in sputum; therefore a sputum smear would test negative.

Over time, the tubercle lesions become calcified. They are then called Ghon complexes and will appear on X-rays and CT scans. The tuberculosis bacilli remain alive and replicate in these Ghon complexes, waiting until their host's immune system becomes deficient. The capsules then burst open, releasing TB bacilli into the body's lungs, cardiovascular system, and lymphatic system. As soon as the TB bacilli break out of the Ghon complexes, the infection is classified as active, or miliary TB, because of the tiny millet seed-sized tubercles that form in the tissues. Because it is fighting a weakened immune system, *M. tuberculosis* defeats the remaining immune defenses and continues to multiply unhindered. Unlike latent TB, active TB is symptomatic. Weight loss, weakness, and coughing up blood are classic signs of active TB infection. The disease was formerly known as "consumption" because the infected person became weaker and weaker, lost weight, and simply seemed to be consumed by the illness (Tortora, Funke, & Case, 2004).

One reason that TB is so hard to treat is that it avoids detection by the body's macrophages by living and replicating inside those very macrophages. Scientists are still puzzled by exactly how the mycobacterium accomplishes this (Alteri, et al., 2007). Alteri, et al. are part of the search for the answer. In the past, scientists believed that mycobacteria did not produce pili. However, Alteri, et al. discovered that TB mycobacteria do indeed produce pili that help them attach to macrophages. In their study, they found that 60% of tuberculosis patients' serum samples tested positive for *Mycobacteria tuberculosis* pili (MTP), but none of the non-tuberculosis infected serum samples did (Alteri, et al., 2007).

MTP are very similar to the pili-like structures produced by the highly virulent bacteria *Escherichia coli* and *Salmonella enterica*. Despite that similarity, MTP are not easily broken down, whereas the pili of *E. coli* and *S. enterica* are (Alteri, et al., 2007). MTP are polymeric, hydrophobic, and protein-based. They bind to laminin, an extracellular matrix protein which is a major component of human cellular basement membranes. Although suspected but not proven to be the case with MTP, other bacterial pili are responsible for allowing bacteria to agglutinate erythrocytes, aggregate bacteria, form biofilm, adhere to cells, and form colonies on mucosal surfaces. All of these functions are related to the virulence of bacteria. MTP allows *M. tuberculosis* to attach to, enter, and colonize first macrophages and then other tissues. If scientists could medically target bacterial pili, they could greatly decrease, if not completely destroy, the TB bacteria's pathogenicity. For this reason, pili have been a focus of vaccine research and development (Alteri, et al., 2007).

M. bovis is a bacterium similar to *M. tuberculosis* that also produces tuberculosis. *M. bovis* infection is acquired by drinking unpasteurized milk. Unlike *M. tuberculosis*, *M. bovis* is not transmissible from person to person. The tubercles found in *M. bovis* infection are normally found in the bones and lymphatic system rather than in the lungs (Tortora, Funke, & Case, 2004).

Drug resistance is a major problem in the treatment of *Mycobacterium tuberculosis* infection. This problem exists due to multiple reasons. First, the treatment of *M. tuberculosis* is prolonged (six months to a year or longer), because *M. tuberculosis* grows slowly. Since treatment is prolonged, there is more time for the bacteria to mutate and develop drug-resistant strains. Secondly, patient compliance decreases the longer the duration of treatment (Lenhe 2007). There are two major classifications for resistant TB strains; multi drug

resistant (MDR) and extensively drug resistant (XDR) TB. Multiple drug resistant (MDR) TB is resistant to two or more TB drugs, usually the first-line drugs Isoniazid and Rifampin. Shah, Wright, Bai, Barrera, Boulahbal, Martín-Casabona, et al. define extensively drug resistant (XDR) TB as MDR-TB with added resistance to three or more of the second-line TB drugs. The World Health Organization's (WHO) guidelines call for MDR-TB to be treated with four or more different TB drugs to which that particular strain is susceptible. However, since XDR TB is, by definition, resistant to three or more second line drugs, and since there are only six classes of second-line drugs, effective treatment of XDR TB is, by WHO standards, absolutely impossible to treat with existing resources.

