MODELLING THE TRANSMISSION OF TUBERCULOSIS IN CLOSED SPACE USING MICROSCOPIC PEDESTRIAN SIMULATION

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by

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When you meet people, show real appreciation, and then genuine curiosity

–Martha Beck

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LIST OF ABBREVIATIONS

TB	Tuberculosis
MTB	Mycobacterium Tuberculosis
SIR	Susceptible-Infected-Recovered/Removed
SI	Susceptible-Infected
CA	Cellular Automata
SFM	Social force model
ABM	Agent-based model

GLOSSARY

MICROSCOPIC SIMULATION	A type of computerized analysis tools that conduct in-depth analysis of activities such as traffic flow at an intersection, financial transactions, or the spread of disease in a population.
PEDESTRIAN SIMULATION	Pedestrian simulation is a computational technique used to model and analyze the movement and behavior of crowds of pedestrians in various scenarios, such as public spaces, transportation systems, and emergency evacuation situations. The goal is to study and understand pedestrian behavior, interactions, and flow patterns, as well as to evaluate the design and safety of environments for pedestrian use.
MICROSCOPIC PEDESTRIAN SIMULATION	Microscopic pedestrian simulation is a type of computer simulation that models the individual behavior and interactions of pedestrians in a crowd (Teknomo et al., 2016). The goal of microscopic pedestrian simulation is to provide a detailed and realistic representation of pedestrian behavior in various scenarios. The results of the simulation can be used to study pedestrian flow patterns, evaluate the design and safety of environments for pedestrian use, and support decision-making in urban planning and transportation planning.

CLOSED SPACE	A closed space refers to an enclosed area with limited or restricted access. A closed space may refer to a room or building with walls or can also be refer to a confined region of a system that is isolated from the surrounding environment.

PERMODELAN PENULARAN TUBERKULOSIS DIDALAM RUANG TERTUTUP MENGGUNAKAN SIMULASI PEJALAN KAKI MIKROSKOPIK

ABSTRAK

Akibat wabak COVID-19, kematian akibat Tuberculosis meningkat untuk kali pertama dalam lebih dari sedekad. Tuberculosis adalah pembunuh berjangkit kedua (selepas COVID-19) dan telah wujud selama berabad-abad. Walaupun vaksin yang cukup tersedia, penyakit ini masih tersebar di seluruh dunia dan menjadi salah satu penyakit utama yang menyumbangan kepada kadar kematian dunia. Tesis ini bertujuan untuk mensimulasikan bagaimana penyakit ini berjangkit dengan menggunakan model *Susceptible-Infected* (SI). Semasa penyelidikan berlangsung, didapati bahawa kajian epidemiologi yang menggunakan kaedah kompartmen mengabaikan heterogeniti interaksi sosial antara manusia. Oleh itu, penyelidikan ini mencadangkan penggabungan model *Social Force* dengan pendekatan SI untuk meniru interaksi manusia yang realistik sambil menangkap proses penghantaran patogen dari satu orang ke orang lain. Tesis ini bertujuan untuk mensimulasikan pergerakan dan interaksi antara orang yang dijangkiti dan orang yang sihat dalam ruang tertutup dengan kehadiran penyakit dengan menggunakan kerangka kerja berorientasikan dan mengikuti tetapan seperti dalam penyelidikan ini. Rangka kerja metodologi yang dicadangkan boleh dibahagikan kepada tiga tahap utama: perincian masalah, pembinaan model dan juga analisis dan penilaian model, yang merupakan proses berperingkat yang ditetapkan untuk mencapai objektif. Disebabkan oleh penularan TB secara rawak, kajian ini mencipta parameter kebarangkalian penularan infeksi, dikenali sebagai P_c, yang merujuk kepada tempoh masa di mana patogen boleh teryebar dan menjangkiti orang lain. Berdasarkan simulasi, kami menemukan bahwa model simulasi menghasilkan $R_0 > 1$ dan masa jangkitan jatuh antara enam jam dan dua tahun. Eksperimen menunjukkan hasil yang menjanjikan dengan kadar penghantaran 0.0135 hingga 0.1372 yang meniru nilai sebenar kadar penghantaran TB dalam persekitaran dunia sebenar.

MODELLING THE TRANSMISSION OF TUBERCULOSIS IN CLOSED SPACE USING MICROSCOPIC PEDESTRIAN SIMULATION

ABSTRACT

Due to the infamous COVID-19 pandemic, Tuberculosis deaths are rising for the first time in more than a decade. Tuberculosis is the second (after COVID-19) deadliest infectious killer that has been exists in this world for centuries. Despite the availability of adequate vaccination, it is still roamed around the world and became one of the leading diseases that contribute significantly to the world's mortality rate. Therefore, this works aims to simulate how this infectious disease spread by utilizing the Susceptible-Infected (SI) model. As the research progresses, it is found that the general epidemiological studies that uses compartmental method ignore the heterogeneous of social interaction between humans. Thus, this research has proposed the integration of the Social Force model with the SI approach to imitate realistic human interaction while capturing the pathogen transmission process from one person to another. This work aims to simulate the movement and interaction between infected person and another susceptible person in a closed space when an infectious disease is present and develop with a process-oriented methodology framework following this setting set in the research. The methodological framework proposed is divided into three major stages: problem characterization, model construction also model analysis and evaluation, which work as step-by-step processes to achieve the objective sets. Due to the randomness of TB transmission, this study creates a parameter of the probability of infection transmission, denoted as P_c, which refers to the duration of

time where the pathogen might spread and infect others. Based on the simulation, we found that the simulation model generates $R_0 > 1$ and the infection time falls between six hours and two years. Hence, the experiments show a promising result with 0.0135 to 0.1372 of transmission rate that mimics the actual value of TB transmission rate in a real-world setting.

