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MODELLING TUBERCULOSIS TREATMENT OUTCOMES USING A DISCRETE TIME MARKOV CHAIN MODEL

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James Kamau Saidi

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Submitted to the School of Mathematics in partial fulfilment for a degree in Master of Science in Biometry

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Masters Thesis

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Abstract

Tuberculosis (TB) is a disease affecting mostly the Lungs and can be fatal when not followed and appropriate measures taken to manage its severity and advancement in a population. Despite TB being preventable and curable, approximately 10 million people worldwide get it every year. This study investigated TB management outcome dynamics, the transition probabilities of TB treatment outcomes and predicted future treatment outcomes using Discrete Time Markov Chain Model. The results showed that there was a gradual increase in transition probabilities from the non-absorbing states to cured/dead states, although the proportion of persons transiting to cure were higher than those transiting to death. Further, transition from the non-absorbing states to again non-absorbing states steadily decline from 80.62% in the 1^{st} year to 0 for most of the transition in the 10^{th} year. In the 13^{th} year, the patients were either in cured or dead state. Those lost to follow up (6.11%) were more than those Transferred out (2.47%) and more patients with Extra-Pulmonary TB (10.94%) were dying despite none having a treatment failure and all completing treatment in comparison to those with Pulmonary TB (7.04%). Future research could investigate why the proportion of Extra-pulmonary TB patients who die is higher than those with Pulmonary TB and why more patients are lost to follow-up. Increasing the patients' follow up period beyond one year would also shade more light on the transiting probabilities of TB treatment outcomes.

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Declaration and Approval

I the undersigned declare that this dissertation is my original work and to the best of my knowledge, it has not been submitted in support of an award of a degree in any other university or institution of learning.

Signature Date

James Kamau Saidi
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In my capacity as a supervisor of the candidate's dissertation, I certify that this dissertation has my approval for submission.

Signature Date

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Dedication

This project is dedicated to my parents, Moses Saidi and Ann Wangoi and my wife, Mercy for their immense support.

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James Kamau Saidi

Nairobi, 2020.

CHAPTER 1
INTRODUCTION

1.1 Introduction

Tuberculosis (TB) is a disease affecting mostly the Lungs and is spread from one person to another through cough, sneeze and spit from a person infected with Mycobacterium Tuberculosis (MTB). Being an air-borne disease, its transmission and by extension infection re-infection rates are high in areas with little or no detection capabilities. It can be fatal when not followed and appropriate measures taken to manage its severity and advancement in a population. This chapter presents the background, problem statement, objectives, methodology and significance of the study.

1.2 Background

According to WHO (2020) TB is responsible for 1.5 million deaths each year, becoming the top killer infectious disease worldwide. A ¼ of the world population is estimated to be infected with TB bacteria where nearly 15% of them fall ill with active TB while the others have the MTB but are not ill and can not transmit the bacteria. Despite TB being preventable and curable, approximately 10 million people get it every year (Harding, 2020).
Another crisis in the prevention and treatment of TB is the emergence of Multidrug resistance to TB (MDR-TB) by the patients on treatment. Between 2018 and 2019, there was an increase in MDR-TB for Rifampicin regimen by 10%, with the statistic of reported cases rising to 206,030 people from previous 186,883 people in 2018 (WHO, 2019). In Kenya in 2019, 86,504 cases were reported and treated for TB where 10% of them were children. As of 2019, 688 cases developed MDR-TB which by extension increased the Drug-Resistant TB treatment costs (more than Kshs 4,500 per treatment) to the government since TB treatment is free in public and Faith-Based Organizations' health facilities (MOH, 2020).

Therefore, in order to achieve 80% drop in TB incidence, 90% drop in TB related deaths by 2030 as targeted by the Sustainable Development Goals (SDGs) and realize vision 2030, TB monitoring will be key to that achievement.

1.3 Problem Statement

TB continues to be a concern among the infectious diseases in Kenya. Its five digit incidence value and three digit value for MDR-TB in only 1 year requires a redress.TB prevention and management has used Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) regimens at various dosage levels. Rifampicin regimen and Isoniazid among the other regimens has widely been used in health facilities in Kenya.

With the emergence of MDR-TB, the dynamics of TB progression needs to be carefully studied. Those who are cured, die, realize a treatment failure, are lost to follow up, complete treatment, did not complete treatment or were transferred out of the health facility to a referral or another facility needs to be considered. Their transition from one state to another will provide the effectiveness of the treatment management program and inform whether the patients develop resistant to Rifampicin regimen or not.

Therefore this study delves into investigating the transition probabilities and predict future TB treatment outcomes.

1.4 Objectives

1.4.1 General Objective

To model the treatment outcomes for patients diagnosed with Pulmonary or Extra-Pulmonary TB in Kenya.

1.4.2 Specific Objectives

In shaping the general objective, the specific objectives are;

1. Describe TB management outcome dynamics,
2. To obtain the transition probabilities of TB treatment outcomes and
3. To predict future TB treatment outcomes.

1.5 Methodology

The theory of Markov Chain, specifically the Discrete Time Markov Chain model is used in this study. In analysis, Octave software was utilized to develop the model and compute the steady state probabilities. Data that was subjected to analysis for this work was obtained from the Kenyan Ministry of Health.

