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ORIGINAL ARTICLE

Modelling the Transitional Dynamics of Mycobacterium Tuberculosis Strain

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The World Health Organization's targets of eliminating Tuberculosis (TB) by 2050 is challenged by the emergence and spread of drug resistance TB. However, the traditional mechanism of resistance is that of acquired resistance, whereby the mycobacterium Tuberculosis (MTB) strain develops mutations under selective pressure of insufficient drug therapy. These mutations have the tendency of changing the drug target protein, restricting the bacteria to the anti-TB agent. We propose a discrete state markov chain model with three disease states: Drug Susceptible (*DS*), Multi Drug Resistant (*MDR*) and Extra Drug Resistant (*XDR*) to further study the transitional dynamics of the MTB strain. The study made use of a retrospective data on resistant pattern to first line and second line anti TB drugs. The structural properties of the model established life expectancies of *DS and MDR* strains as well as the probability of first resistance of the *DS* strain. Key estimates were assessed by the bootstrapping procedure which converged in estimates to the actual data. If the experiment were repeated infinitely many times, in 95 out of 100, the interval 2.782 x 10^{-7} to 0.018 will contain the true probability of first mutation of the *DS* strain. A key contribution of this study is the revealing therapeutic cycle of the treatment regime of the TB disease based on the TB progression data which saw the period after the 20th cycle of the treatment being prominent in some key strain dynamics. These findings may also help explain further the pharmacodynamic properties of the "first line" anti-Tuberculosis drugs for enhance TB treatment.
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INTRODUCTION

Tuberculosis (TB) remains the world's leading cause of death (WHO, 2004). The emergence and the spread of Drug Resistant (*DR*) TB has grown to be a major threat to the treatment and control of TB. Even though, the Mycobacterium grows slowly, routine Drug Susceptibility Testing (DST) which is one of the standard methods of testing DR TB can take weeks to months. Patients who delay in receiving suboptimal therapy in the course of DST may further lead to development of additional resistance (Dye & Williams 2010).

The World Health Organization (WHO) in 2010 indicated that a consequence of inadequate TB treatment and management has given birth to Multidrug-Resistant TB (*MDR*-TB) which has emerged in all parts of the world and now accounts for approximately 8 -9% of all TB deaths (WHO, 2010). The need for standard methods of diagnosing *DR* TB which relies heavily on culture and phenotypic DST are being developed in recent times. These new development relies on information about mutations that leads to *DR* TB.

This study briefly review below, some extensive research in both molecular and mathematical models on the dynamics of the *MTB* strain which has increase our knowledge on the mutational capabilities of the bacteria and subsequent development of therapies. For instance, Blower *et al.,* (1995) developed two mathematical models that studied infected individuals that can develop TB either by fast

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progression or endogenous reactivation. Their analysis shows a longer period (years) for the rise and fall of TB epidemic to reach equilibrium and suggested that natural behaviour of the epidemic may help reduce TB.

In 2001, the work of Blower *et al.,* was extended by *Ziv et al., (*2001*),* their model focused on the effectiveness of early therapy for latently infected individuals. Their analysis indicates that TB epidemic can be controlled if latently infected individuals are given therapy at the early stages of the diseases. Nishiura *et al.,* (2004) model concentrated on failure trend of *DR* TB in Thailand even though their study anticipated a dramatic decline in Drug Sensitive (*DS)* cases, DR cases were predicted to go up slowly such that more than half of the TB strains would not be *DS* after 2020. Bhunu & Garira (2009) developed a two strain TB transmission model with therapy and quarantine. Their analysis among others shows that effective chemoprophylaxis and treatment of infections result in a reduction of *MDR*-TB cases.

Abukari *et al.,* (2013) developed a stochastic branching process model to determine the containment of a bacillus population with conferred mutations to first line anti TB drugs Isoniazid (INH) and Rifampin (RIF). Their analysis indicates that if the total number of *MTB* strain is less than 39,062,500 and 4,444,444,444 with selective effect to INH and RIF respectively, the explosion of the *MTB* stain can be contained. These metrics were far less than the clinical bacterial load of 10^{10}. Christopher *et al.,* (2013) attempted to address the question of why *MTB* strains from East Asian Lineage and Beijing sub lineage acquire *DR in vitro* more quickly than *MTB* strains from Euro – American Lineage. Stochastic model was used to demonstrate that the observed differences in the mutation rate predict a substantially higher probability that patients infected with *DS* lineage from East Asian will habour *MDR* bacteria at the time of diagnosis.