CHAPTER 1

INTRODUCTION

1.1 Introduction

As a communicable disease, Tuberculosis (TB) is known to exist for a very long time and still manages to survive to this day. In addition, many medications and vaccination available to treat this illness. This research attempted to identify and employ a suitable method to model the transmissibility of TB in a closed space. For such a modelling problem, the combination of microscopic pedestrian movement model and a compartmental model is used in solving the research dilemma. This chapter presents the introduction to the core of the study including the current situation of TB especially in Malaysia, discussion on problem statements, research questions and objectives, research scope, methodology used, expected contribution and lastly, thesis outline.

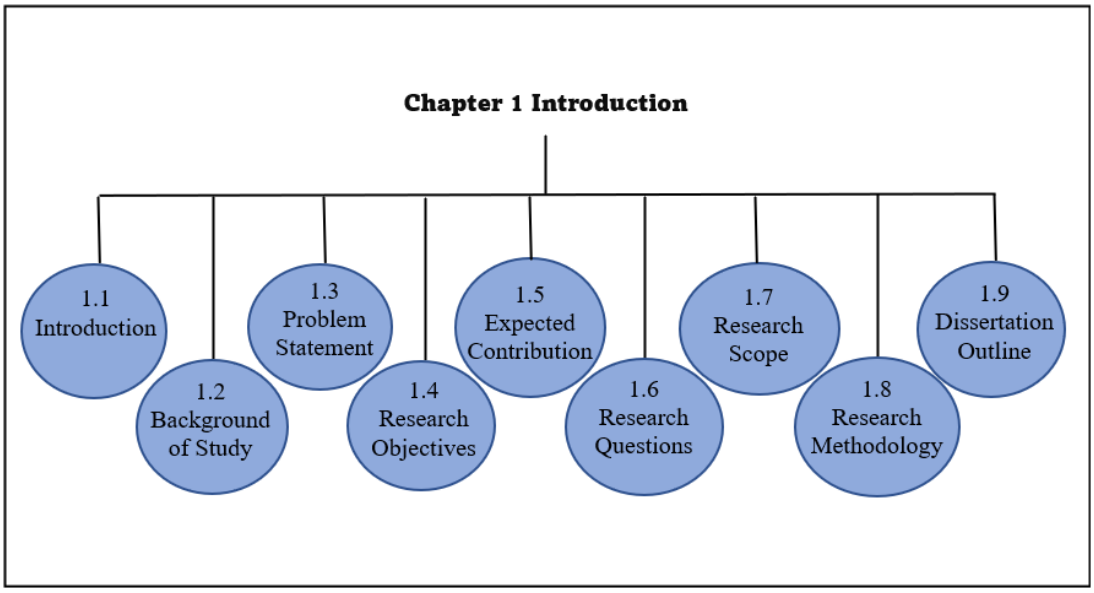

Figure 1.1 Chapter 1 Content Coverage

1.2 Background of Study

Tuberculosis (TB) is an ancient communicable disease that was discovered centuries ago (Kapur et al., 1994; Parsons, 1922; Rundi, 2010) where the traces of this disease have been found not only in humans but also in animals (Parsons, 1922). This chronic disease continues to contribute to the world mortality rate despite the availability of effective vaccination (Kaur et al., 2020). According to World Health Organization (2021), the death associated with TB are soaring for the first time in more than a decade since the infamous COVID-19 pandemic was introduced to the world. It is stated that TB is caused by bacteria named bacillus *Mycobacterium tuberculosis* (MTB) (Parsons, 1922; Rashid Ali et al., 2015; Rundi, 2010; Schlossberg, 2020; Smith, 2003) which is expelled into the air by the sick and has been maintaining its rank to be in the top 10 causes of death around the globe for a single infectious agent (World Health Organization, 2020). TB was mainly associated with the male population as the cases of TB involving men were significantly higher compared to women (Abdul Rasam et al., 2020; Jetan et al., 2010; Nissapatorn et al., 2005; Venugopalan, 2004; World Health Organization, 2020) which can be seen especially on pulmonary TB cases (Elamin et al., 2004; Ismail, 2004; Nissapatorn et al., 2005). The number of death linked to TB was also higher in the population of males (Swarna Nantha, 2014).

Table 1.1 shows the number of TB cases in Malaysia according to its states alongside the TB death case, TB notification rate, and TB mortality rate per 100,000 population in 2015. Based on Table 1.1, the most affected state is Sabah with 4464 cases recorded in the same year followed by Selangor with 4429 cases. The notification rate of TB per 100,000 people in Sabah also recorded the highest with

126.0 which is almost twice than the national average of TB notification rate. The least cases recorded was in WP Labuan with 16 cases and the TB death case recoded in 2015 is half of the TB cases registered in the same year. Even so, the TB notification rate is the second highest with 119.8 due to the small population that resides the island.