Screening Methods

Several tests are used to determine TB exposure. The tuberculin skin test (TST) is an intradermal injection of *purified protein derivative* (PPD), which is an *M. tuberculosis* antigen. If the patient has been infected with TB and has a functional immune system, there will be a local reaction (hardness) around the injection site. In an immunocompromised patient (such as one with AIDS – acquired immune deficiency syndrome), a smaller reaction size is adequate to diagnose exposure to TB. This is because the immunocompromised patient's immune system cannot react as well as a healthy person's would, producing a weaker reaction. A PPD will not test positive unless a person has been infected for six weeks or more (Pagana & Pagana, 2007).

Chest radiography is a very accurate way to diagnose TB, and is often done to check for tubercles in the lungs after a positive PPD. A chest x-ray cannot distinguish between latent and active TB. It also will not be positive (show tubercles) in the early stages of the

disease, because there has not been enough time for the macrophages to form tubercles around the bacteria and calcify into Ghon complexes.

The QuantiFeron-TB Gold blood test is another test to determine TB exposure. This test uses a blood sample to determine TB exposure. It is equally as effective as the TST, results are known more rapidly (24 hours), and it only requires one doctor visit rather than the two needed for the TST. This test is not as widely available as other tests (Lenhe 2007).

The sputum smear is one of the quickest, most accurate methods available for diagnosing active TB infection. The process is simple and painless for the patient. A sputum sample is taken, which is transferred to a slide, stained with acid-fast dye, and viewed under a microscope to note the presence of mycobacteria bacilli. The problem with the sputum smear is that it can only diagnose active pulmonary TB, which means that it will test negative if the infection is latent or resides anywhere but the lungs.

DOTS, formerly simply an acronym for “directly observed therapy, short-course”, is the WHO’s international standard for TB treatment. It was implemented as standard care in TB treatment because of patient non-adherence. In DOTS, a healthcare worker observes the patient when they are taking the drugs to ensure that the medicine is taken. Now, DOTS refers not only to the direct observation aspect of TB treatment, but also to the world health organization’s (WHO) entire public health strategy for TB. It includes directly observed therapy, a chemotherapy and first-line drug regimen, use of sputum-smear microscopy to diagnose TB, supportive measures taken for patients on long-term (6-9 month) therapy, and records of drug supplies and distribution.

Since its institution, DOTS therapy has been very successful, with cure rates of over 80% (Salomon et al., 2006). However, DOTS only catches active cases of TB. Everyone

who comes to a clinic, with symptoms of TB (persistent coughing, etc.) is examined and sputum-smear tested for the disease. This works well to test for active cases, but since in latent TB the sputum contains no TB bacteria, this method of screening if used alone is ineffective in the eradication of tuberculosis.

Many different immune-based tests are being sold commercially in developing nations. These test serum antibodies, antigens, and immune complexes, for evidence of TB infection. It would seem that these would be reliable diagnostic tests. They are much faster and simpler than sputum smears. A systematic review of the literature was performed, which found that no commercial immune-based test is accurate enough to replace the sputum smear as a diagnostic tool for TB. Also, none of them could accurately diagnose TB in children or patients co-infected with human immunodeficiency virus (HIV). A concern is that since the commercial tests are sold widely in developing nations, they will distract resources from the more accurate sputum smear test (Steingart, Henry, Laal, Hopewell, Ramsay, & Menzies, et al., 2007).

In addition to traditional methods of TB screening, some scientists are thinking outside the box when it comes to checking for the disease. Scientists in Morogoro, Tanzania, are attempting to use rats in the detection of TB in sputum samples. The rats are trained to recognize the smell of TB mycobacterium in human sputum. These researchers have already trained rats to sniff out landmines, so with their keen sense of smell, the rats are capable of such work. With their ability to sniff through over 200 samples an hour, the rats are capable of working much faster than human lab technicians, who can only work through about 20 samples a day. Early results indicate that with their accurate sense of smell, the rats also find fewer false positives (Holden, 2004). If this method of TB detection proves reliable, the

diagnostic process would be faster and more accurate than technician-checked sputum smears.