Generally, most of these studies and others discussed the spread of the TB disease among population of humans. Those that discuss the dynamics of the *MTB* strain still needed to determine appropriate probability metrics that will help design more vigorous treatment strategies for the control and cure of the TB disease. In this study, discrete state Markov Chain model was proposed to study the transitional dynamics of the *MTB* strain. The study also focuses on determining the probability of initial mutation of the *DS* strain, the expected progression from *DS* to *MDR* strain and the life expectancy for *DS* and *MDR* strain. Specifically, the study focuses on determining: The average length of time a *DS* strain spends before mutating to *XDR* strain and the life expectancy for *DS* and *MDR* strain. It is expected that this study will help in the design of new treatment strategies for enhanced TB treatment and control.

METHODOLOGY

Markov Chain

A discrete time stochastic process $\{X_t\}$ is called a Markov chain if $t = 0,1,2,\ldots$ and all states $P(X_{t+1} = i_{t+1} \mid X_i = i_t)$ ———[1]
In essence, this means that the probability distribution of the state at time t+1 depends on the state at time $t(i_t)$ and does not depend on the states the chain passed through on the way to i_t at time t (Wayne, 2004).

A further assumption that for all states i and j, $P(X_{t+1} = j \mid X_i = i)$ ———[2] is independent of t. This assumption allow us to write equation [2] as P_{ij} where P_{ij} is the probability that given the system is in state i at time t, it will be in a state j at time $t+1$. If the system moves from state i during one period to state j during the next period, we say that a transition from i to j has occurred. The P_{ij}'S are often referred to as the transition probabilities for the Markov chain. [2] presupposes that the probability law relating the next period's state to the current state does not change over time.

We also must define q_i to be the probability that the chain is in state i at the time 0; in other words, $P(X_0 = i) = q_i$ ———[3]. The vector $q = [q_1, q_2, \ldots..,q_s]$ was called the initial probability distribution for the Markov chain (Wayne, 2004).

Classification of States in a Markov Chain
In markov chains, a state *j* is reachable from state *i* if there is a path leading from *i* to *j*. Two states *i* and *j* are said to communicate if *j* is reachable from *i*, and *i* is reachable from *j*.

A set of state *S* in a Markov Chain is a closed set if no state outside of *S* is reachable from any state in *S*. A state *i* is an absorbing state if p_{ij}=1. A state *i* is a transient state if there exists a state *j* that is reachable from *i*, but the state *i* is not reachable from state *j*. If the state is not transient, it is called a recurrent state. A state *i* is periodic with period k > 1 if k is the smallest number such that all paths leading from state *i* back to state *i* have a length that is a multiple of k. If a recurrent state is not periodic, it is referred to as aperiodic.

If all states in a chain are recurrent, aperiodic, and communicate with each other, the chain is said to be ergodic. (Wayne, 2004). This paper focuses on absorbing markov chain since we are modeling disease states that finally absorbs into a state that neither communicate nor reachable from other states in the course of the disease progression.

The Model
In the context of this study, three discrete states was defined: Drug susceptible (*DS*), Multi Drug Resistant (*MDR*) and Extra–Drug Resistant (*XDR*). This simplified framework does not account for the history of the *MTB* strain (i.e., a *DS* strain remains inexperience).

For instance, a *DS* strain can progress to an *MDR* state and an *MDR* strain can retrogress back to a *DS* state. Similarly, an *MDR* strain can progress to an *XDR* state. Once an *MDR* strain progresses to an *XDR* state, it stays there forever and cannot become an *MDR* strain or *DS* strain. Johnson *et al.,* (2009), have indicated 60% treatment success for suboptimal treatment cure for *MRD* TB with second line anti-TB drugs. The *DS* and *MDR* states are referred to as 'transient states' while *XDR* is referred to as 'absorbing state because once an *MTB* strain enters that state it can never leave, it stays there forever. The transition probability matrix may be denoted as:

$$P = \begin{pmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{pmatrix}$$

The rows represents the state of a process for a given *MTB* strain (1=*DS*, 2 = *MDR*, 3 = *XDR*) at time step *n* and the column indicate the state of the process at time step *n+1*. Sequentially, the states are DS ↔MDR→XDR