Table 1.1 Total TB cases, Notification Rate, TB Death and TB Mortality Rate in every states of Malaysia in 2015 (Malaysia, 2016)

States	Total Case	TB Notification Rate (Per 100,000 population)	TB Death	TB Mortality Rate (Per 100,000 population)
Johor	2409	67.8	135	3.8
Kedah	1279	61.7	142	6.8
Kelantan	1233	71.8	93	5.4
Melaka	513	58.8	39	4.5
Negeri Sembilan	667	60.7	60	5.5
Pahang	1657	57.7	80	4.9
Perak	130	66.9	162	6.5
Perlis	130	52.8	14	5.7
Pulau Pinang	1283	77.1	132	7.9
Sabah	**4464**	**126.0**	**264**	**7.4**
Sarawak	2575	97.7	195	7.4
Selangor	4429	75.4	255	4.3
Terengganu	710	61.6	58	5.0
WP Kuala Lumpur	1819	98.0	58	3.1
WP Labuan	16	119.8	9	9.3
MALAYSIA	**24220**	**79.4**	**1696**	**5.5**

TB is also nicknamed “the disease of poverty” as most people who suffer from this infection come from countries that face economic distress, vulnerability, marginalization, stigma and discrimination (Liew et al., 2015; World Health Organization, 2020). Malaysia is classified as an upper-middle-income country located in the South-East Asia region, where the highest TB cases have been reported for several consecutive years (Kaur et al., 2020; World Health Organization, 2020). Currently, Malaysia is considered an intermediate level for TB affliction as the national notification rate is less than 100 per 100,000 populations (Malaysia, 2016) but this country is located between countries with a high level of TB burden, such as Indonesia, Philippines, Thailand, Cambodia and Vietnam (Kaur et al., 2020; Liew et al., 2015; World Health Organization, 2020). Over the years, Malaysia recorded a significant increment in the notification rate of TB cases which in 2010 were 68.4 cases per 100,00 populations and 79.6 cases per 100,00 populations in 2015 (Malaysia, 2016). In order to monitor TB transmission all over the country, Malaysia established a National TB Control Program in 1961 and a TB registry in 1973 with the aim to halves the TB reported cases (Liew et al., 2015).

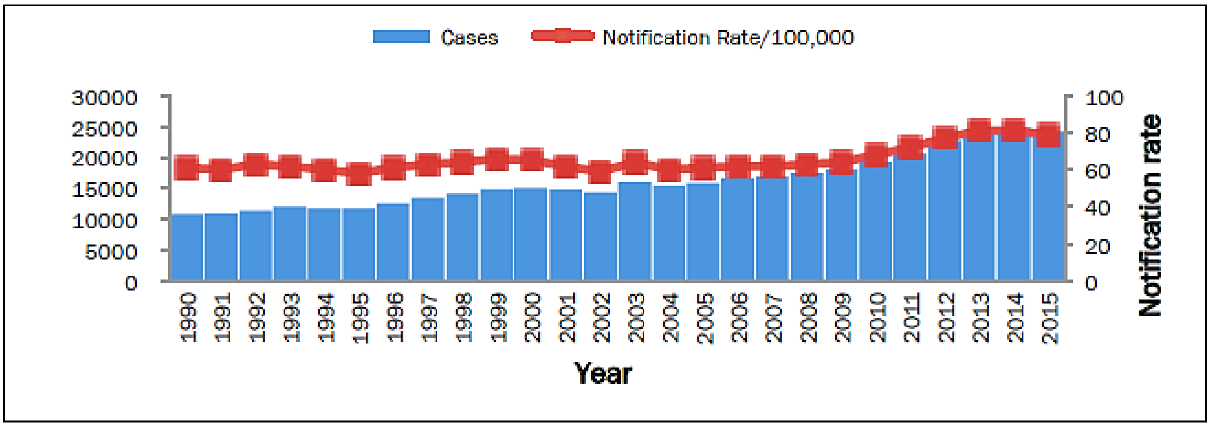

Figure 1.2 TB Notification Rate in Malaysia, 1990-2015 (Malaysia, 2016)

For 16 years, starting from the year 2000 to 2015, Malaysia's TB mortality rate of TB was stable between 4.5 to 5.5 per 100,000 population (Malaysia, 2016). Table 1.2 below shows the recorded death rate associated with TB in the country. Despite all the progress shown by Malaysia's TB Control Program, many challenges still need to be overcome. For instance, the low case detection of TB. According to Malaysia (2016), the number of cases of TB detected in Malaysia is still lower than the World Health Organization estimates. In 2014 alone, Malaysia's incidence rate was estimated to be 103 cases per 100,000 population while only 81 cases per 100,000 population were recorded. Malaysia (2016) indicated that about 6000 cases were yet undetected in the nation.

