MAT3395

The Effect of Vaccination against Tuberculosis (TB)

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Tuberculosis, or TB, is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. [1] However, not everyone infected with TB bacteria becomes sick.

As a result, two conditions exist: latent TB infection and active TB infection. A latent TB infected person does not show any symptoms of the disease and cannot infect others, though may live as long as possible if it does not develop into active TB. Only actively infected people are sick and infectious. Overall, about 10% of infected persons will develop active TB disease at some time in their lives. About half of those people who develop active TB will do so within the first two years of infection. [2] TB has been a leading cause of death in the world for centuries. Today, about one third of the world’s population is estimated to be infected with TB and it remains the second leading cause of death by infectious disease worldwide—9 million new cases and 3.1 million deaths per year. [3] TB has been declared as a global emergency by World Health Organization and cases are still increasing annually. Although latent TB is common, it kills more than half of its victims if left untreated. With treatment most people even infected with active TB make a full recovery thus developing vaccine like could save many lives globally.

Bacilli Calmette-Guérin (BCG) vaccine is one of the most widely used vaccines against TB all over the world. This contains a live weakened strain of mycobacterium tuberculosis that lost its virulence in human by culturing in an artificial medium for years. The bacilli have retained enough to become an effective vaccine for the prevention of human TB. [2] Since its first use in humans in 1921, BCG has been given by a variety of routes, including by mouth, by intradermal injection, and using a multipuncture injection device. It is used because it is effective in reducing the severity of TB in infants and young children. That is especially important in areas of the world where TB is highly prevalent, and the chances of an infant or young child becoming exposed to an infectious case are high.

The immunization coverage with BCG at birth varies by regions in the world. It is currently given at or soon after birth to children in over 100 countries to minimize the potential for serious forms of TB disease. [4] In the United States BCG is not used, because TB is not prevalent and the chances are small that infants and young children will become exposed. [2] Instead, they more focus on interrupting transmission from
patients who have active infectious TB and skin testing children and adults who are at high risk for TB. Some countries such as Russia, most countries in Asia and south America has high percentage of coverage of BCG also some Asia countries give BCG at birth and again around age of 12. The percentage of taking BCG in Africa showed relatively low. The largest number of new TB cases in 2005 occurred in the South-East Asia Region, which accounted for 34% of incident cases globally, were estimated by World Health Organization. However, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the South-East Asia Region, at nearly 350 cases per 100 000 population. [5] Both the highest number of deaths and the highest mortality per capita are in the Africa Region. The global annual incidence of tuberculosis continues to increase in Africa because of the HIV epidemic, whereas in all other regions it is stable or falling. [6] Reported rates of the protective efficacy of BCG vaccines might have been affected by the methods and routes of vaccine administration and by the environments and characteristics of the populations in which BCG vaccines have been studied. Protective efficacy rate of BCG varies from 0 to 80%, overall average efficacy of 60%. [2] In young children, the estimated protective efficacy rates of the vaccine have ranged from 52% to 100% for prevention of tuberculosis meningitis and military TB and from 2% to 80% for prevention of pulmonary TB. [2] The variable protective efficacy of BCG lies in variability in exposure to environmental mycobacterium. [7] Environmental mycobacterium is ubiquitous organisms which live in the soil, and exposure to this mycobacterium is universal but increases with increasing proximity to the equator. [8] The duration of protection by BCG is normally 10 to 15 years. [9]

Objectives

1. We could see the effect of BCG on people in countries where proper treatment and supply of drugs for TB is insufficient but the immunization with BGC coverage is still ongoing.
2. We could predict the change in population for years and how much BCG could hold back the TB disease
3. We could predict the change in prevalence of active TB in one of the countries which has low BCG coverage with different efficacy levels of BCG
Fig 1: Flow diagram of tuberculosis (TB) vaccine model
The mathematical model (Fig 1) is built to see how much BCG could affects to TB population flow. The countries that don’t support mass immunization intentionally such as U.S. and Canada are not considered in this model. It is much easier to see the effect of vaccine in countries where the medication to TB is insufficient, but the vaccination of BCG is well covered.

\[ b \]  Natural birth rate

\[ p \]  Probability of people vaccinated with BCG

\[ e \]  Success rate of vaccine(BCG)

Whenever a new individual comes into the model at a rate of \( b \), he/she is chosen to take BCG. Most of vaccinated population tends to get the BCG at infants except re-vaccination usually provided in some Asian countries. Since the proportion of vaccinated population varies over regions, \( p \) could be any value between 0 and 1, but normally over 0.5(50%) according to WHO. There are success rate of BCG because it is not true every vaccinated get advantages of vaccine. Approximately 20% of vaccinated failed to get covered by the effect of vaccine due to inoculation failure or poor quality of the vaccine etc. So, \( e \) is fixed to 0.8(80%) in this model.