For example, P_{12} (the element in row 1 and column 2) is the probability of transitioning from the *DS* to *MDR* in one step (conditional on escape from *MDR*/Survival), commonly referred to in disease literature as the discrete time force of infection. The elements P_{13} and P_{23} reflect on the inability of the *DS* strain to escape *XDR* status. In this context, it indicates treatment failure. P_{21} is the defective probability (Cohen, 1973). In this context, it reflects on the treatment success of the diseases. The last row of the matrix represents the probabilities of treatment failure as *XDR* cannot be treated, hence it is an absorbing state. Once an *MTB* strain enters that state, it can never recover and remains there forever.

In order to ensure that the transition process occur on a biologically meaningful time scale, this study consider number of hours as the time course of the *MTB* stain to make a transition. At any given time an *MTB* strain must be in any one of the three states, which reflect the fact that each of the rows always sum up to one.

This means the *n*-step transition probabilities of the markov process can therefore be examined by raising the matrix to n^{th} power, thus P^n. The probability that a process initially at state *i* will be in state *j* after exactly *n* steps is exactly the elements of P^n denoted by P_{ij}^n. The elements of the matrix P^n provide information on the markov chain at the n^{th} time step: Nothing can be inferred about the state of the process during any of the *n-1* time step (Wayne, 2004).

The metrics of interest from the elements of P_{ij}^n can be computed. Further, the probability that a *DS*

strain initially becomes *MDR* strain during the interval between *m-1* and in *m* time steps can also be determined.

Clearly, for the state of the *MTB* strain of interest, it is only possible for one transition to occur within one logical order of time step. We define the initial time step as *n* and examine the intervals between *n, n+1,……, n+m.* The probability that an observed patient with a *DS* strain progresses to *MDR* strain after one step is simply P_{12} and the probability that a patient with *DS* strain remain as *DS* is P_{11}. Thus the probability that a *DS* strain first becomes *MDR* strain after two steps is simply the probability that it remain *DS* for exactly one step and the become *MDR* strain during the next time step: $P\ (X_{n+2}=1, X_{n+1}=0/X_n=0) = P_{11}\ P_{12}$ ——— *[4]*

Following this sequence, the probability that a DS strain progresses to MDR state for the first time between the *m-1* and *m* time steps would be $f^m_{12} = P\ (X_{n+m}=1, X_{n+m-1}\ldots X_{n+1}=0/X_n=0) = P^{\,m-1}_{\ 11}\ P_{12}$ ———-[5]. For $1<m<\infty$. Equation [5] is usually referred to as a sub-distribution of probabilities.

f^m_{12} is defined as the first step probability that a *DS* strain first progresses to an *MDR* strain in exactly *m* steps for all possible values of *m*. This will enable us to calculate the total probability that a *DS* strain will progress to an *MDR* strain or an *MDR* strain will progress to an *XDR* strain or an *MDR* strain will recover from *MDR* during the time period of the study and the speed with which this procedure occurs.

Our Markov Chain model also allows us to calculate the life expectancies for the *DS* and *MDR* strain. In this study, we define life expectancy as the expected time to absorption of each *MTB* strain (i.e. absorption into the *XDR* state).

We denote as T_i for $i = 1,2$.To examine life expectancies of the various states, we create a matrix Q that contains only transition probabilities for the recurrent transitions for the transient states (ie process of MDR and recovery from resistance). Note that in this model, we have defined two transient states *1* and *2* (i.e. *DS* and *MDR*) and one absorbing state *3* (*XDR*), therefore
The life expectancy for an *MTB* strain is $N = (I-Q)^{-1}$

$$Q = \begin{pmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{pmatrix}$$

Where

$$I = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

The term life expectancy is a vector containing the expected times to a strain becoming an *XDR* strain starting from the *DS* state (first element of *N*) and *MDR* state (second element of *N*) respectively.