1.6 Significance of the Study

Among the standard TB treatments identified by WHO, Isoniazid (H), Rifampicin (R), pyrazinamide (Z) and Ethambutol (E) regimens are recommended for prevention and management of TB at various dosage levels (Maher D., et al., 1997). Specifically, Rifampicin (R) regimen will be weighed in relation to the transiting probabilities of patients' progression or retrogression towards cure and death respectively in Kenya. This will complement the recent policies on Injectable Free Regimen and latent TB infection treatment that was launched in June 30th 2020. The policies addressed the treatment of MDR-TB treatment that does not use injections as fostered by WHO and preventive treatment for inactive TB to those at risk of developing active TB respectively.

Further, towards the realization of the national strategic plan to control TB that envisions curing atleast 597,000 cases of TB by 2023 which was launched in 2018, it will inform the careful monitoring of patients at various states to hasten treatment successes.

In addition, it shades light on the state of those who develop Rifampicin MDR-TB within our country, predicts the number of years it would take for them to be rid-off the MTB, with the prevailing treatment program remaining constant.

CHAPTER 2
LITERATURE REVIEW

Many previous studies have explored different aspects of Tuberculosis including risk factors, efficacy of diagnostic tests, diagnosis, disease progression and its co-morbid outcomes. In this chapter, some previous works that have been conducted are presented.

Hoad et al. (2009) while studying the infection transmission dynamics of TB, used stochastic Markov chain model to find out the effects of local and global parameters on the possibility of contracting TB in Gem and Asembo Divisions of Western Kenya. That is, determine whether local (cluster) effect is stronger than the general global effect. Their results indicated that the local transmission coefficient was higher than the global coefficient in all model variations. Furthermore, a slight increase in the local effect and decline in the global effect was observed. In relation to grouped (cluster) randomized trial, the effectiveness of an intervention policy could be assessed by applying to one group and not the other.

In another study, Ozcaglar et al. (2012) used Ordinary differential equations (ODE) and Markov Chain Monte Carlo methods to explain the different types of TB dynamics, current treatment strategies effectiveness, multi-drug resistant TB (MDR-TB) and co-infections in the US between 1980 and 2009. Their results indicated that the risk factors to TB transmission was Social clusters, overcrowding in confined spaces and public transportation. Further, they realised that treatment which focuses on genetically susceptible persons could be successful and would potentially reduce TB prevalence. On multi-drug resistant TB and co-infections (HIV/TB), exclusive treatment of one disease may reduce prevalence and new infections or death from that disease, but may worsen the other disease. That is, transmission may be active for the second disease while the first one is suppressed.

In a study conducted by Hill et al. (2012) on TB trends in the US, a system of differential equations was used. They evaluated the intervention strategies on time to elimination, treatment of TB active cases, the treatment of inactive (latent) infection and reducing foreign-born persons who enter the country with latent TB infection. The study realised that it could take more than 20 years to achieve elimination among the US-born population when the treatment for chronic Latent TB infection was to be doubled. However, for the foreign-born population, if the treatment rate for chronic latent TB infection was accelerated four fold and the proportion of the foreign-born entering US was to be reduced by 50%, then it was possible to achieve zero TB incidence.

In Kenya, Kosgei et al. (2015) used Multivariate and logistic regression to explain the impact of gender difference towards the treatment outcomes for 15 to 49 year old persons diagnosed with pulmonary TB. Further, they investigated the factors linked to poor outcomes evident in Kenya. Their results indicated that more females as compared to males got a poor treatment outcome. They attributed the higher likelihood of poor pulmonary TB treatment outcomes for females on cultural inequalities and socio-economic differences in comparison to males. The poor treatment outcomes farther varied from one county to another, some having low while others having high poor outcomes.

In China, Xu et al. (2017) used Markov Chain model to arrive at the factors associated with TB and the measures which will ultimately end TB towards the realization of World Health Organisation (WHO) goal of ending TB by 2050. Their results indicated that, TB prevalence will reduce at a high rate in the next 8 years (after 2017) and then flatten. Undetected smear-negative TB formed the majority of the infected patients and with the current interventions remaining constant, TB prevalence will stagnate at 163 cases per 100,000 after 50 years. The controllable factors for attaining the WHO target were to escalate the proportion of notified cases, inhibit the progression of latent TB to active TB and increasing the TB treatment success rate.

Onyango et al. (2018) used bivariate and Cox proportional hazards regression to explain the epidemiology of childhood Tuberculosis in Kenya. From the results, Pediatric TB accounted for 9% of all the TB patients, co-infection of TB/HIV was 28% and 4% of the children under TB treatment died as 90% recorded a treatment success. Among the risk factors identified were being HIV infected but not on ARV therapy, being HIV infected and on ARV therapy, being a child with TB below the age of 5 years and diagnosed with pulmonary disease. In addition, most TB pediatric cases (71%) were detected through self-referral.

