Challenges and solutions to the worldwide tuberculosis epidemic

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ABSTRACT

Tuberculosis is an infectious bacterial disease responsible for a current worldwide epidemic which results in 1.5 million deaths per year. Citizens of developing countries, especially in Africa and Asia, are at a higher risk of infection and death. In some developing countries, as much as 80% of the population tests positive for latent tuberculosis infection, in comparison to approximately 5% for developed countries such as the United States. Studies of the current vaccine Bacillus Calmette-Guerin show that elicits a decreased immune response in patients from some areas of the world. In treating tuberculosis, the World Health Organization has developed DOTS, Directly Observed Treatment, Short course, a program which has evolved from a simple treatment regiment to a complete guideline on political involvement, logistics and medical operations and has been met with astounding success rates. New diagnostic techniques and vaccines currently in research bring promise to combatting and ending the tuberculosis epidemic.

KEYWORDS

Tuberculosis, DOTS, MVA85A, Bacillus Calmette Guerin

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INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease that results in over 1.5 million lives every year. 75% of TB cases cause lesions in the lungs which can spread to other parts of the body *(1)*. The World Health Organization declared tuberculosis an epidemic in 1993 *(2)*. In developing countries, poor standards of medical care lead to misdiagnosis and mistreatment of the disease and result in a high number of tuberculosis-related deaths, as well as the development of drug resistant strains of the bacteria. Environmental conditions lead to decreased efficacy of the only existing tuberculosis vaccine, *Bacilius Calmette-Guerin* (BCG). Coinfection of HIV and TB have also resulted in especially high mortality rates in certain parts of the world, especially Sub-Saharan Africa *(3)*.

The bacterium responsible for TB, *Mycobacterium tuberculosis*, is primarily spread by the coughing and sneezing of individuals in whom the disease has become active. Infection begins when the mycobacteria reach the lungs and begin to replicate, forming the primary tuberculosis lesion, termed a "Ghon focus". Secondary lesions often form in other areas of the lungs and can form anywhere in the body once the bacteria enter the bloodstream *(4)*.

A distinction should be made between active and latent tuberculosis. The active tuberculosis disease is responsible for the deaths and symptoms and is the treatable form of the disease. However, humans can still carry the bacteria without showing symptoms and can spread it through coughing and sneezing – this is known as latent tuberculosis infection (LTBI).

GEOGRAPHICAL DISPARITY & VACCINE EFFICACY

Incidence of tuberculosis is not uniformly spread throughout the globe. Citizens of developing countries, especially in Africa and Asia, are at a higher risk of infection and death. In some developing countries, as much as 80% of the population tests positive for LTBI, in comparison to approximately 5% for developed countries such as the United States. TB mortality is more than ten times higher in Africa than in North and South America *(5)*.

Currently, the only vaccine available for tuberculosis is *Bacilius Calmette-Guerin* (BCG). Although vaccination rates are high in some areas where tuberculosis is endemic, data has suggested that vaccine efficacy may vary by geographical location. In general, BCG produces about 60-80% protection in individuals when administered in North America, while clinical studies in tropical climates usually show that the vaccine has little to no effect.

Reasons for variable efficacy of the vaccine are currently not fully understood. Suggested hypotheses include variation in the strain of the vaccine, genetic variation in the vaccinated population, and variable background exposure to tuberculosis bacteria and the vaccine strain itself. There is evidence suggesting that the vaccine efficacy diminishes in tropical regions because the vaccinated population experiences more background exposure to mycobacteria than the populations of non-tropical regions. A study published in 2002 suggested a negative correlation between existing mycobacterial resistance and vaccine effectiveness. The study tested schoolchildren from Malawi and the UK by administering an interferon-gamma response test and a tuberculin protein skin response test, testing for vaccine response. The results suggest that because the Malawian children had an existing immunity to mycobacteria, the introduction of the BCG vaccine (also a mycobacteria) produced no change in their immune systems. In contrast, the British schoolchildren, with no previously existing bacterial immunity, developed mycobacterial resistance from the BCG vaccine *(6)*.

TREATMENT OF ACTIVE TUBERCULOSIS DISEASE: DOTS & MORE

Treatment of tuberculosis begins with a diagnosis. The main diagnostic test used in clinical care is a sputum smear microscopy test, which is inexpensive and can be performed in a matter of minutes. In this test, sputum (matter expelled from the lungs) is stained using carbol fuschsin and methylene blue and examined under a microscope *(7)*. The current treatment regimen focuses only on smear-positive tuberculosis cases.

Tuberculosis is treated with many drugs at a time, a practice known as combination therapy. Combination therapy has proven successful several decades and has proven successful; the use of many drugs prevents the TB bacteria from developing resistance to the entire drug regimen. Resistance to a single drug may develop, but because of its variety, the drug regimen will remain effective *(8)*.