Probability Matrix

For each cycle, a count matrix was constructed based on the number of patients with the respective MTB strains making the transitions. The count matrices were summed to give the overall summation (*S*) matrix (Jain, 1986). The summation matrix was used to construct the estimates P_{ij} of the probability (*P*). The probability of transitioning from state *i*, the previous state, to state *j*, the future state, given by:

$$\tilde{p}_{ij} = f_{ij}(k) \Big/ f_i(k) \qquad [6]$$

Where $f_{ij}(k)$ the frequency or count of patients making the transition from state *i* to state *j*, f_i is the sum of observed patients initially in state *i* and *k* is the cycle with a total of *K* cycles (Craig & Sendi, 2001). Hence, the sum of each row of the *P* matrix is one as indicated in Table 1.

Resistant Pattern Data

We adopt a retrospective data on resistant pattern to first line and second line anti TB drugs from a study conducted by Rizwan *et al.* (2012). The data consist of a total of 1180 *MTB* positive patients receiving various anti TB drugs and suspected of having drug resistance. These patients were referred to the specialized research center for TB at Lahore for culture and drug susceptibility testing against first line and second line anti TB drugs.

Primarily, isolation for *MTB* was performed using

Table 1: Summation of row of *P* matrix

		DS	**MDR**	**XDR**	$\sum$
	DS	$\sum_{K=1}^{K} f_{11}(k)$	$\sum_{K=1}^{K} f_{21}(k)$	$\sum_{K=1}^{K} f_{31}(k)$	f_1
S =	MDR	$\sum_{K=1}^{K} f_{21}(k)$	$\sum_{K=1}^{K} f_{32}(k)$	$\sum_{K=1}^{K} f_{23}(k)$	f_2
	XDR	$\sum_{K=1}^{K} f_{31}(k)$	$\sum_{K=1}^{K} f_{21}(k)$	$\sum_{K=1}^{K} f_{33}(k)$	f_3
		DS	MDR	XDR	$\sum$
	DS	p_{11}	p_{12}	p_{13}	1
P =	MDR	p_{21}	p_{22}	p_{23}	1
	XDR	p_{31}	p_{31}	p_{33}	1

the recommended procedure for culturing with standard concentrations and critical concentrations as recommended by Sidiqqi *et al.* (1985). The data on key states defined for the study was extracted. Out of the 1180 suspected *MDR* patients tested, 201 (17%) showed resistance to both INH and RIF, 4 (2%) were XDR cases (Rizwan *et al.,* 2012).

Note that these were patients who were on various treatment regimens hence our choice for adoption of proportions as case probabilities for our markov chain model. The case probabilities are illustrated as shown below:

		DS	**MDR**	**XDR**	$\sum$
	DS	179	201	0	1180
S =	MDR	0	197	4	201
	XDR	0	0	4	4
		DS	MDR	XDR	$\sum$
	DS	0.83	0.17	0	1
P =	MDR	0	0.98	0.02	1
	XDR	0	0	1	1

The transition matrix of the resistant pattern data in a canonical form is written as:

$$P = \begin{pmatrix} 0.83 & 0.17 & 0 \\ 0 & 0.98 & 0.02 \\ 0 & 0 & 1 \end{pmatrix}$$

This study make the following assumptions:

1. An *MTB* strain that progresses into an *XDR* strain remains there forever. We refer to this as the treatment failure in our model
2. We assume that strains jumps between states (DS ↔MDR→XDR)
3. The transition from DS → XDR is sequential
4. Patients tested with *DS, MDR* and *XDR* are declared as those statuses respectively.
5. The period of transition in discrete period is measured in hours.

Estimating our probabilities and life expectancies, we obtain the canonical form of the matrix, thus:

$$P = \begin{pmatrix} Q & R \\ 0 & 1 \end{pmatrix}$$

$$Q = \begin{pmatrix} 0.83 & 0.17 \\ 0 & 0.98 \end{pmatrix}, R = \begin{pmatrix} 0 \\ 0.02 \end{pmatrix}, I = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

$$N = (I-Q)^{-1} = \begin{pmatrix} 5.88 & 50 \\ 0.00 & 50 \end{pmatrix}, B = NR = \begin{pmatrix} 1 \\ 1 \end{pmatrix} \quad and \quad SD(N) = (2.94, 0),\ Cov(N) = \begin{pmatrix} 8.6 & 0.0 \\ 0.0 & 0.0 \end{pmatrix}$$

Where:

$$SD(N)=\sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(N_i-\bar{N}\right)^2} \quad and \quad Cov(N_n)=\frac{1}{n}\sum_{i=1}^{n}\left(N_i-\bar{N}\right)\left(N_i-\bar{N}\right)^T$$

An *MTB* strain starting as *DS* strain will spend an average of 5.9 ± 2.9 hours in that state, and starting as *MDR* strain, it will remain in that state for an average of 50 hours before it progresses to *XDR* state. Table 2 below consists of the summary of the model analysis.