In another study by Li et al. (2020), Markov modelling was used to investigate the challenges posed by multi-drug-resistant TB in China. They projected the impact of improved detection rate, expanded treatment coverage and when increased detection rate and expanded treatment coverage are intertwined. Their results indicated that, with the prevailing interventions remaining unchanged, a substantial decline (67% reduction) in drug susceptible TB untreated (DS-TB^{+}) prevalence and a considerable increase (three fold) in MDR-TB prevalence from 2019 to 2050 will be observed. In addition, untreated MDR-TB prevalence would rise three folds, whereas treated MDR-TB would exhibit a limited increase by 2050. By the same year, 74% of Tuberculosis cases would be MDR-TB, whereas most, 86% of those cases would remain untreated. MDR-TB detection and treatment coverage solely would reduce prevalence but would not stop the increase of MDR-TB.

Adeboye et al. (2020) used a joint model that consisted of a generalized logit model for binary variables and Cox proportional hazards for survival times to TB diagnosed dataset for Eastern Cape Province in South Africa. Their results showed that age, gender, smoking status and Diabetes were significant covariates as smoking status and Diabetes were significant factors for time-to-event in adults with TB. The joint model provided a better predictive power for Tuberculosis prognostic factors.

In summary different studies have been conducted and different methods have been used to study TB. In this work, Discrete Time Markov Chain model with Absorbing States has been explored.

CHAPTER 3

DISCRETE TIME MARKOV CHAIN MODEL WITH ABSORBING STATES

3.1 Introduction

Events in life usually occur naturally in a random manner. Random occurrences follow a stochastic process which evolve in time or space according to probabilistic laws. States are the possible positions occupied thus the state space comprises of all the possible states of the system. Occasionally some events transition between specific states, some of which may be permanent states. In section 3.2 which follows, a few definitions are presented after which the Discrete Time Markov Chain Model with Absorbing States is presented in section 3.3.

3.2 Definitions

I Stochastic process

A stochastic process $X(t)$, $t \, \varepsilon \, T$, is a collection of random variables indexed by the time parameter t. Hence $X(t)$ is the state of the process at time t.

II Markov process

A Markov process is a stochastic process such that the last state depends only on the immediate former state, that is,

$$\begin{aligned} P[X(t) \leq x / X(t_n) = x_n, X(t_{n-1}) = x_{n-1}, \cdots, X(t_0) = x_0] \\ = P[X(t) \leq x / X(t_n) = x_n] \end{aligned} \tag{3.1}$$

III Discrete Time Markov Chain

A Discrete Time Markov Chain is a Markov process with discrete state space and discrete parameter space.

IV Markov Property

The Markov Property states that the present state depends on the immediate past state and not on the remote past state.

V Absorbing and Non-Absorbing States

An absorbing state is a state which when entered becomes a permanent state. On the other hand, a Non-absorbing state is a state from which it is possible to exit. In section 3.3 which follows, the Markov Chain model with Absorbing States is presented.

3.3 The Model

A matrix $P = ((P_{ij}))$ of transition probabilities is a stochastic matrix if its elements are non-negative and all its row sums are unity. Consider a Markov Chain model with s non-absorbing states $1,2,3,\cdots,s$ and r absorbing states $1,2,3,\cdots,r$. Thus $r+s=N$,that is,the total number of possible states of the system. The general transition probability matrix is of the form;

$$P = \begin{pmatrix} 1 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & \cdots & 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 & 0 & 0 & 0 & \cdots & 0 \\ r_{11} & r_{12} & r_{13} & \cdots & r_{1r} & q_{11} & q_{12} & q_{13} & \cdots & q_{1s} \\ r_{21} & r_{22} & r_{23} & \cdots & r_{2r} & q_{21} & q_{22} & q_{23} & \cdots & q_{2s} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ r_{s1} & r_{s2} & r_{s3} & \cdots & r_{sr} & q_{s1} & q_{s2} & q_{s3} & \cdots & q_{ss} \end{pmatrix} \tag{3.2}$$

Which is compactly represented as;

$$P = \begin{pmatrix} I & O \\ R & Q \end{pmatrix} \tag{3.3}$$

Where;
I is an $r\,x\,r$ identity matrix which gives the transition probabilities between absorbing states.
O is an $r\,x\,s$ zero matrix which gives the transition probabilities from absorbing to non-absorbing states.
$Q = ((q_{ij}))$ is an $s\,x\,s$ matrix, q_{ij} being the probability of moving from state i at time $(t-1)$ to state j at time t; $i,j = 1,2,3,\cdots,s$.

$R = ((r_{ik}))$ is an $s\ x\ r$ matrix, r_{ik} being the probability of moving from state i at time $(t-1)$ to state k (absorbing state) at time t; $i = 1,2,\cdots,s$ and $k = 1,2,\cdots,r$.
The n-step transitional probability matrix is presented in section 3.4 as follows.