Table 1.2 Death Rate associated with Tuberculosis in Malaysia (D. o. S. Malaysia, 2021)

Year	Death rate (Per 100,000 population)
2000	5.57
2001	5.52
2002	5.27
2003	4.11
2004	5.26
2005	5.50
2006	5.37
2007	5.53
2008	5.49
2009	5.59
2010	5.50
2011	5.68
2012	4.82
2013	5.37
2014	5.33
2015	5.56
2016	6.14

Out of all the states affected by infectious cases in all forms that have risen steadily over the past few years, the state of Sabah was heavily impacted by TB (Dony et al., 2004; Jelip et al., 2004; Rundi, 2010). The following Figure 1.3 illustrates the number of reported cases and the number of death cases caused by TB in Sabah state for five years, from 2014 to 2018. Sabah, Malaysia, located north of Borneo, has contributed 20% to 30% of Malaysia's TB cases each year since 2012 while having only 10% of the country's total population (Avoi & Liaw, 2021; Goroh et al., 2020; Rundi et al., 2011). In 2019 alone, Avoi and Liaw (2021) reported that Malaysia's TB incidence rate was 92 cases per 100,000 population, with an estimated mortality rate of 4 cases per 100,000 population per year. Compared to the national record, Sabah documented 128 cases per 100,000 population for incidence rate and an 8% rate of fatality for TB infections alone (Avoi & Liaw, 2021). It has been discovered that Sabah's TB epidemic is mainly due to delays in seeking health treatment and limited admission to TB care (Avoi & Liaw, 2021; Rashid Ali et al., 2015). Sabah also recorded the highest cases of TB among health care workers (Jelip et al., 2004).

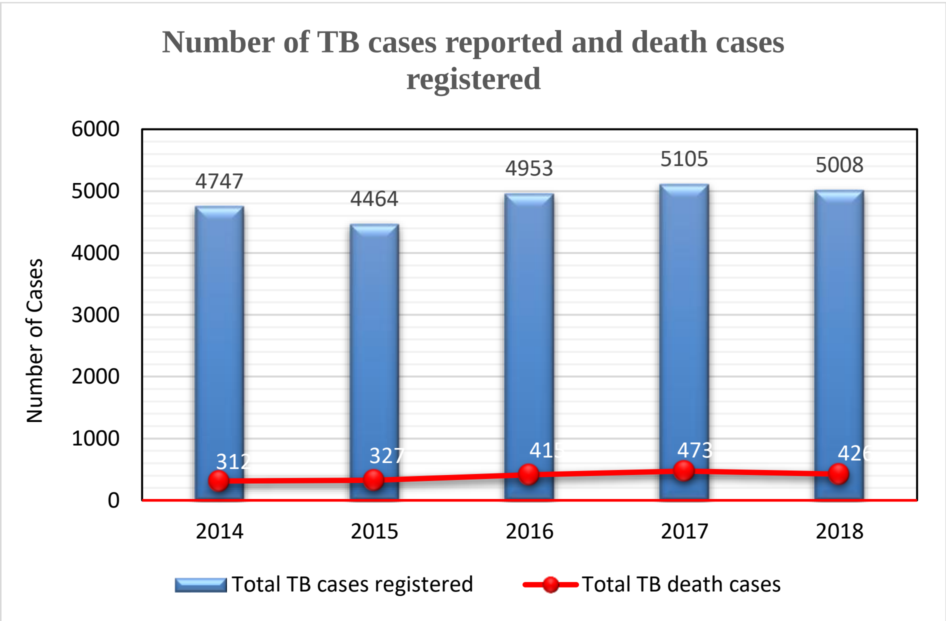

Figure 1.3 Number of reported TB cases and TB death cases by year in Sabah, 2014-2018 (Avoi & Liaw, 2021)

Abdul Rasam et al. (2018) added that the increment in case numbers in a place is slightly related to and non-forested area of the state. Kaur et al. (2020) also stated that close spaces such as shopping complexes, public transport, and public recreational areas with a high concentration of humans provide a very conducive scenario for TB to be transmitted. This statement can be proven by looking at the cases recorded in a closed area such as the prison. Table 1.3 below illustrates the number of TB cases in prison in Malaysia from the year 2011 to 2015. In order to understand TB transmission in a local setting, Abdul Rasam et al. (2020) suggested that it is crucial to gain the primary data on TB from the participation of the public and actual site observation. However, Malaysia notified TB cases information system (MyTB) only obtained their data from patients' records and secondary data, which is not enough to assess the real situation (Rundi, 2010).

Table 1.3 Number of TB cases in prison, Malaysia (2011-2015) (Malaysia, 2016)

Year	TB cases in prison	TB incidence in prison (per 100,000 population)	TB cases in population	Incidence in population
2011	272	774.8	20666	71.3
2012	231	608.0	22710	77.4
2013	219	518.2	24071	81.0
2014	340	683.6	24711	82.1
2015	344	653.8	24220	79.4

In Malaysia, the follow-up and monitoring TB patients with anti-TB treatment is by hospital visit for about five times in a duration of six months following the specific regimen (M. o. H. Malaysia, 2021). Patients who show persistent smear positive will be referred to the specialists for further management while patients who completes their treatment will be doing self-monitoring if any symptoms of TB recurrence. However, if any complication happen, the patient will be referred to respiratory physicians (M. o. H. Malaysia, 2021). Since contact at higher risk for TB infection are those who spend a lot of time and share the same airspace with the patients, the targeted community are the patient's household or workplace. Due to the unspecific amount of time for a person to contact TB disease, there is no technological advances such as MySejahtera developed for TB patients contact tracing.