\[ W \]  Probability of vaccine wanes

Even if the susceptible are successfully vaccinated with BCG, they don't get the effects of the vaccine permanently. This is the ‘duration’ that was mentioned in introduction of BCG. On average, the effect of BCG wanes 10–15 years so the value for \( w=1/5475 \) days\(^{-1} \) is fixed in this model. In fact, the vaccine effect decreases gradually over a period. However, we assumed successfully vaccinated people always get some protection by BCG in given duration to see an impact of vaccine more clearly.

\[ i \]  Infection rate to latent TB from susceptible

\[ a \]  Breakdown rate to active from latent

It is hard to claim what exact rate a person with active TB could infect others annually.
The factors such as environment conditions, the number of contacts between susceptible and actively infected people and control of the disease will influence a numerical value of infection rate. By WHO [1], each person with active TB will infect on average between 10 and 15 people each years. So, we just assumed that active TB could infect 10 people per year so $i=0.02739$ is fixed. Also, the progression from 10% of latent TB to active TB occur averagely so $e=0.1$ is fixed.

$\mathbf{d_1}$ Degree of protection by BCG when the infection occurs to latent TB from susceptible

$\mathbf{d_2}$ Degree of protection by BCG when ‘breakdown’ to active TB from latent TB

These two parameters are only applicable for the successfully vaccinated people who still be protected by some degrees of BCG. In this model, these two parameters are separated but usually both are considered same rate as the efficacy rate of BCG. For example, when the efficacy rate of BCG is 50%, the infection rate is decreased by half and also the progression rate from latent to active is decreased by half. By varying the efficacy level of BCG, we could investigate how much the vaccine impact the control of disease depends on the quality of vaccine.

$\mathbf{r_1}$ Recovery rate of latent TB

$\mathbf{r_2}$ Recovery rate of active TB

$\mathbf{n}$ Natural death rate

$\mathbf{u}$ Death rate due to the infection of active TB

We chose some random high rate for recovery rates. These recovery rates could be any percentage value since it totally depends on kinds of therapy is provided to TB infected people. But the recovery rate of latent TB is relatively higher than the recovery rate of active TB. Natural death rate is considered as $n$, which is assumed 1 death in 60 years that is $1/21900$ days$^{-1}$. About 5–10% of actively infected with TB die so we chose 0.05% for parameter $u$. 
Equations

\[ \frac{dS_V}{dt} = bpe-(1-d_1)iSA_N-(1-d_1)iS_NA_N+r_1L_V+r_2A_V-wS_V-nS_V \]

\[ \frac{dS_N}{dt} = b(1-pe)-iSA_V-iS_NA_N+r_1L_N+r_2A_N+wS_V-nS_N \]

\[ \frac{dL_V}{dt} = (1-d_1)iSA_V+(1-d_1)iS_NA_N-r_1L_V-a(1-d_2)L_V-wL_V-nL_V \]

\[ \frac{dL_N}{dt} = iS_NA_V+iS_NA_N-r_1L_N-aL_N+wL_V-nL_N \]

\[ \frac{dA_V}{dt} = a(1-d_2)L_V-r_2A_V-wA_V-(n+u)A_V \]

\[ \frac{dA_N}{dt} = aL_N-r_2A_N+wA_V-(n+u)A_N \]

These are ordinary differential equations derived from the model diagram (Fig 2). S means the number of susceptible. L means the number of infected people with latent TB and A means the number of infected people with active TB. The subscript V represents the successfully vaccinated populations and the subscript N represents the unsuccessful or never vaccinated populations.

We need to note that every people with active TB can infect others (susceptible) regardless possession of the vaccine. Then, the infection to any state of latent TB can be occurred by both state of people infected with active TB.

Only people are infected with active TB are sick and may be dead so the parameter u is only applicable to A.
Analysis

With the model and the equations, the time course is the one of good options to see change in number of population. A couple of cases are considered as following:

1. There is no vaccination available where TB is prevalent.
2. There is 50% vaccination with 60% efficacy rate where TB is prevalent.

For the second case, 60% efficacy rate is chosen because this is an average efficacy rate. [2] Most of countries where BCG vaccination is available and even the countries where BCG vaccination rate is relatively low have over 50% vaccination rate according to WHO. Is vaccination really helpful by only covering half of its population?

![The time course of the TB population in un-vaccinated group](image)

By looking graph Fig 2, almost everybody gets infection with TB when there is no vaccine available. Since there is no protection by the vaccine, the infection from susceptible to latent TB and the progression from latent to active occur at rate of ‘i’ and ‘a’ respectively. The rate of infection flow into latent TB is quite fast, so this looks very contagious with the chosen infection rate here (‘i’). Once there is almost no
susceptible to be infected, the population with latent TB is decreasing because progression into active TB occurs at a rate of 10%. The progression into active TB and also the death due to active TB disease in addition to natural death continuously occur so the number of people with active TB tends to remain constant.