3.4 The n-Step Transition Probability Matrix

By the Chapman-Kolmogorov result, the n-step transition probability matrix is given by;

$$P^{(n)} = P^n \tag{3.4}$$

From equation 3.3,

$$P^{(2)} = \begin{pmatrix} I & O \\ R & Q \end{pmatrix} \begin{pmatrix} I & O \\ R & Q \end{pmatrix} \tag{3.5}$$

$$= \begin{pmatrix} I & O \\ R+QR & Q^{(2)} \end{pmatrix}$$

Therefore in general

$$P^{(n)} = \begin{pmatrix} I & O \\ (I+Q+Q^{(2)}+Q^{(3)}+\cdots+Q^{(n-1)})R & Q^{(n)} \end{pmatrix} \tag{3.6}$$

Hence

$$P^{(n)} = \begin{pmatrix} I & O \\ R^{(n)} & Q^{(n)} \end{pmatrix} \tag{3.7}$$

Where;
I is an $r\ x\ r$ identity matrix which gives the transition probabilities between absorbing states in n-steps.
O is an $r\ x\ s$ zero matrix which gives the transition probabilities from absorbing states to non-absorbing states in n-steps.
$R^{(n)} = ((r_{ik}^{(n)}))$ which equals to $(I+Q+Q^{(2)}+Q^{(3)}+\cdots+Q^{(n-1)})R$ is an $s\ x\ r$ matrix which gives the probability of moving from state i at time $(t-1)$ to absorbing state k at time t in n-steps; $i = 1,2,\cdots,s$ and $k = 1,2,\cdots,r$.
$Q^{(n)} = ((q_{ij}^{(n)}))$ is an $s\ x\ s$ matrix, which gives the probability of moving from state i at time $(t-1)$ to state j at time t in n-steps; $i, j = 1,2,3,\cdots,s$.
As follows in section 3.5, the long run or steady state transition probability matrix is presented.

3.5 The Fundamental Matrix

From equation 3.6 and equation 3.7,

$$R^{(n)} = (I + Q + Q^{(2)} + Q^{(3)} + \cdots + Q^{(n-1)})R \tag{3.8}$$

And using Calculus where,

$$\frac{1-x^n}{1-x} = 1 + x + x^2 + x^3 + \cdots + x^{(n-1)} \tag{3.9}$$

Then

$$\frac{I-Q^{(n)}}{I-Q} = I + Q + Q^2 + Q^3 + \cdots + Q^{(n-1)} \tag{3.10}$$

This implies that

$$(I-Q)^{-1}(I-Q^{(n)}) = I + Q + Q^2 + Q^3 + \cdots + Q^{(n-1)} \tag{3.11}$$

Therefore substituting in equation 3.8 we have that

$$R^{(n)} = (I-Q)^{-1}(I-Q^{(n)})R \tag{3.12}$$

Thus

$$P^{(n)} = \begin{pmatrix} I & O \\ (I-Q)^{-1}(I-Q^{(n)})R & Q^{(n)} \end{pmatrix} \tag{3.13}$$

Suppose we expand the following expression

$$(I-Q)(I+Q+Q^{(2)}+\cdots) = (I+Q+Q^{(2)}+\cdots-Q-Q^{(2)}-\cdots) = I \tag{3.14}$$

Then, taking limits of equation 3.10 ;

$$\lim_{n\to\infty}(I-Q)(I+Q+Q^2+\cdots+Q^{(n-1)}) = \lim_{n\to\infty}(I-Q^{(n)}) \tag{3.15}$$

$$\lim_{n\to\infty} I = \lim_{n\to\infty} I - \lim_{n\to\infty} Q^{(n)} \tag{3.16}$$

Thus

$$\lim_{n\to\infty} Q^{(n)} = O \tag{3.17}$$

In general,substituting in equation 3.17 for $(I-Q^{(n)})$ then

$$\lim_{n\to\infty} P^{(n)} = \begin{pmatrix} I & O \\ (I-Q)^{-1}R & O \end{pmatrix} \tag{3.18}$$

The matrix $(I-Q)^{-1}R$ is called the Fundamental matrix of the absorbing Markov Chain. The Fundamental matrix gives the steady state probabilities of moving from the non-absorbing states to the absorbing states. In chapter 4 which follows, We apply the Absorbing Markov Chain Model to TB patients' transition.

CHAPTER 4

APPLICATION OF THE DISCRETE TIME MARKOV CHAIN MODEL

4.1 Introduction

TB management involves diagnosis and follow up where the patients will be given treatment regimens (for this study Rifampicin regimen applies) then complete the treatment which will result to cure. However, there are those who will be cured, die, lost to follow up, move to treatment category 4, will not complete treatment and those who will be transferred to referral or another facility. In exploring the various states, this chapter presents the data for the study, the initial and n-step transition probability matrices and discussion.

4.2 Data for the Study

The TB data for the study was obtained from the Kenyan Ministry of Health. The sample data captured 1456 patients who had been diagnosed and placed on treatment for TB between January 2017 and December 2017 in various government hospitals across th country. Their pre-existing co-morbid conditions and different type of Extra- pulmonary TB were not included in the study. The treatment regimen for TB was narrowed to Rifampicin drug and whether the patients developed Drug Resistance (DR) from it or not. The states that were occupied by the TB patients were, for the absorbing or permanent states, Cured (C) and Dead (D), while for the non-absorbing states were, MTB Detected (MD), MTB Not Detected (MND), Rifampicin Resistant (RR), not Rifampicin Resistant (NRR), Pulmonary TB (P), Extra-Pulmonary TB (EP), treatment failure (F), lost to follow up (LTFU), moved to category 4 treatment (MT4), not completed treatment (NC), completed treatment (TC) and transferred out (TO). The TB data for the study is shown in Table 4.1.