A bacterial culture is the gold standard for TB testing. A sputum sample is put on a culture medium and screened every 24 hours for growth. Once there is enough bacterial growth, it is checked by microscope to test what kind of bacteria it is. If a sputum sample grows *M. tuberculosis*, then the patient certainly has the disease. However, it is a lengthy process because *M. tuberculosis* grows extremely slowly.

MDR and XDR TB are difficult to detect. Testing for resistance to second-line drugs is not as available in developing countries as testing for resistance to first-line drugs. Shah, et al. tested TB isolates from laboratories that had received samples from forty-eight countries. Out of 17000 samples, almost 20% were MDR and almost 10% were XDR. They found XDR TB in every region of the world that was tested in the study. Since XDR TB is untreatable by WHO standards, it is a considerable threat to public health worldwide. If WHO's DOTS guidelines are not strictly adhered to, the incidence of XDR TB will greatly increase (Shah, et al., 2007).

Tuberculosis Drugs

Isoniazid is the drug of choice in TB treatment. It is more effective, less toxic, cheaper, and easier to use than other TB drugs. Isoniazid is selective to *M. tuberculosis*, and can kill the bacilli at concentrations much lower than it would take to kill gram positive or negative bacteria. It is bactericidal when mycobacteria are actively dividing, but bacteriostatic when they are not. For this reason, it is more effective during the first phase of treatment, when active TB is being defeated. A problem with Isoniazid is that the TB bacilli spontaneously mutate during treatment, and can develop resistance. If multiple drugs are

used to treat tuberculosis, resistant strains of TB will not emerge in that patient. When treating active TB, Isoniazid must always be administered with one or more other anti-TB drugs to prevent resistance, but when treating latent TB it can be used alone. Isoniazid has many undesirable side effects. It is hepatotoxic, and when its use causes vitamin B6 deficiency, peripheral neuritis results- manifested by tingling, burning, numbness, clumsiness, and unsteadiness. Vitamin B6 deficiency is easily treated with administration of vitamin B6. However, in a developing nation, enough of the vitamin may not be available because of an already malnourished diet, and vitamin pills may not be available at all (Lenhe 2007).

Rifampin is another first-line drug, and it is similar to Isoniazid in effectiveness. It is well tolerated, but does have some strange, adverse effects – it causes sweat, tears, and other body fluids to turn reddish-orange. Like Isoniazid it is hepatotoxic, and a combination of those two and other TB drugs, almost all of which are hepatotoxic, is especially dangerous for the liver. Unfortunately, this combination is standard in TB treatment. Rifampin causes the body to accelerate its metabolism of many drugs, which is important because this decreases the effectiveness of HIV drugs. A first-line TB drug that does not increase the metabolism of HIV drugs is Rifabutin (Lenhe, 2007).

Since they are less effective and more toxic than their first-line counterparts, second-line TB drugs are only used when mycobacterium are found to be resistant to the first-line drugs. To prevent further drug resistance, second-line drugs are always used in conjunction with one or more first-line drugs. In addition to hepatotoxicity, many second-line drugs are nephrotoxic, and all have very unpleasant side effects. Several cause severe gastrointestinal (GI) disturbances; one causes balance disturbance and hearing loss; and one even crosses the

blood-brain barrier entering the cerebrospinal fluid (CSF). This action can cause psychoses, seizures, depression, and other central nervous system (CNS) effects. Due to their toxicities, caution must be exercised when using these drugs to treat patients (Lenhe 2007).

R207910, a diarylquinolone, is one of several new TB drugs that were recently discovered. This drug is still being tested, but researchers say that it is highly promising for the treatment of TB and even MDR TB. It is bactericidal and bacteriostatic, so it would be able to treat both active and latent TB infection (Biava, Porretta, Deidda, & Pompei, 2006). Laboratory studies done on mice concluded that when R207910 replaced one of the drugs in the normal 3-drug cocktail (Isoniazid, Rifampin, and Pyrazinamide), it worked twice as fast as the conventional drug regimen. They found that it also treats MDR TB. Mycobacteria do develop resistance to R207910, so it would have to be given in conjunction with other TB drugs, but it could significantly shorten treatment time (Cohen, 2004). As of October, 2007, it was still in the testing stage, so whether it will be effective throughout the rigorous human trials and be affordable for people in developing countries remains to be seen (Barry & O'Conner, 2007).