Table 2 Analysis of Resistant Pattern Data

Description	Metric (Hours)
Expected Time to Treatment Failure	50
Life Expectancy for the DS Strain	5.9 ± 2.9
Life Expectancy of the MDR Strain	50
Expected Time to Treatment Failure for MTB strain	55.9 ± 2.9

Simulated Data

We generated 50 chain cycles of the probability distribution of both the mutation of the *DS* strain at each cycle and the probability distribution of drug resistance at each given time step of the chain cycle. Clinically, most patients under treatment of various TB regimes usually do not complete the drug cycle or even lost to follow up. The model allowed as to use the transition probability matrix of the drug susceptibility data to determine the future states of the diseases given that each entered into their various treatment regime at the same time. In the absence of further visits of the patients, the simulated chain enables us to determine the future states of the diseases in some number of steps (Figure 4.1 and Table 3).

Table 3: Summary Statistics of the Original Transition Matrix and the Simulated Cycles of the Probability of First Mutation of the MTB Strain

Number of Cycles	SD	Mean	Figure
1	0.17	0.17	-
50	0.04	0.02	Fig. 4.1
100	0.29	0.01	Fig. 4.1A
200	0.021	0.005	Fig. 4.1B
1000	0.01	0.01	Fig. 4.1C

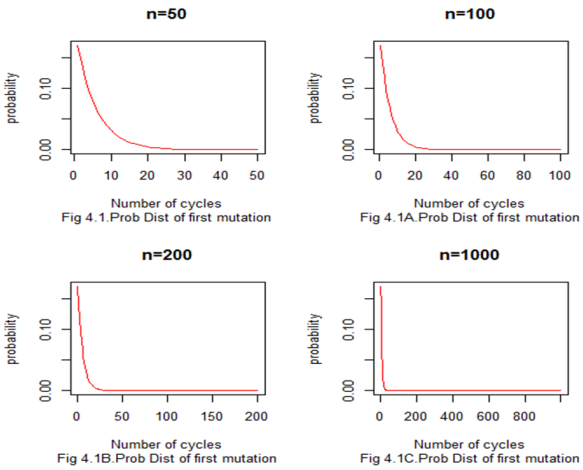

Figure 4: 4.1, 4.1A, 4.1B and 4.1C are 50, 100, 200, and 1000 cycles of the probability of first mutation of the *DS MTB* strain respectively.

Table 3 shows a decreasing trend in the deviations as the number of cycle increases. However, the means exhibited similar trend but increase slightly at the 1000th cycle.

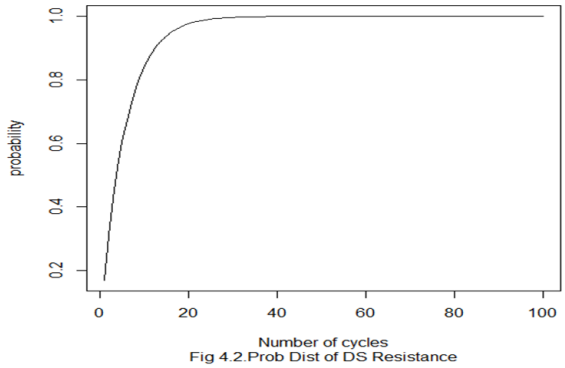

Figure 4.2 illustrate the probability of resistance of the *MTB* strain at each time cycle

In Figure 4.1, Probability distribution of first mutation from *DS* to resistant strain decreases exponentially over the cycle. The decreasing trend becomes steady after the 20th cycle. Apparently, the DS strain is sensitive to the anti TB drugs and as such mutations at each cycle will continue to reduce and consequently approaches 0, by which time all the *DS* strain would have been wiped out as a result of

the drug effect. This is because the first time the strain is visited with the drug, the chances of the *DS* strain becoming resistant is very low. Our simulated chain is consistent with the fact that mutation of susceptible *MTB* strain can be reduced when antimicrobial agents are adhered to over time course of treatment.