Table 4.1. 2017 Tuberculosis Data

	Cured	Dead	F	LTFU	MT4	NC	TC	TO	Total
MTB-Detected (MD)	776	69	7	82	11	2	185	30	1162
MTB-Not Detected (MND)	6	36	0	7	2	0	237	6	294
Rifampicin Resistant (RR)	29	4	1	4	2	0	21	0	61
Not Rifampicin Resistant (NRR)	753	101	6	85	11	2	401	36	1395
Pulmonary TB (P)	780	98	7	88	12	2	371	34	1392
Extra-Pulmonary TB (EP)	2	7	0	1	1	0	51	2	64

4.3 Initial and n-Step Transition Probability Matrices

4.3.1 The Transition Matrix

Let the states of the TB patients be denoted by the integers $1,2,\cdots,N$ at times $t = 1,2,\cdots$. Let p_{ij} denote the probability that a patient in state i at time $(t-1)$ will be in state j at time t, hence the transition matrix, $P = ((p_{ij})); i, j = 1,2,...,N$. Then assuming time homogeneity equation (3.3) holds. Let $n_{ij}(t)$ represent the number of patients in state i at time $(t-1)$ who transit to state j at time t. Also let $n_i(t-1)$ represent the number of patients in state i at time $(t-1)$, then the transition probabilities are estimated from;

$$p_{ij} = \frac{n_{ij}(t)}{n_i(t-1)} \tag{4.1}$$

where $I, j = 1,2,\ldots,N$. This is the proportion of patients who were in state I at time $(t-1)$ who transit to state j at time t.

4.3.2 Initial Transition Probability Matrix

In this sub-section the one-step, initial transition probability matrix is obtained. Thus, for example, the one-year transition probability of patients who were MTB-detected and ended up being cured is 776/1162=0.6678 while the proportion of patients who were MTB-detected and completed their treatment is 185/1162 =0.1592.

Hence assuming time homogeneity, the one-step transition probability matrix P with the two absorbing states is given by;

$$P = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.6678 & 0.0594 & 0.0060 & 0.0706 & 0.0095 & 0.0017 & 0.1592 & 0.0258 \\ 0.0204 & 0.1224 & 0 & 0.0238 & 0.0068 & 0 & 0.8062 & 0.0204 \\ 0.4754 & 0.0656 & 0.0164 & 0.0656 & 0.0327 & 0 & 0.3443 & 0 \\ 0.5398 & 0.0724 & 0.0043 & 0.0609 & 0.0079 & 0.0014 & 0.2875 & 0.0258 \\ 0.5605 & 0.0704 & 0.0050 & 0.0632 & 0.0086 & 0.0014 & 0.2665 & 0.0244 \\ 0.0313 & 0.1094 & 0 & 0.0156 & 0.0156 & 0 & 0.7968 & 0.0313 \end{pmatrix} \tag{4.2}$$

4.3.3 n-Step Transition Probability Matrices

The two-step transition probability matrix is obtained as;

$$P^{(2)} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.7687 & 0.0832 & 0.0010 & 0.0133 & 0.0026 & 0.0002 & 0.1246 & 0.0063 \\ 0.4766 & 0.1847 & 0.0041 & 0.0523 & 0.0076 & 0.0011 & 0.2526 & 0.0208 \\ 0.6962 & 0.1010 & 0.0024 & 0.0266 & 0.0046 & 0.0005 & 0.1585 & 0.0102 \\ 0.7104 & 0.1038 & 0.0016 & 0.0209 & 0.0036 & 0.0004 & 0.1501 & 0.0092 \\ 0.7201 & 0.1005 & 0.0015 & 0.0197 & 0.0034 & 0.0004 & 0.1456 & 0.0087 \\ 0.4866 & 0.1719 & 0.0042 & 0.0522 & 0.0080 & 0.0011 & 0.2552 & 0.0207 \end{pmatrix} \tag{4.3}$$

Considering the categories MTB Detected (MD), MTB Not Detected (MND), Rifampicin Resistant (RR), Not Rifampicin Resistant (NRR), Pulmonary TB (P) and Extra-Pulmonary TB (EP) separately, then the n-step transition probabilities are summarized in Tables 4.2, 4.3, 4.4, 4.5, 4.6 and 4.7 as shown.

Table 4.2 shows the n-step transition probabilities for the patients who were MTB Detected.