Tuberculosis Treatment

Drug therapy for active TB must use at least two drugs. The chance of *M. TB* mutating so that it is resistant to one drug is one in 10^8 . Since there are generally this many bacteria in an infected individual, the likelihood of drug resistance development is very high. The chance of a single bacterium developing resistance to *two* drugs is 10^{16} . The likelihood of resistance developing with those odds is nil if the treatment regimen is completed. Therefore, if TB is treated with two or more drugs, even if a bacterium develops resistance to one of the drugs used in treatment, the other would kill it, eliminating drug resistance in that

individual (Lenhe 2007). DOTS treatment requires at least two drugs, but usually three or more are used as a precaution.

— First-line drugs are used for six months in patients who have never before been treated. Second-line drugs are used for 8 months to two years in patients who have contracted a resistant strain of TB. (TB must be treated for 12-24 months *after* the sputum is no longer positive for the bacilli.) In theory, when all of WHO's treatment guidelines are in place, cure rates for TB can be up to 90%. However, the emergence of multi-drug resistant TB lowers this cure rate. (Lenhe 2007; Espinal & Dye, 2005; Nathanson, et al., 2006).

The existence of multi-drug resistant bacteria necessitate the testing of the bacilli of each infected individual for drug susceptibility. These tests can take as long as 4-6 weeks. Meanwhile, the patient is started on a combination of 4 drugs (usually Isoniazid, Rifampin, Pyrazinamide, and Ethambutol). This first phase (the induction phase) is to eliminate the active and multiplying bacteria and usually lasts two months. If resistance is suspected or discovered, the patient is started into the second phase (continuation phase) and up to seven other drugs are added to the regimen (Lenhe 2007). The continuation phase lasts four months, and Isoniazid and Rifampin are used (Lenhe 2007). The goal is to kill the remaining bacilli that are dormant in the tubercles, so that they cannot re-emerge and cause active infection.

Any TB strain that is resistant to second-line drugs is very difficult, if not impossible, to treat with existing drugs. Shah, et al. says, "resistance to TB drugs results primarily from non-adherence by patients, incorrect drug prescribing by providers, poor quality of drugs, or erratic supply of drugs." Each of these problems is rampant in third-world countries. It is no surprise that drug-resistant TB is rife in those countries as a result (Shah, et al., 2007).

Suarez, et al. did a study on the cost-effectiveness of using second-line drugs on chronic TB in Peru. They found that there was an increase in the number of patients who were cured when second-line drugs were used on MDR TB. However, they also found that treatment with second-line drugs was less cost-effective than with first-line drugs, and using second-line drugs also prolonged treatment, resulting in a high dropout rate for the study. Findings concluded that only half of the subjects were cured (Suarez, et al. 2002).

This study gives a glimpse of one facet of the problem of MDR TB. It is a problem that perpetuates itself. Drug-resistant TB is created when tuberculosis treatment is not completed, which, because of long treatment time, occurs frequently. Non-completion can happen for a variety of reasons, such as when patients stop taking the medication because they forget, because they begin to feel better after defeating the active infection, or because the side effects are so unpleasant. Another problem, especially in developing countries, is that the supply of TB treatment drugs is unreliable and only intermittently available (Suarez, et al. 2002).

In 2006, Eva Nathanson, et al. completed a study on the treatment of MDR TB in five developing countries. Half of the subjects were resistant to both first-and second-line TB drugs. Nathanson, et al. found an average cure rate of 70%, with a higher cure rate among those who had never been treated than those who had been treated previously. Patients involved in the study received DOTS treatment, and in some of the countries studied, also received free transportation, food and money incentives to participate in the DOTS, and housing and financial support if needed. Nathanson, et al. concluded that the treatment of MDR TB could be as effective in developing countries as in wealthier nations. However, in one country, default rates (the number of patients who discontinued treatment for two or

more consecutive months) were low because many of the subjects were imprisoned and thus were literally captive participants. The patients in another country were hospitalized during treatment, which would also falsely lower default rates because it cuts out real-life factors such as transportation costs and lodging in the town where DOTS treatment is offered. In the Philippines, for example, default rates were high because no DOTS incentives, such as free transportation to and from DOTS facilities, were offered (Nathanson, et al., 2006).