The reverse is the case in Figure 4.2. The Probability distribution of *DS* becoming resistant increases over the time course of the cycle. If subsequent visits of the drugs to the *DS* strain is interrupted or taken below prescribed concentrations, chances are high for the strain to become resistant. As shown in Figure 4.2, the Probability of the *DS* strain becoming resistant over the time course of the treatment increases. Coincidentally, this also occurs after the 20th cycle of the treatment regime. This consequently reaches an absorption state.

We further generated a number of cycles (*n=100, n=200 and n=1000*) for the probability of first mutation of the *DS* strain. The deviations of the various cycles shows a decreasing trend , nonetheless, the steady state of the process was after the 20th cycle which was consistent with all the cycles generated in Figure 4.1, 4.1A, 4.1B, and 4.1C respectively. Same conclusions can be made about Figure 4.2 based on the generated cycles. No matter the number of times we generate the cycles of the disease transition, the steady state will occur after the 20th cycle for both probability of first mutation of the *DS* strain and the probability of *DS* resistance hence the focus on 50 cycles. In terms of clinical practice, resistance of *MTB DS* strain should be prevented before the 20th cycle of the course of treatment.

Assessment of Estimates

Since we ran 50 cycles of the resistant pattern data and determined certain metrics of interest on the transitional behaviour of the *MTB* strain. The 50 random generated cycles was used as the empirical data to further assess the simulated results of the Markov Chain. Looking at the distribution of the data in Figure 4.1G and 4.1J respectively for the probability of first mutation from *DS* to *MDR* and the probability of resistance of the *DS* strain, it seem not right for further analysis. Computing the mean of first *DS* mutation and *DS* resistance level of the *MTB* strain alone given this distribution may not have meaning and may not describe the situation well.

Hence, a more important objective of this study is primarily to understand the variability of the *DS* and *MDR* level for the *MTB* strain dynamics. Again, the law of averages does not work well for this kind of distribution, unless one has a very large data set, say $n = 1000$ or more. This is a case where the bootstrap can be a useful technique. Bootstrap techniques are generally categorized as either nonparametric or parametric. Parametric bootstrap techniques assume that the data are generated from a standard parametric probability model (such as the Normal, Poisson etc.).

Nonparametric bootstrap techniques are more versatile and suit our illustration of the data to the model much better. Because of their versatility, nonparametric bootstrap techniques are the more popular type of bootstrap applications. The beauty of the nonparametric bootstrap is that, since there are no assumptions of the underlying model, you can apply it to any dataset. The essence of what the nonparametric bootstrap is doing is sampling from the empirical cumulative density function (CDF) of the data. The empirical probability distribution assigns an equal probability to each of the data points, $1/n$. Hence when we resample, every data point has an equal chance of being sampled. Using the CDF is what allows us not to rely on a particular probability model as seen in Figure 4.1E and 4.1H.

Basically, the process is a form of pseudo sampling from the original dataset to determine the variability of the dataset. This process may sound too easy and simplistic, yet it is a very robust and statistically sound technique for measuring standard errors. The R package *stepfun, plot, Stepfun and bootstrap* were used to plot the empirical CDF for the data set and subsequent selection of 1000 bootstrap samples from the original resistant pattern data. Table 4 consists of the summary measures of the process.

Table 4 Comparison of Summary Measures of Original Data and Bootstrap Results

Description	Mean		Standard Error		C.I (95%)	Bias
	Original Data	Bootstrap	Original Data	Bootstrap	Bootstrap	
Probability of First Mutation of DS Strain	0.01	0.0101755	0.0289	0.009178075	2.782228e-07 and 0.01811307	0.00017
Probability of Resistance of DS Strain	0.9511765	0.9511253	0.1412794	0.0446325	0.9153687 and 0.9999986	0.00001
Steady State Probability of MTB Strain	2.24	2.23856	0.6869037	0.6801311	2 and 2.46	0.00144

It is observed that the mean of the bootstrap samples converges to the mean of the original data for both first time mutation from *DS* state to *MDR* state and the probability distribution of *DS* resistance.