Table 4.2. n-Step Transition Probabilities for MTB Detected

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.6678	0.7687	0.8411	0.8706	0.8845	0.8908	0.8937	0.8950	0.8956	0.8959
D	0.0594	0.0832	0.0945	0.0996	0.1020	0.1030	0.1035	0.1037	0.1038	0.1039
F	0.0060	0.0010	0.0007	0.0003	0.0001	0.0001	0	0	0	0
LTFU	0.0706	0.0133	0.0085	0.0036	0.0017	0.0008	0.0003	0.0002	0.0001	0
MT4	0.0095	0.0026	0.0014	0.0006	0.0003	0.0001	0.0001	0	0	0
NC	0.0017	0.0002	0.0002	0.0001	0	0	0	0	0	0
TC	0.1592	0.1246	0.0501	0.0237	0.0107	0.0049	0.0022	0.0010	0.0005	0.0002
TO	0.0258	0.0063	0.0035	0.0015	0.0007	0.0003	0.0001	0.0001	0	0

Table 4.3 shows the n-step transition probabilities for the patients who were MTB Not Detected.

Table 4.3. n-Step Transition Probabilities for MTB Not Detected

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.0204	0.4766	0.6270	0.7029	0.7365	0.7520	0.7590	0.7622	0.7637	0.7643
D	0.1224	0.1847	0.2120	0.2246	0.2303	0.2329	0.2341	0.2347	0.2349	0.2350
F	0	0.0041	0.0014	0.0007	0.0003	0.0001	0.0001	0	0	0
LTFU	0.0238	0.0523	0.0184	0.0091	0.0040	0.0019	0.0008	0.0004	0.0002	0.0001
MT4	0.0068	0.0076	0.0032	0.0015	0.0007	0.0003	0.0001	0.0001	0	0
NC	0	0.0011	0.0004	0.0002	0.0001	0	0	0	0	0
TC	0.8062	0.2526	0.1297	0.0572	0.0263	0.0120	0.0054	0.0025	0.0011	0.0005
TO	0.0204	0.0208	0.0080	0.0038	0.0017	0.0008	0.0004	0.0002	0.0001	0

Table 4.4 shows the n-step transition probabilities for the patients who were Rifampicin Resistant.

Table 4.4. n-Step Transition Probabilities for Rifampicin Resistant

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.4754	0.6962	0.7900	0.8334	0.8531	0.8621	0.8662	0.8680	0.8689	0.8693
D	0.0656	0.1010	0.1170	0.1243	0.1276	0.1291	0.1298	0.1302	0.1303	0.1304
F	0.0164	0.0024	0.0009	0.0004	0.0002	0.0001	0	0	0	0
LTFU	0.0656	0.0266	0.0113	0.0052	0.0024	0.0011	0.0005	0.0002	0.0001	0
MT4	0.0327	0.0046	0.0019	0.0009	0.0004	0.0002	0.0001	0	0	0
NC	0	0.0005	0.0002	0.0001	0	0	0	0	0	0
TC	0.3443	0.1585	0.0739	0.0335	0.0153	0.0070	0.0032	0.0014	0.0007	0.0003
TO	0	0.0102	0.0048	0.0022	0.0010	0.0005	0.0002	0.0001	0	0

Table 4.5 shows the n-step transition probabilities for the patients who were Not Rifampicin Resistant.

Table 4.5. n-Step Transition Probabilities for Not Rifampicin Resistant

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.5398	0.7104	0.7982	0.8369	0.8547	0.8628	0.8665	0.8682	0.8690	0.8693
D	0.0724	0.1038	0.1183	0.1249	0.1279	0.1292	0.1299	0.1301	0.1303	0.1303
F	0.0043	0.0016	0.0008	0.0004	0.0002	0.0001	0	0	0	0
LTFU	0.0609	0.0209	0.0105	0.0047	0.0021	0.0010	0.0004	0.0002	0.0001	0
MT4	0.0079	0.0036	0.0017	0.0008	0.0004	0.0002	0.0001	0	0	0
NC	0.0014	0.0004	0.0002	0.0001	0	0	0	0	0	0
TC	0.2875	0.1501	0.0658	0.0303	0.0138	0.0063	0.0029	0.0013	0.0006	0.0003
TO	0.0258	0.0092	0.0044	0.0020	0.0009	0.0004	0.0002	0.0001	0	0

Table 4.6 shows the n-step transition probabilities for the patients who had Pulmonary TB.

Table 4.6. n-Step Transition Probabilities for pulmonary TB

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.5605	0.7201	0.8052	0.8424	0.8596	0.8674	0.8709	0.8725	0.8733	0.8736
D	0.0704	0.1005	0.1145	0.1208	0.1237	0.1250	0.1256	0.1259	0.1260	0.1261
F	0.0050	0.0015	0.0008	0.0003	0.0002	0.0001	0	0	0	0
LTFU	0.0632	0.0197	0.0102	0.0045	0.0021	0.0009	0.0004	0.0002	0.0001	0
MT4	0.0086	0.0034	0.0017	0.0007	0.0003	0.0002	0.0001	0	0	0
NC	0.0014	0.0004	0.0002	0.0001	0	0	0	0	0	0
TC	0.2665	0.1456	0.0632	0.0292	0.0132	0.0060	0.0028	0.0013	0.0006	0.0003
TO	0.0244	0.0087	0.0043	0.0019	0.0009	0.0004	0.0002	0.0001	0	0

Table 4.7 shows the n-step transition probabilities for the patients who had Extra-Pulmonary TB.