Patient incentives such as free treatment for DOTS appear to be one of the reasons that cure rates were so high in Nathanson's study. In the countries in which patient incentives were offered, there was increased patient compliance (decreased default rates). In the countries where there were no incentives, patient compliance decreased. While those incentives may have been offered for study purposes, they are not offered for general treatment. Also, outside of scientific studies, patients must pay for transportation to and from DOTS facilities. In some places, patients live so far away from a DOTS facility that they also must pay for lodging and food for the duration of the treatment. For a subsistence farmer, this may be too high of a price to pay. If patients do not understand that in order for treatment to be effective they must take the entire drug regimen for six or more months, those in developing countries might start treatment but have to stop when they run out of funds. This pattern increases the incidence of drug-resistant TB because the treatment is not completed. Once the patient has MDR TB their treatment is even less affordable because the treatment regimen is even longer (Nathanson, et al., 2006). Thankfully, in many countries the government pays for TB treatment. This can cause problems because developing nations do not have enough money to spend on TB treatment, resulting in intermittent drug supply, contributing to TB resistance. It is a vicious cycle.

The same drugs that are being used to treat TB today are the same ones that have been used for the past 30 years (Salomon et al., 2006). These drugs are highly toxic, and the mycobacteria they attempt to kill are becoming more and more resistant. Why haven't newer, more efficient drugs been researched and developed to extinguish TB around the world? The sad answer is that there is not a fortune to be made by pharmaceutical companies to research and develop new TB drugs. Since the majority of TB patients live in low to middle-income countries, they would not be able to pay for an expensive new drug, even if it was more effective and less toxic. Even if the governments of each nation paid for the new drug treatment as some do now, it would still be too expensive, because developing nations cannot afford to pay a lot of money for TB treatment. Without this financial incentive, pharmaceutical companies and researchers have turned to the development of more profitable drugs for other diseases, leaving TB patients without alternatives. In the cases of those with MDR or XDR TB, this also leaves patients without treatment.

Ridley, Grabowski, and Moe proposed an idea to help give incentives to pharmaceutical researchers in the United States to develop new and more effective TB drugs. They proposed that vouchers be given to pharmaceutical companies who develop FDA-approved drugs for TB which are superior to the existing drugs. Also, in order to receive a voucher, the company would have to forgo patent rights and find a manufacturer for the drug. The vouchers given to the companies for their newly developed TB drugs would be auctioned to major pharmaceutical companies. Each voucher would give its bearer a "priority pass" – enabling one of the drugs that they are developing to "cut in line" so to speak, and go through the FDA's red tape more quickly (cutting down the time it would take before that drug hit the market from 18 to six months). This would be profitable (and

therefore an attractive offer) for the buyer of the voucher because the more time a drug spends on the market, the more money the company makes. The company holding the voucher would have to pay a user fee in addition to the amount for which they bought the voucher. This user fee would cover the cost of the FDA hiring more people, buying more equipment, etc. required to prioritize that drug (2006).

Vaccinations

The traditional vaccine for TB is the Bacillus Calmete-Guérin (BCG). The BCG vaccine was developed in the early 1900's and its use was widespread in France in the late 1920's. In the 1980's however, it was discovered that TB caused more deaths in AIDS patients (especially those who had been vaccinated with the BCG vaccine) than did any other disease.

Surprisingly, the BCG vaccine was found to be more effective against leprosy (caused by *Mycobacterium leprae*) than against TB. Kumar, Malhota, and Goswami concluded that the BCG vaccine appears to be more effective against systemic mycobacterial infection than against local pulmonary TB infection (2003).