There are two crucial steps needed to be carried out to understand the pathogens' spread: (1) Identify and quantify the behavior, environment and social factors that affect the transmission of the disease and (2) Generate larger-scale patterns of disease transmission. Instead of focusing on one-to-one transmission, this study aims to simulate the transmission of the disease in a closed setting where several humans exist. Before diving into the possible parameters to quantify the transmission of the disease, understanding the clinical part of this illness is a must.

1.3 Problem Statement

Tuberculosis is an ancient disease that still roams around the globe and kills thousands of lives every year. TB is known to have mutated into drug-resistant types, and the effect on human worsen if an individual suffers other chronic diseases. Currently, researchers focus more on the effect of TB when other chronic illnesses present. However, not much study has been done on the transmissibility of the disease, especially in a closed setting. By incorporating the pedestrian movement, the correlation study of contact rates and infectious rates can be modelled if the parameters that matter are known. At present, many details regarding the ecology, genetics, microbiology, and pathology of Tuberculosis are already known. Unfortunately, even with all the technological advances, humankind still does not have a robust answer on how likely multiple waves of re-emergence of infectious diseases are and what types of interventions may be applied to stop the spread of these diseases. The main problems are: (1) the continuous and everlasting mutations of the pathogens and (2) the complexity of the disease transmission mechanism.

Tactlessly, in a real-life predicament, even if the research succeeds in coming up with a vaccine tailor-made for an emerged pathogens strain, it is doubtful that it will put a stop to the endemic. Therefore, by pinpointing the parameters that may involve in the pedestrian simulation on the movement, behavior and interaction related to the disease transmission, many developments and advancements in quantitative approaches could be made, which may lead to potentially transformative progress in the study of TB and beyond. According to Wang (2020), many countries, especially China, implemented strong disease control measures, which include large-scale quarantine, strict isolation of infected individuals, expanded medical facilities and social distancing as precautions to reduce the transmission of the air-borne disease which can be very effective in some places in the world. However, the transmission rates may vary depending on the epidemiological and socioeconomic status of a country which can severally impact the control outbreak. When the infection level becomes high, people will voluntary take action to protect themselves and their families from infected individuals and contaminated environments, which may decrease the actual transmission rates with an ascending outbreak case. Therefore, by focusing on the strategy of pedestrian movement, every individual can implement it to protect themselves.

The spread of infectious disease in a crowded environments especially in closed setting is a major concern for public health due to the limited spaces which lead to the increment of interaction between pedestrians. Understanding and modeling the behavior and interactions of individuals in this nature is crucial for predicting and mitigating the spread of disease. While macroscopic models provide valuable insights into the behavior of large groups of people, they lack the resolution to accurately capture the interactions and movements of individual pedestrians, which are key factors in the spread of disease. Microscopic pedestrian simulation, which focuses on the behavior and interactions of individual pedestrians, has the potential to provide more accurate representations of disease spread in crowded conditions. However, the development of these models is often complex and computationally intensive, making it challenging to apply them in real-world environments.

The purpose of this research is to develop a microscopic pedestrian simulation framework that can captures the behavior and interactions of individual pedestrians in closed setting, with a focus on the spread of infectious diseases. The framework will incorporate models of disease transmission to represent the spread of disease among individuals. The simulation will be validated through comparison with real-world data. The result of the simulation framework will provide a valuable tool for public health organizations, urban planners, and emergency management agencies to predict and mitigate the spread of disease in closed environments. The framework will also provide a foundation for further research into the spread of infectious diseases in these environments, contributing to the development of more effective strategies for controlling the spread of disease.

1.4 Research Questions

The obvious entities in simulating the disease transmission would be the disease itself and the pedestrian who is present in the confined setting. Vinten-Johansen et al. (2004) stated that to describe and sustained the spread of disease, quantitative framework is needed. However, for infectious disease that transmitted from one person to another, the mobility of the pathogen carrier also need to be considered as it affect the speed of infection to spread (Clancy, 1996). Modelling pedestrian movement can help reduce the impact of a disease by providing insights into how individuals interact and move in public spaces, and how this movement can contribute to the spread of an infectious disease. This knowledge can be used to advise the advancement of interventions aimed at reducing the spread of the disease. Hence, the research questions that are contrived are listed as follows:

(1) What are the quantitative parameters of contact spread and infection spread for TB transmission in a closed area?

(2) How to simulate pedestrian movement and SI model to produce near-realistic simulation?

Consequently, the hypothesis of this research is:

The microscopic pedestrian movement modelling approach following a microscopic simulation conceptual framework can simulate the movement and interaction between an infected person and another person in a closed space when an infectious disease is present. It is noted that the process-oriented methodology framework following this setting is not available.

1.5 Research Objectives

The microscopic pedestrian movement modelling approach following a microscopic simulation conceptual framework can simulate the movement and interaction between an infected person and another person in a closed space when an infectious disease is present. It is noted that the process-oriented methodology framework following this setting is not available. In relation to the research question from the previous sub-section, two research objectives are depicted as follows:

(1) To determine the quantitative parameters of contact and infection rates in closed setting for TB transmission simulation model.

(2) To design a pedestrian simulation with SI model by modeling the movement and interaction between an infected and susceptible pedestrian during the TB transmission process in a closed setting.