Further, the graphs below depict the variability structure of both the original data and the bootstrap samples. Both graphs of the original data (Figure 4.1G and 4.1J) exhibited high level of skewness, yet the bootstrap samples graphs of first *DS* mutation and *DS* resistance (Figure 4.1F and 4.1I) exhibited a fairly normal distribution. This is evident in Table 4 where the Bias in both cases are almost 0.This provides a very sound statistical basis for the conclusive results on the dynamics of the *MTB* strain in terms of the first time the *DS* strain becomes resistant over the course of treatment regime (cycle) and the probability distribution of *DS* resistance over the course of the treatment regime (cycle).

The confidence interval further allowed for the interpretation of the estimates with a certain probability. A 95% confidence interval for our parameter estimate for the probability of first mutation of *DS* strain is (2.782×10^{-7}, 0.018). Thus, if the experiment is repeated (drawing random samples of size 50 from the empirical data) and made confidence intervals for each sample mean point estimate, then 95% of the time, the confidence interval derived (2.782×10^{-7}, 0.018) would contain the true mean of the first *DS* mutation. Similarly, a 95% confidence interval for our parameter estimate for the probability of *DS* resistant strain is (0.92 and 0.10). Thus, if this experiment is repeated (drawing random samples of size 50 from the empirical data) and made confidence intervals for each sample mean point estimate, then 95% of the time, the confidence interval derived (0.92 and 0.10) would contain the true mean of the *DS* resistance.

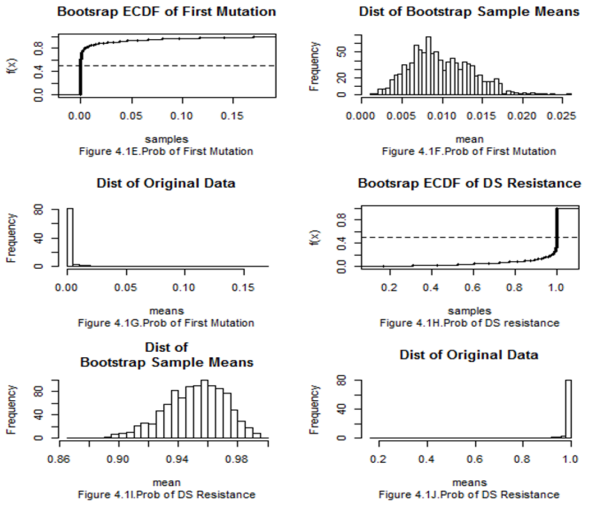

Figure 4.1E and 4.1H are the empirical cumulative distribution function of *DS* first mutation and *DS* resistance. Figure 4.1G and 4.1J are the graph of the original data for *DS* first mutation and *DS* resistance. Figure 4.1F and 4.1I depicts the distribution of bootstrap samples for both *DS* first mutation and *DS* resistance

RESULTS AND DISCUSSION

The transitional period of the *MTB* strain from *DS* to either *MDR* or *XDR* is very crucial in TB treatment. It represent the period of difficulties in TB treatment because of the random behaviour of the *MTB* strain partly due to drug to drug interactions and other physiological effects .Our study discusses the transient state of this period and guarantees an absorption into the *XDR* state of the disease in course of treatment. It is established that a drug effect is often related to its concentration at the site of action, hence monitoring of this concentration is very crucial. This study can be optimized with knowledge of appropriate transitional dynamics of the *MTB* strain so as to reduce the side effect of anti TB drugs and enhancing drug efficacy.

In clinical efficacy, minimum inhibitory concentration (MIC) has been chosen as a predictive factor with for instance 0.025-0.05 ug/ml for INH. The therapeutic range of serum concentration is approximately 3 ug/ml to be maintained for at least 6 hours (EMA, 2012). With knowledge of life expectancies for the *MTB* strain, appropriate MIC over the time course can be determined for optimal therapeutic benefits. This analysis can be applied to other anti TB drugs.