An alternative to the live attenuated BCG vaccine is the auxotrophic BCG vaccine. The bacteria in this vaccine are genetically mutated so that they lack the ability to replicate for very long. These bacteria do not suppress the host immune system (the attenuated vaccine does), so they can be safely administered to AIDS patients. The drawback is that the mutated bacteria only last a few months and after that the immunity is lost.

Several ideas about TB vaccines are being explored. Live TB mycobacteria have the ability, once they enter a host, to suppress its immune system. Little is known about how they accomplish this. If scientists could discover and isolate the part of the mycobacterium

that triggers, but does not suppress the immune response, they could use this in the development of a vaccine against *M. tuberculosis*. Another vaccine option being explored is a DNA vaccine. This could be dangerous though because it could cause mutation in the anti-tumor portion of DNA and allow uncontrolled tumor growth (Kumar, Malhotra, Goswami, & Bamezai, 2003).

HIV/AIDS And Its Effect On Tuberculosis Treatment

The HIV-infected population is remarkably more vulnerable to TB when compared to the general population. These immunosuppressed patients are six times more likely to become infected with tuberculosis in the first year of contraction with HIV, and rates only increase from there. If an HIV patient develops an active tuberculosis infection they are 100 times more likely to progress to full-blown AIDS. TB is one of the main causes of death in AIDS patients (Silversides, 2006). Fully one third of those with HIV are co-infected with TB. The two diseases have a reciprocal relationship. HIV increases susceptibility to TB, and TB increases the pathogenicity of HIV (Chen, 2004). Treatment of TB in HIV patients is complicated. As a result of their immunocompromised status, HIV patients' immune systems cannot aid the drugs in fighting the TB invasion. Treatment must continue for several months longer than it would with patients not infected with HIV. Drug interactions are also highly problematic. Rifampin and rifabutin increase the metabolism of NNRTI's (HIV drugs). As a result, this combination of TB and HIV drugs cannot be taken together. Whichever drug type is chosen (HIV or TB) results in the other condition not receiving optimal treatment (Lenhe 2007). Some people advocate that using drugs for TB prophylaxis while also always testing for TB *and* HIV will help relieve the HIV/TB co-infection crisis (Silversides, 2006).

The Incidence Of Tuberculosis In Healthcare Workers

Joshi, Reingold, Menzies, & Pai proposed that in low and middle-income countries, healthcare workers lack the resources to prevent nosocomial infection of TB (2006). In researching past studies on this subject, they found that an average of 54% of healthcare workers have a latent TB infection (69 – 5,780 per 100,000 workers). In contrast, in high-income countries, the incidence of TB in healthcare workers was less than 25 in 100,000 per year. This could be partly due to the increased number of TB carriers in the general population in low and middle-income countries as compared to high-income ones. The presence of latent TB infection in lower-level nursing/medical students in the studies surveyed correlated with the TB rate of the general population in their respective countries. Several studies focused on nursing and medical students and found that senior-level students had two to three times higher rates of latent TB infection than junior-level students. Therefore, the more time spent in the patient care setting, the more likely a student was to have a latent TB infection. Correspondingly, in the general healthcare worker population, the more years spent working in healthcare, the higher the prevalence of TB. In addition, the jobs with more patient contact (nurses, paramedics, lab technicians, and physicians) had a higher incidence of TB than those with low patient contact (administrative staff) (Joshi, et al., 2006).

Low-income countries, because of their limited resources and high incidence of TB, focus those resources on detection and DOTS treatment of TB. Prevention of healthcare worker infection is not part of the budget. In high-income settings, the rate of TB in healthcare workers has been shown to decrease when infection control methods are implemented. The conclusion that Joshi, et al. came to is that TB is an occupational risk for

healthcare workers in low to middle-income countries due to high exposure and insufficient infection control methods (2006).

Ethical Implications

The development of drugs for tuberculosis has been gaining more attention recently than it had in the past, but publicity alone is not enough to cause pharmaceutical companies to develop drugs to cure this disease. Tuberculosis is very much a disease of poverty. Healthcare has become a commodity sold to the highest bidder. This is not an ethical way to view healthcare. As one nurse researcher put it, “to abandon medical ethics to the marketplace would be to abandon the meaning of illness, and the trust on which healing is based” (Benner, 1998, p. 122).