1.6 Expected Contribution

The expected outcome of this project is to recognize the correlation between contact rates and infection rates for the transmission of TB infection, which will lead to the identification and analysis of the quantitative parameters associated with the disease spread and the microscopic simulation model. Then, the study will come up with the process-oriented methodology of the microscopic simulation conceptual framework based on the movement and interaction between an infected person and another person in a closed space during the presence of an infectious disease.

Table 1.4 Mapping Research Questions, Objectives and Expected Outcomes

	Objectives	Research Questions	Expected Contribution
1	To determine the quantitative parameters of contact and infection rates in closed setting for TB transmission simulation model.	What are the quantitative parameters of contact spread and infection spread for TB transmission in a closed area?	Recognizing the correlation between contact rates and infection rates for the transmission of TB infection will lead to the identification and analysis of the quantitative parameters associated with the disease spread and the microscopic simulation model.
2	To design a pedestrian simulation with SI model by modeling the movement and interaction between an infected and susceptible pedestrian during the TB transmission process in a closed setting.	How to simulate pedestrian movement be integrated into the SI model to produce near-realistic simulation?	Designing a process-oriented methodology of the microscopic simulation conceptual framework based on the movement and interaction between an infected person and another person in a closed space during the presence of infectious disease.

1.7 Research Scope

Research associated with the field of health specified in communicable disease covers a very large area of study. This research focuses on how the infected individuals move and interact could possibly transmit the disease. The simulation considers that the infected entity who will spread the TB pathogen suffers only from an Active TB with no combination of other illnesses. The pedestrian present in the closed area is considered susceptible to the disease except for the infected individual. The closed space in this study refers to a room where no movement in or out of the area is designed in the simulation, and the pedestrians that will be investigated are only limited to those who are present in the room. The simple representation of the research is illustrated in Figure 1.4.

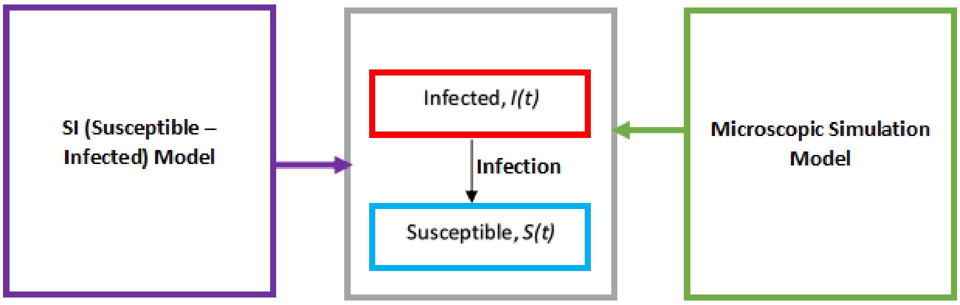

Figure 1.4 Research representation

1.8 Research Methodology

This study aims to devise the pedestrian simulation conceptual framework by modelling the movement and interaction between an infected and susceptible pedestrian during the TB transmission process in a closed setting. The following Figure 1.5 is the methodology framework that will be used in this research. The method can be separated into three stages which include: (1) problem characterization stage, (2) model construction and (3) analysis and evaluation stage. Stage 1 focuses more on understanding the current situation and deciding the suitable model for the situation. In the second stage, it aims to have all the data needed to be plug in into the formulation based on the model chosen in stage one. This stage also expected the simulation was done. The last stage aims to ascertain the formulation done and, eventually, the framework suggested.

Stage 1: Problem Characterization

There are three processes that make up the first stage: understanding of current research situation, insight on disease types and the setting of the experiment, and the decision on models that satisfy the research scope. The purpose of the first process is to understand the current state of TB scenario through the expert opinion such as the researcher in medical field who specialized in TB and through reviewing past literature about TB research. The second process focuses more on the biological features of TB, such as the mechanism of spread and the survivability of the pathogens in a specific setting so that the contact spread, and infection spread of this disease can be known. Since the study simulate the spread of disease from one individual to another, the contact spread, and infection spread is crucial as it determine how fast the disease can be transmitted.

The third process circulate around choosing the best model that fit into description of the research. Since this research has two main domain which are the disease spread and human mobility, the models chosen are epidemiological model and pedestrian simulation model to cover both areas. The details on both models will be discussed in chapter 2, section 2.2, and section 2.3. The last process in this stage is the construction on the formulation of simulation. The formulation will be also divided into two different area following the number of models we decide in the previous process. In the epidemiological part, the formulation will cover the number of total population, the number of infected individual introduced in the beginning of the simulation, the total number of contacts per individual at a time and the number of infection days until the end of the simulation. As for the pedestrian part, forces of attraction towards the destination, forces between pedestrian and other pedestrian in the whole population will be considered. Every parameter with the assumption made to make the simulation work will be further discussed in the later chapter.