Life expectancy is a common measure of success for clinical studies and forms the bedrock for clinical decision making. Beck & Pauker (1983) defined life expectancy as the average future life time of a cohort of subjects with identical features. In this study we established that a *DS* strain will reside in that state for an average of 5.9 ± 2.9 hours before progressing to *MDR* state. Similarly, an *MDR* strain will reside in that state for an average of 50 hours before progressing to an *XDR* state. These serves as life expectancies for both *DS* and *MDR* strain respectively. The progression from *MDR* state to *XDR* signifies treatment failure of the disease since treatment failure and relapse rates are higher than drug-susceptible strains (Mak *et al.,* 2008). Further, we estimated that it will take an average of 55.9 ± 2.9 hours for the *DS* strain to be finally absorbed into the *XDR* state. It is observed that the average time to absorption and life expectancy of the *MDR* strain remains the same 50 hours since progression from *MDR* state to *DS* state was not possible. This is evidenced in the fact that patients who are *MDR* require much lengthier treatment (Mak *et al*., 2008). Our study revealed that the probability of absorption for both *DS* and *MDR* strain is certain with a large difference of life expectancies.

We further simulated the transition probability data of the susceptibility test of the 1180 patients on various TB treatment regimes. It was realized that the probability distribution of first mutation from *DS* to resistant strain decreases exponentially over the cycle, whiles the probability distribution of *DS* becoming resistant increases over the time course of the cycle. Steady state probabilities of the *MDR* and *XDR* state saw a large dramatic cycle as compared to *DS* state. A 95% confidence interval for our parameter estimate for the probability of first mutation of *DS* strain is $(2.782 \times 10^{-7}, 0.018)$. Our simulated chain is consistent with the fact that mutation of susceptible *MTB* strain can be reduced when antimicrobial agents are adhered to over time course of treatment.

CONCLUSION

In our model, we established that it will take an average of 55.9±2.9 hours for an *MTB* strain to mutate to *XDR* stage with a certain probability. In the clinical sense, it represents treatment failure since *MDR* can be managed with second line anti TB drugs, even though the treatment success is very slim. The life expectancies for the *MDR* strain (50 hours) appears to be higher than *DS* strain (5.88 hours) probable due to compensatory mutation. Our study shows the transient state (*DS and MDR*) of this period which leads to the development of Extra Drug Resistant State (*XDR*) of the disease in the course of treatment. The findings of the study are consistent with the observation that a simple plot of drug concentration versus time profile following intravenous drug infusion reflects plasma drug concentration.

Probability distribution to first mutation from *DS* decreases exponentially over the cycle. Probability distribution of *DS* becoming resistant increases

over the time course of the cycle. The bootstrap results provided sound statistical basis for the conclusive results on the dynamics of the *MTB* strain in terms of the first time the *DS* strain becomes resistant over the course of a treatment regime (cycle) and the probability of *DS* resistance over the course of the treatment regime (cycle).

KEY CONTRIBUTIONS

1. The major contribution of this study is the revealing therapeutic cycle of the treatment regime of the TB disease based on the TB progression data which is of biological interest.
2. The time unit in hours of the resident time of the *MTB* strain has been determined to facilitate further experimental studies.
3. The results opened a new window for therapeutic drug monitoring for enhanced TB treatment.

BIOLOGICAL BENEFITS

This study is useful for a number of purposes:

1. In clinical efficacy, minimum inhibitory concentration (MIC) has been chosen as a predictive factor with for instance 0.025-0.05 ug/ml for INH. The therapeutic range of serum concentration is approximately 3ug/ml to be maintained for at least 6 hours (EMA, 2012). With knowledge of life expectancies for the *MTB* strain, Appropriate MIC over the time course can be determined for optimal therapeutic benefits.
2. For describing the basic dynamics of the *MTB* strain and can assist medical researchers to explore key aspects of the *MTB* mutation and explosion.
3. In pharmacodynamics, it can be used to determine the virulence of the *MTB* strain and possible containment by inspecting thoroughly how probabilities of *DS* and *DR* recovery would change under various control strategies. It can also help in determining plasma concentration range that is safe for treatment of TB.
4. With knowledge of life expectancies for the *MTB* strain, appropriate MIC over the time course can be determined for optimal therapeutic benefits.

LIMITATIONS OF THE STUDY

The isolates were obtained from patients who were already suffering from various forms of *DR* TB. This affected the recovering probability in the transient state thus, from *MDR* to *DS*.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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