Fig 3: The time series of population change with TB when 50% BCG vaccination is available with 60% efficacy rate.

With 50% vaccination coverage for an average efficacy rate, we got a different result. Since 50% vaccination is provided, nearly 40% of new infants (since successful rate is 80%) get some degree of protection by BCG.

We can see that the vaccine slowed down the rate of infection flow into latent TB than no vaccination case because once they get protection by BCG, they have a new infection rate that is \((1 - \text{efficacy rate}) \times \text{infection rate}\).

Although the vaccine slowed down infection rate, there is only small decrease in number of infected population with TB. It seems almost over 80% of population will still gets infection and this also looks very contagious.

Similarly, the vaccine slowed down the progression into active TB than no vaccination case because they have a new progression rate that is \((1 - \text{efficacy rate}) \times \text{progression rate}\). The lower progression rate into active TB also decreases the rate of death.
occurred since only people suffering with active TB may be dead.

We can see change in population more precisely if time series is in long term. It is easy to see that the rate of decrease in population of infected with latent TB is slower when there is 50% vaccination coverage than no vaccination coverage. Similarly, the rate of
increase in number of dead is slower when there is 50% vaccination coverage than no vaccination coverage. So, we can tell that the BCG vaccination somewhat slows down the rate of infection or progression and the number of death due to TB disease.

But this was the result when the efficacy rate is 60%. We know that 60% efficacy rate is an average but we also know that it is possible to achieve 80% efficacy rate at maximum. So what if we assume that every vaccinated population we are considering here will have 80% efficacy rate?

![The time course of the TB for efficacy rate=80%(tf=100)](image)

**Fig 4:** The time series of population change with TB when 50% BCG vaccination is available with 80% efficacy rate.

Now it is more obvious to see the improvement of TB disease control by the BCG vaccine. At maximum of efficacy rate, the vaccine can save a lot of people even 50% vaccination coverage as we can see the increase in number of susceptible remained for 100 days. The decrease in number of infection to latent TB also decreases progression to active TB as well as the number of death due to disease.

**Prediction**
The African countries such as Nigeria and Somalia currently have 50% vaccination
coverage just like we considered so far. But most of countries that support BCG inoculation at birth have over 90% immunization coverage. So what would happen if countries like Nigeria and Somalia will enhance their BCG supports up to 90% immunization coverage?

The table below shows the reported TB case in Nigeria by WHO. The number of TB prevalence here is per 100,000 populations in Nigeria.

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>13,423</td>
</tr>
<tr>
<td>1996</td>
<td>15,020</td>
</tr>
<tr>
<td>1997</td>
<td>16,660</td>
</tr>
<tr>
<td>1998</td>
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<tr>
<td>2005</td>
<td>62,598</td>
</tr>
<tr>
<td>2006</td>
<td>70,734</td>
</tr>
<tr>
<td>2007</td>
<td>84,471</td>
</tr>
</tbody>
</table>

The graph above shows linear fit to the reported TB cases from 1995 to 2007. The TB prevalence in Nigeria is increasing year by year as we can see the slope of linear fit is positive. By WHO, approximately 50% of new infants at birth are vaccinated with BCG at 2007.
Then, we can assume that there was a massive immunization with BCG in Nigeria at years after 2007. So what would happen with 60%, 70%, 80% and 90% vaccination coverage? Suppose here efficacy rate for BCG is the average efficacy level that is 60%.

Fig 5: The prediction of TB prevalence with different vaccination coverage rate after 2007.

As we can see Fig 5, even more than 50% vaccination coverage could not eradicate the TB disease. However, this higher vaccine coverage at least holds back the increase in TB prevalence. Although there can be found an increase trend in TB after an immediate reduction in TB for 60% and 70% vaccination coverage, this could have been a lot worse compared to the slope of linear fit for 50% vaccination coverage. For 80% and 90% vaccination coverage, the number of TB prevalence almost tends to remain constant until 2050. A slight increasing trend in TB prevalence can be predicted after 2050 for 80%, but not sure for 90%. So, we could check that the BCG vaccine alone will be able to stop increasing TB prevalence with higher rate of immunization coverage, but cannot decrease number of TB prevalence in long term and eradicate disease forever.
Conclusions

It is now obvious that BCG gives better control of TB disease. But, this model tells BCG by itself only slows down the infection, but cannot stop increasing prevalence of latent TB or progression into active TB.

So in order to achieve good control of TB, proper drug treatment or DOTS which is the control strategy recommended by WHO should be given with high percentage of coverage with BCG.
References