Table 4.7. n-Step Transition Probabilities for Extra-Pulmonary TB

$P^{(n)}$	$P^{(1)}$	$P^{(2)}$	$P^{(3)}$	$P^{(4)}$	$P^{(5)}$	$P^{(6)}$	$P^{(7)}$	$P^{(8)}$	$P^{(9)}$	$P^{(10)}$
C	0.0313	0.4866	0.6386	0.7150	0.7489	0.7644	0.7715	0.7747	0.7762	0.7769
D	0.1094	0.1719	0.1993	0.2120	0.2177	0.2204	0.2216	0.2221	0.2224	0.2225
F	0	0.0042	0.0014	0.0007	0.0003	0.0001	0.0001	0	0	0
LTFU	0.0156	0.0522	0.0186	0.0091	0.0041	0.0019	0.0009	0.0004	0.0002	0.0001
MT4	0.0156	0.0080	0.0032	0.0015	0.0007	0.0003	0.0001	0.0001	0	0
NC	0	0.0011	0.0004	0.0002	0.0001	0	0	0	0	0
TC	0.7968	0.2552	0.1304	0.0576	0.0265	0.0120	0.0055	0.0025	0.0011	0.005
TO	0.0313	0.0207	0.0081	0.0039	0.0017	0.0008	0.0004	0.0002	0.0001	0

4.3.4 Fundamental Matrix

As was shown in equation 3.18, the Fundamental matrix gives the steady-state probabilities of moving from the non-absorbing states to the absorbing states. Thus the Fundamental matrix is given by;

$$(I-Q)^{-1}R = \begin{pmatrix} 0.8961 & 0.1039 \\ 0.7648 & 0.2351 \\ 0.8696 & 0.1304 \\ 0.8696 & 0.1304 \\ 0.8738 & 0.1261 \\ 0.7774 & 0.2226 \end{pmatrix} \tag{4.4}$$

which refers to the probability of patients' moving from Non-Absorbing to Absorbing States in the long run within the program.

4.4 Discussion

From the dataset, 95.6% of the patients were diagnosed with Pulmonary (P) TB while 4.4% of them were diagnosed with Extra-Pulmonary (EP) TB. Among the 1,456 patients diagnosed with either Pulmonary or Extra-Pulmonary TB, 53.71% were cured (C), 7.21% died (D), 0.48% got a treatment failure (F), 6.11% were lost to follow-up (LTFU), 0.89% were moved to category 4 treatment (MT4), 0.14% had not completed treatment (NC), 28.98% had completed treatment (TC) and 2.47% patients were transferred out (TO).

In relation to developing resistance for Rifampicin regimen among the patient placed on TB treatment, 4.19% of the patients developed resistance while 95.81% did not develop resistance. In the n-Step transition probability matrix, transition from Absorbing to non-absorbing states (C/D to F, LTFU, MT4, NC, TC, TO) gave a zero probability as none of the persons in the cured/dead states exited from those states. There was a gradual increase in probability on transitions from the non-absorbing states (MD, MND, RR, NRR, P and EP) to cured/dead state as the number of years advanced from 1 to 10, although the proportion of persons transiting to cure was higher than those transiting to death. However, transition from those non-absorbing states to again non-absorbing states (MD, MND, RR, NRR, P and EP to F, LTFU, MT4, NC, TC and TO) steadily decline from 80.62% for MND to TC in the 1^{st} year, which had the highest probability, to 0 for most of their transition in the 10th year.

In table 4.2, 66.78% of the MTB detected patients were cured in the 1^{st} year, the proportion increasing to 89.59% in the 10^{th} year. Conversely, 5.94% of the same patients died in the 1^{st} year, the value increasing to 10.39% in the 10^{th} year. 0.17% and 2.58% did not complete treatment and were transferred out of the facility by the end of the 1^{st} year. their proportion gradually declined to 0 by the 10^{th} year.

In table 4.4, the proportion of Rifampicin resistant patients was 47.54% for those who were cured and 6.56% for those who died in the 1^{st} year. Their proportion gradually increasing over 10 years to 86.93% and 13.04%.The proportion of those whose treatment failed (1.64%) or were lost to follow up (6.56%) was higher for those who developed Rifampicin resistance as compared to those who didn't at 0.43% and 6.09% in table 4.5 respectively.

In table 4.6 and 4.7, the proportion of those cured was 56.06% and 3.13% for the patients diagnosed with Pulmonary TB and Extra-Pulmonary TB. on the other hand, the proportion of those who died was 7.04% and 10.94% for the patients with Pulmonary and Extra-Pulmonary TB in the 1^{st} year. The proportion cured from Pulmonary TB was very high in comparison to those cured from Extra-Pulmonary TB. Then for those who died, the proportion was higher in Extra-Pulmonary as compared to Pulmonary TB patients, despite none of the patients having Extra-Pulmonary TB realized a treatment failure or did not complete treatment in that year.