The second support for combination therapy is that each of the TB drugs can have a different mode of action. Certain tuberculosis drugs have different properties under different conditions. The three main properties of anti-tuberculosis drugs are bactericidal activity (the ability of the drug to kill the bacteria), sterilizing activity (preventing the bacteria from reproducing) and finally the ability of the drug to prevent resistance to itself or other drugs. The six essential first line drugs are isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone *(9)*. First line drugs are the first set used to treat a patient after their initial diagnosis; a patient receives a regimen of four of these six. If a resistance develops, the regimen can be altered. Tuberculosis treatment with antibiotics must be carefully controlled; when antibiotics are misused, multi-drug resistant tuberculosis can develop *(10)*.

If the infection develops a resistance to these drugs, the infection is called multi-drug resistance tuberculosis (MDR-TB), and second line drugs are used to treat it. However, these drugs are more expensive and have more severe side effects. Severe mistreatment of tuberculosis can lead to the development of extensively drug resistant tuberculosis (XDR-TB). This strain is even more difficult to treat than MDR-TB, and must be treated with third line drugs, which are more expensive and have more side effects than both the first and second line drugs *(11)*.

The first goal of tuberculosis treatment is to cure the patient of the disease and to prevent death from the disease or its late effects. The second goal is to prevent the relapse of tuberculosis following the treatment. The containment of the infection is also paramount, such that the patient does not spread tuberculosis to others. Finally, treatment aims to prevent the development of drug resistant strains of tuberculosis (MDR-TB and XDR-TB).

With this treatment ideology in mind, the World Health Organization launched the DOTS (Directly Observed Treatment, Short course) strategy for tuberculosis treatment in 1995. Originally the protocol was a regimen for six months for tuberculosis treatment. It has evolved to include advice on recommendations

to governments to tuberculosis treatment, including practices of managing treatment centres, diagnostic techniques such as sputum smear microscopy, and direct observation of patients' doses to ensure adherence to the treatment regimen. DOTS has become the foundation of tuberculosis treatment worldwide and has had much success in tuberculosis management. In 2010, the WHO reported that DOTS had successfully treated 86% of all new tuberculosis cases worldwide *(12)*, with successful treatment defined as either cured (a negative sputum bacteriology test) or treatment completed *(13)*.

Improving case detection rates (CDRs) is very important to the treatment and overall elimination of tuberculosis. The current goal of DOTS is to achieve and maintain a 70% CDR and to successfully treat 85% of the detected cases. In 2009, researchers at John Hopkins University constructed a computer model to test whether these short term reductions in TB incidence could be maintained in the long term, while maintaining these case detection and treatment rates. Indeed, the computer model showed that as case detection rates improved, the incidence of tuberculosis fell. However, as case detection rates stabilized, tuberculosis incidence, while still decreasing, would decrease by diminishing margins each year. From this model, researchers concluded that continuously trying to increase CDRs (above and beyond the 70% mark) is equally as important as quickly reaching a certain CDR goal *(14)*.

In improving CDRs, increased test frequency is already implemented as part of DOTS protocol *(15)*. Diagnostic test sensitivity can also be improved. The currently used sputum smear microscopy method only detects around 20-60% of cases even when properly implemented *(16)*.

In recent years, the non-profit organization, Foundation for Innovative New Diagnostics (FIND) has addressed the need for new tuberculosis diagnostics by issuing a plan outlining new tests they hope to develop and proposed deadlines for other development. FIND recognizes the need for tests at both the primary health care level and in the larger lab environment. For the clinical health post, it plans to develop a urine detection test – TB bacteria have been shown to be excreted in patients' urine and an antigen test may prove successful. For the laboratory setting, a set of liquid culture tests, dubbed the Mycobacterium Growth Indicator has been developed which will allow larger labs to identify the bacteria and test for the infection's drug susceptibility *(17)*.

NEW VACCINES

The Centre for Clinical Vaccinology and Tropical Medicine at the University of Oxford has developed a recombinant modified vaccinia virus, which has shown promise in phase 1 clinical trials. This vaccine is intended as a booster, meaning that when used in conjunction with BCG, it is intended to elicit a greater immune response. The vaccine is modified vaccinia Ankara, expressing antigen 85A (MVA85A). The phase 1 study showed that the MVA85A vaccine induced high levels of antigen-specific T cells when given to patients who had not received a BCG vaccination, thus producing the desired TB immunity through the TH1-type cellular immune response. When used within 24 weeks of a BCG vaccination, the increase in these antigen secreting T-cells was 5-30 times greater than BCG used alone. Measured is the amount of interferon gamma secreted by the T-cells, as shown by a tuberculin skin test and an antigen 85 response test (Fig. 1). As the graph shows, the count for patients vaccinated with both vaccines is higher than the count for those vaccinated with the two vaccines individually. Used in conjunction with BCG, this vaccine has the potential to offer anti-mycobacterial immunity in tuberculosis-endemic areas *(18)*.