Any disease that affects less than 200,000 Americans is labeled an orphan disease - it is essentially a disease that is rare *in the United States*. This narrow definition does not take into account that a so-labeled orphan disease could be highly prevalent in other areas of the world. In fact, many “orphan diseases” are diseases of poverty that are rampant in low and middle-income countries. For years these orphan diseases such as tuberculosis were practically ignored in the realm of pharmaceutical research and development (R&D) (Towse & Kettler, 2005, World Health Organization).

In order to help counteract this neglect, the US Orphan Drug Act (ODA) was put into effect in 1983. In the ODA, the US government recognized that if any pharmaceutical company tried to develop a drug for an orphan disease, it would result in financial loss for that company. The ODA uses “push” and “pull” mechanisms to give pharmaceutical companies incentives to develop drugs for diseases that normally would not be profitable enough for them to even consider developing. Some examples of the “push” mechanism are

providing grants to defray the costs of developing the drug, tax breaks, and expedited drug approval by the FDA. The “pull” mechanism is identified as a period of seven years of exclusive rights for that drug on the market. The push mechanism is fairly effective, and new drugs have been developed for some diseases of poverty as a result of this mechanism.

The problem with TB is that it has recently lost its orphan disease status because it now has infected slightly over 200,000 people in the United States. This is unfortunate, because when it was an orphan disease pharmaceutical companies could get government-provided incentives to develop drugs to treat it. Now, they will not get those incentives, and since it is so close to the orphan disease cutoff there are still not nearly enough people in developed nations to justify formulating new TB drugs.

Even if TB dropped back to orphan disease status, there are still problems with the pharmaceutical incentives provided. Although the push mechanisms are fairly effective in providing incentives for the development of orphan drugs, the pull mechanism is not a very effective incentive for the research and development (R&D) of drugs for diseases of poverty. Seven years of exclusive rights to sell a drug to a poverty-stricken population is not profitable to a pharmaceutical company for the very reason that the country is poor, and thus would not be able to afford high drug prices. The current pull mechanism of ODA does nothing to increase the buying power of the people who need the drug. Towse and Kettler suggest that governments should set a purchase price for each new drug developed that would take into account the amount of time spent developing the drug, the cost of developing the drug, and the cost of failed tries in the process. This would provide an extremely strong push mechanism, making a poor pull mechanism not as significant a deterrent for pharmaceutical companies (Towse & Kettler, 2005, Food and Drug Administration, 2007).

In addition to examining the biological and economic issues of the R&D of TB drugs, the spiritual and ethical issues involved need to be discussed. Some questions arise, such as why should people in the United States care about diseases of poverty that affect so few people in the US? In order to focus on tuberculosis and why the development of new drugs is essential, this paper promotes the premise that the Bible is the infallible word of God and thus is true. Each human is a created being who, bearing the image of his or her creator, has worth in the eyes of God. Genesis 1:27 says, “So God created man in his own image, in the image of God he created him; male and female he created them.” Since all humans have worth in the eyes of God, their lives should also have worth in the eyes of believers and followers of Jesus. Christians are also challenged to follow the words of Christ and care for the ones who need treatment the most but can’t afford it (the “least of these” – Matthew 25: 40). The fact that some individuals do not have money to pay for the treatment of their disease should not exclude them from obtaining treatment.

Nurse theorist Patricia Benner emphasizes a need for strangers who are compassionate to one another. She points out that many people, when reading the story of the Good Samaritan (Luke 10:25-37), tend to view the story with themselves playing the role of the Samaritan. Benner goes on to suggest that this thought should be reversed, and that people should instead imagine themselves as the wounded man, lying on the side of the road in desperate need of help. Those with tuberculosis and other diseases of poverty are like the man on the side of the road. The fact that someone can identify with the suffering man should spur that person to act compassionately and care for those in need – for example, by working to convince pharmaceutical companies to develop new TB drugs. Each person hopes that someday when they are suffering, someone will care for them. That common

human feeling should cause people to care for others who are presently suffering (Benner, 1998).