Stage 2: Model Construction

The second stage consist of six main processes: data pre-processing, quantification of parameters that affect the bacteria transmission, quantification of parameters that affect pedestrian movement, design the simulation, begin simulation and lastly obtain the result from the simulation. The aim of the first process is to ensure that the data is ready to be used for the next five processes. The second and third process where quantification of parameters that affect both bacteria transmission and pedestrian movement is prepared. In this stage, the data needed will be quantified and set so that the calculation unit is standardized. When every data has been standardized, the formulation of the simulation will be complete. Next, the design of simulation is determined. In this process, the size of setting will be adjusted so it can contained all the population. In the two last processes, the simulation will be run up to ten times and the result on the simulation will be collected. The detailed discussion will be in chapter three and chapter four.

Stage 3: Analysis and Evaluation

In the last stage, the validation process will be done. After obtaining result from the previous stage, the result will be calculated again to matched the real data. After comparing the results with the real data, the validated result will be mark with two different colors as indicator if the result calculated in process 3.1. The Red color box indicate that the result does not fall within the range of real data, while Green color box falls into the range of real data. The result will be further discussed in chapter five.

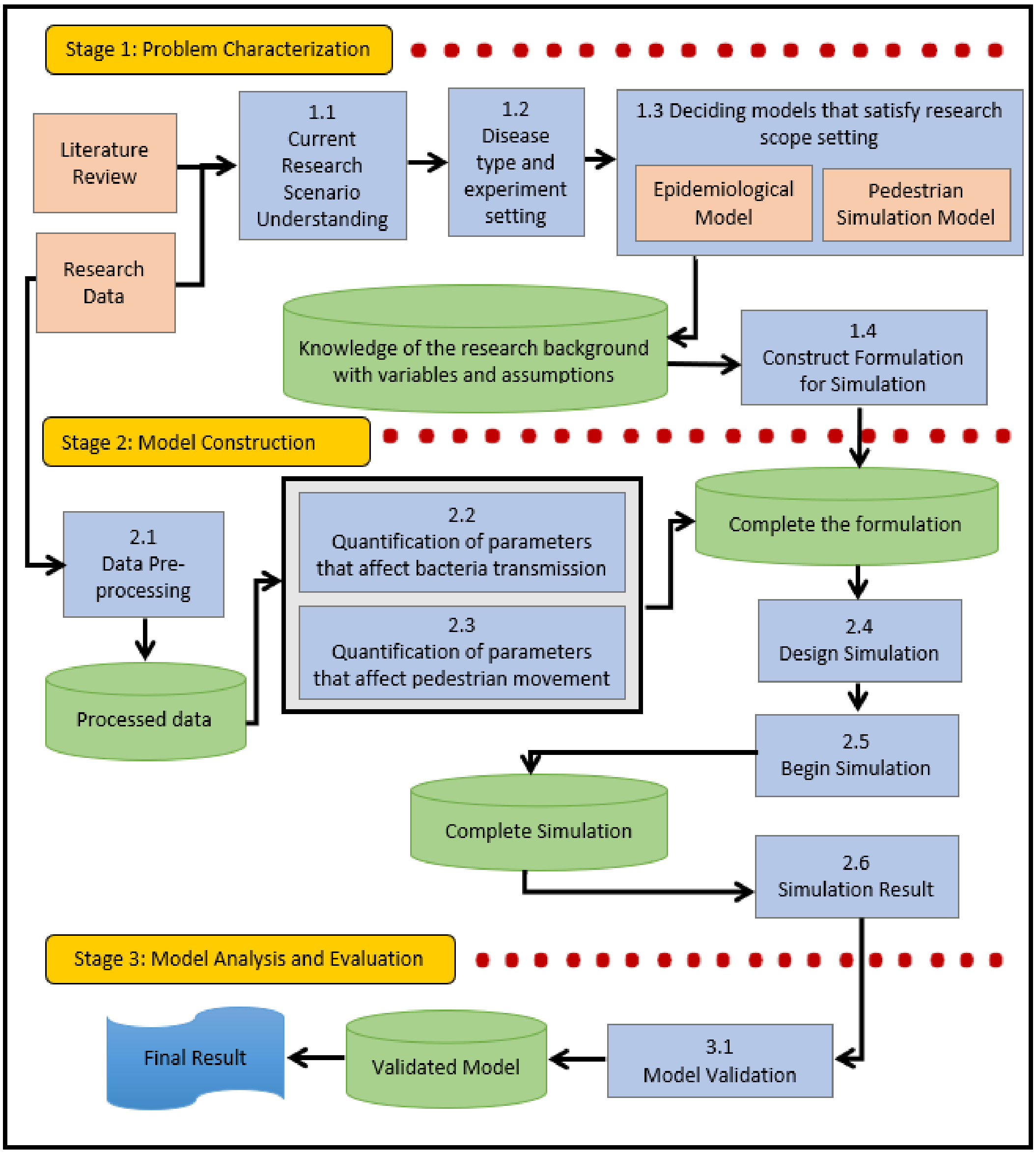

Figure 1.5 Methodology Framework

1.9 Dissertation Outline

The first chapter presents the introduction to the core of the study, discussion of problem statements, research questions and objectives, research scope, expected contribution, methodology used, and lastly, the thesis outline. The second chapter discusses the outcomes from the reviews of the literature on research related to the mathematical model of epidemiology, pedestrian movement during disease spread, types of microscopic pedestrian simulation modelling approaches and other related fields, particularly on the aspects of approaches employed and limitations of these approaches. The third chapter illustrates the processes involved in the first stage of the proposed framework where the research data, potential variables and assumptions are concerned and also presents the formalization of the simulation. The fourth chapter presents the formulation of the intended simulation through implementation of simulation designed. The fifth chapter discusses results analysis and validation processes performed on the model output. The last chapter concludes the entire research by summarizing the whole research and its outcomes, contributions, limitations, and suggestions for future work in the research.