Researchers at the University of Cape Town have tested the immunogenicity and safety of this new vaccine in South African patients. Monitoring patients for a year, they found that adverse reactions were limited to temporary swelling and redness around the injection site. Similar to the results of the previously mentioned , the results showed that the vaccine induced potent polyfunctional T-cell boosts. This study provided evidence that this vaccine has the potential to overcome the shortcomings of BCG (diminished efficacy due to patient's background mycobacterial exposure) *(19)*.

In 2009, Oxford researchers conducted the first study of any new vaccine in latent tuberculosis infected individuals. The results of the trial showed that there was no increase in adverse reactions in comparison to previous trials of non-tuberculosis infected individuals. The immune response generated was similar to the two previous trials *(20)*. The results of this study are important because since it is often not possible to detect LTBI in a clinical situation, the vaccine must be safe for these individuals as well *(18)*.

In addition to booster vaccines, recombinant strains of the original BCG vaccine are currently in development. The only recombinant vaccine currently investigated in human clinical trials is rBCG30, which secretes large amounts of the M. Tuberculosis 30 kDa major secretory protein. The introduction of this recombinant BCG vaccine causes the body to produce large amount of T-cells that respond to the 30 kDa protein. The proteins that the *Mycobacteria tuberculosis* secretes are composed of approximately 25% 30 kDa. It was therefore hypothesized that by causing the body to increase T-cell production specific to those proteins, the recombinant DNA strain increases protection against the TB bacteria *(19)*.

After initial trials in guinea pigs at UCLA, the vaccine was tested in phase 1 clinical trials by the Department of Internal Medicine at St Louis University. The double blind study randomly gave either the original BCG vaccine or the new recombinant vac-

cine to 35 healthy human subjects. rBCG30 induced a greater T cell response and an increased IFN-gamma secretion. Based on these results, researchers claimed that the recombinant strain can enhance human tuberculosis immunity. The data supports further development of this recombinant vaccine *(19)*.

HIV AND TB

HIV and tuberculosis coinfection is particularly deadly, and is not uncommon in certain parts of the world, especially Africa. The integration of tuberculosis and HIV treatment has started to yield positive results in some countries. The country of Malawi is currently a hotspot for HIV and tuberculosis coinfection, with a large percentage of the population infected with HIV and in need of antiretroviral therapy (ART). The HIV Unit, under the Department of Clinical Services, and the National Tuberculosis Program (NTP) have begun to work together; they established national guidelines and national policy for cotrimoxazole preventative therapy, the scale up of ART to deal with the HIV epidemic, and the co-administration of tuberculosis treatment and ART *(20)*.

A challenge faced by ART is that patients tend to not adhere to the treatment regimen. Combined treatments for the two infections calls for ART to begin after the initial intensive phase of tuberculosis treatment, and patients who receive tuberculosis treatment are often deterred from seeking ART. As patients feel better during the intensive phase of tuberculosis treatment, they feel no reason to seek ART for their HIV and so they tend to ignore this treatment. Evidence of this fact is that only 18% of patients receiving ART in Malawi have ever been diagnosed with tuberculosis; this is small in comparison with the fact that over 80% of tuberculosis patients are co-infected with HIV *(20)*.

CONCLUSIONS

The fight against tuberculosis is multi-faceted and fraught with issues spanning scientific research, environmental and logistical challenges, and government policy. The existing DOTS protocol has been shown to be successful. The continued implementation of this strategy will result in decreased tuberculosis incidence and will greatly further the goal of eliminating this epidemic. In addition to the continued support of the DOTS strategy, there are a few other scientific developments that have been discussed that can contribute to fighting the tuberculosis epidemic. The booster vaccine MVA85A has shown promise in trials, but it is still decades away from implementation, during which other phases of clinical trials must take place.

The implementation of new diagnostic tests, such as those being developed by FIND, will allow case detection rates to increase by increasing diagnostic sensitivity and test frequency. Based on the computer models discussed earlier, the continuous increase of these rates is necessary if tuberculosis is to be eliminated. Additionally, the continued integration of HIV and tuberculosis treatment centers can improve patient care and increase adherence to treatment.

The current tuberculosis epidemic has a huge array of challenges that must be overcome before this epidemic can be stopped. The steps taken by the World Health Organization thus far have attempted to decrease the severity of the epidemic; however an end is still a long way off. The current plan by WHO has an optimistic goal of ending the epidemic by 2050; with both their commitment and that of the scientific community, hopefully this goal can be realized.

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