In the case of drug R&D, money is power. Benner (1998) states that, “Those who are powerful are able to demand that others care for them” (p. 124). In the high-tech world of modern medicine, there is a tendency to focus on healthcare as a commodity. Pharmaceutical companies, which have obligations to their shareholders, look for the R&D projects that will bring the most profit. R&D for new TB drugs would be a very risky financial maneuver. Developing drugs for diseases that are prevalent in rich nations is more likely to be profitable, because those are the ones that have health insurance companies that can afford to buy drugs at high prices.

The worldwide impact of TB is difficult for Americans to grasp because there are so few people in the US that have the disease. Though tuberculosis affects millions worldwide, but it has been placed in the same category as rare cancers that affect only a few thousand Americans. Americans should care about tuberculosis treatment because the drug-resistant strains have tremendous potential to spread to developed nations, increasing the number of untreatable cases in the US. MDR and XDR TB are on the rise, and there are few to no drugs that can treat these strains.

Current Status

The same drugs that were being used to treat TB decades ago are still being used today. Despite new discoveries about medicine and technology no new TB drugs have been developed in the last 30 years. The drugs currently used to treat tuberculosis are not very effective, and thus have a long course of treatment. They also have unpleasant side effects and are toxic to many body organs. If people stop taking the medicine because they lack

funds, because of the unpleasant side effects, or because of the long course of treatment, the risk that the TB bacteria will develop drug resistance is increased. This has been a common scenario over the last few decades of TB treatment. Multi-drug resistant TB has become more and more prevalent in the world. Once a person has contracted multi-drug resistant TB, other (second-line) drugs must be used. These drugs are even more toxic, more expensive, and have an even longer course of treatment. This further decreases patient compliance with taking the medicine and increased mortality rates (Spigelman & Gillespie, 2006; Global TB Alliance, 2007).

In addition to multi-drug resistant TB, there is now a strain of TB (XDR) that is resistant to almost every TB drug, making it virtually untreatable. New drugs need to be developed that are capable of treating this new form of TB and the original form as well. New drugs need to be developed because this virtually untreatable disease – XDR TB – could spread across country borders and become epidemic in the US and the rest of the world (Global TB Alliance, 2007).

The threat of spreading extensively drug resistant TB is a very real and frightening threat. Previously it was thought that drug resistant TB could be contained in developing countries and not affect the United States. Then, in the spring of 2007, a man infected with extensively drug resistant TB traveled to Europe and back to the US; exposing everyone on the planes and in the airports he was in to the threat of his disease. Fortunately, he did not transmit it to anyone that the center for disease control (CDC) is aware of, but the threat of exposure during air travel is there. As previously mentioned, people who have AIDS are especially susceptible to TB because their immune systems are already compromised. It is also difficult to treat TB along with AIDS because of the incompatibility of TB and HIV

drugs. Countries where AIDS is already a problem could be overwhelmed with tuberculosis if a more effective treatment is not found soon (World Health Organization).

Several organizations have been formed in the past decade to publicize the need for and facilitate the development of new TB vaccines and drugs. The Global Alliance for TB Drug Development (Global Alliance) is one of the front-runners of this movement. Their main goal is to discover and develop new drugs that will shorten the duration of and simplify TB treatment, improve the treatment of latent TB, and effectively combat multi-drug resistant TB and extensively drug resistant TB. The Global Alliance is using private companies partnered with and funded by public entities in adherence with the ODA. These agencies work to get contracts granting reduced sale prices for the newly developed drugs that would be affordable for the impoverished people to whom the drugs would be marketed (Wheeler & Berkley, 2001).

In conclusion, as one of the largest causes of mortality in the world, tuberculosis has been gaining more publicity in recent years. With the emergence of MDR and XDR TB, it has become a threat not only to impoverished developing nations, but also to rich developed nations. If no treatment for drug resistant TB is found, it could spread and become an epidemic in the US. New drugs need to be developed that shorten drug therapy, are less toxic, and are affordable to the impoverished people that tuberculosis strikes.

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