In the long run, at the 13^{th} year, the patients cease to transit from non-absorbing to non-absorbing states as all of them would either be cured or dead. Matrix 4.4 shows that 89.61%, 76.48%, 86.96%, 86.96%, 87.38% and 77.74% of those with MTB-Detected, MTB-Not detected, Rifampicin resistance, no Rifampicin resistance, Pulmonary TB and Extra-Pulmonary TB respectively will be cured. While 10.39%, 23.51%, 13.04%, 13.04%, 12.61% and 22.26% of them with MTB-Detected, MTB-Not detected, Rifampicin resistance, no Rifampicin resistance, Pulmonary TB and Extra-Pulmonary TB respectively will have died.

CHAPTER 5
CONCLUSION

5.1 Introduction

In this chapter, TB treatment outcome dynamics, the transition from the first to the 13^{th} year projection probabilities and the absorbing rates will be discussed. Of importance will be the group that tested positive for MTB, developed resistance against Rifampicin regimen and had either Pulmonary or Extra-Pulmonary TB. Section 5.2 which follows present the summary of findings.

5.2 Summary

During the analysis of 1,456 patients' data on TB, 53.71% were cured, 7.21% died, 0.48% had a treatment failure, 6.11% were lost to follow-up, 0.89% moved to treatment category four, 0.14% had not completed treatment, 28.98% had completed treatment and 2.47% were transferred out to a referral facility or the patients' preferred facility. Most of the patients had pulmonary TB (95.6%) while only 4.4% had Extra-Pulmonary TB. In regards to developing resistance to Rifampicin regimen, 4.19% developed resistance and a majority of them (95.81%) did not.

Transition from absorbing to absorbing states had an identity matrix of probabilities, transition from absorbing to non-absorbing states produced a zero matrix while transition from non-absorbing to absorbing states or from non-absorbing to non-absorbing states produced probabilities ranging from 0.8062 which was the highest to 0 in the 1^{st} year. Specifically, 66.78% of the patients who tested positive for MTB were cured, with the proportion increasing to 89.59% in the 10^{th} year. Conversely, 5.94% of the positive MTB patients died, with their number rising to 10.39% at the 10^{th} year. On the other hand, 15.92% of the patients who tested positive for MTB completed treatment. Contrasting those who did not complete treatment and had tested positive for MTB with those who completed treatment, 0.17% did not complete treatment within the first year but ended up completing after the 4^{th} year, while 15.92% completed treatment by the 1^{st} year with the rest completing theirs at the 9^{th} year. Those who were lost to follow-up were more than those transferred out of the facility in the first year, 7.06% and 2.58% respectively but their proportion declined to 0.01% and 0 in the 10^{th} year. With regards to developing resistance, 47.54% developed resistance to Rifampicin and were cured, 6.56% died and there proportions increased steadily to 86.93% and 13.04% respectively at the 10^{th} year. Although neither of them were transferred out nor did not complete treatment, 6.56% were lost to follow-up. Comparing those who had Pulmonary TB against those who had Extra-pulmonary TB, 56.05% and 3.13% were cured and their proportions increased to 87.36% and 77.69% respectively at the 10^{th} year. However, more

deaths inclined towards those with Extra-Pulmonary TB than those with Pulmonary TB, having a proportion of 10.94% and 7.04% during the first year to 22.25% and 12.61% respectively at the 10^{th} year. Furthermore, 79.68% of those with Extra-Pulmonary TB completed treatment and their proportion was higher in comparison to those with Pulmonary TB and had completed treatment (26.65%) in the 1^{st} year.

After projection upto the 13^{th} year, the absorbing rates indicated that 89.61%, 76.48%, 86.96%, 86.96%, 87.38% and 77.74% of the patients with MTB detected, MTB-not detected, developed Rifampicin, did not develop resistance, with pulmonary and Extra-Pulmonary TB respectively will be cured. Conversely, 10.39%, 23.51%, 13.04%,13.04%, 12.61% and 22.26% of the patients with MTB detected, MTB-not detected, developed Rifampicin resistance, did not develop resistance, with pulmonary and Extra-Pulmonary TB respectively will have died.

5.3 Conclusion

Since the End TB Strategy envisions a fatality rate of 6.5% by 2025, the 2017 data indicated a slightly higher yearly fatality rate for Kenyans towards that end. While the increasing proportion of cure for the MTB positive patients plus those who develop resistance is commendable, the worrying steady increase in the projected proportion of those who die from MTB needs a redress. A need also to reduce the proportion of those patients that are lost to follow-up and find out why those with Extra-Pulmonary TB are more at risk of dying than those with Pulmonary TB despite their efforts to complete treatment plus not having treatment failures. Overly, the proportion of those dying from the various non-absorbing states in the long run was more than 10%, which needs to be lowered to below 6.5% before 2025.

CHAPTER 6
FUTURE RESEARCH

This study focused on TB patient who had been followed for only one year to develop the transition probabilities. The treatment regimen was narrowed to Rifampicin drug but Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) drugs at different dosage levels and phases are also administered to TB patients. Future studies can consider expanding the follow-up period so as to check whether it has a significant impact to the time until the absorption rates is achieved and include the other TB treatment regimens in evaluating resistance development.

Future researchers can also find out why the proportion of Extra-pulmonary TB patients who die is higher than those with Pulmonary TB despite their efforts to complete treatment and not realize a treatment failure, in the country.

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