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter is dedicated to reviewing and discussing other studies related to this research which covers the understanding of the disease model itself, theories of research, their strength, shortcomings, gaps, and technological advances regarding the current research problems. A fragment of review is on the disease study, mainly on the epidemiological factor and the transmissibility of TB. A significant focus of this chapter is on the approaches - compartmental model and microscopic pedestrian movement model - employed in this study. This chapter is further subdivided into four sections which include the understanding of TB transmission behavior, understanding the modelling of TB, previous studies that combine pedestrian movement and disease spread and lastly, the summary of the chapter.

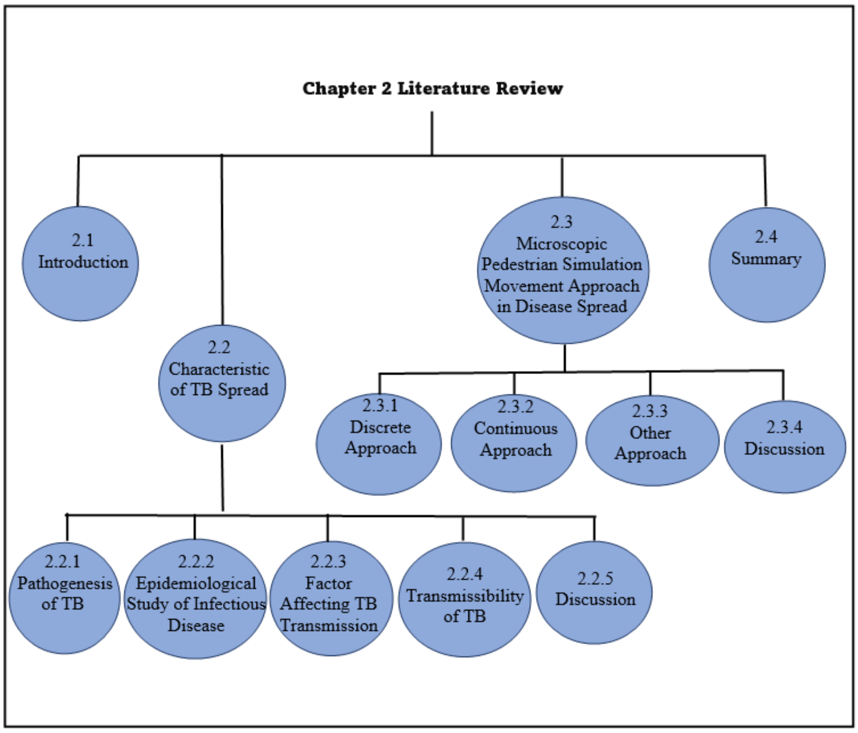

Figure 2.1 Chapter 2 Content Coverage

2.2 Characteristic of Disease Spread

Characteristic of disease spread in this study refers to the pathogenesis of TB, epidemiological study of infectious disease, the transmissibility of TB, and factor affecting TB spread. This sub-chapter aims to review the compartmental part of the study and identify the major details of Stage 1 part 1.2 from the methodology framework suggested (Figure 1.5).

2.2.1 Pathogenesis of TB

First and foremost, before further exploring deeper into this research, the pathogenesis of TB needs to be known. As mentioned before, TB is one of the diseases that are closely related to mammals, including humans and other animals that are warm-blooded vertebrates with hair (Parsons, 1922). Even so, different bacteria are responsible for these two different beings. For animals, the bacteria involved are *Mycobacterium Bovis*, and for *Homo sapiens*, the culprit is *Mycobacterium Tuberculosis* (MTB) (Parsons, 1922). As this study only focuses on TB infection in humans, there are two different branches of this illness that will be further elaborated which are: (1) Latent TB and (2) Active TB. Latent TB is a condition where the TB bacteria is living inside a human body without making the host sick because the body can fight the bacteria and stop them from growing and spreading. In this case, the TB bacteria will become dormant and possibly inactive for the rest of their life or can even transform into active TB if their immune system grows weaker (Centers for Disease Control and Prevention, 2012). As for Active TB, it can be further extended into two main domains, which include: (1) Pulmonary tuberculosis and (2) Extra pulmonary tuberculosis (Swarna Nantha, 2014).

Generally, this pathogen called bacteria only attack the lungs; however, TB bacteria are known to travel and attack other organs such as the brain, kidney and spine (Centers for Disease Control and Prevention, 2012). The infection that stays in the lungs is known as pulmonary tuberculosis, and if it is already growing into different organs of the body, it is known as extrapulmonary tuberculosis. In pulmonary TB, there are two main characteristics based on the radiographic and clinical features, which are: (1) Primary Pulmonary TB and (2) Secondary Pulmonary TB. As stated by Geng et al. (2005), primary TB is a contagious infection through an airborne mechanism that destroys lung tissues, whereas secondary TB is the reactivation of primary TB. A simple illustration of the types of TB is presented as follows:

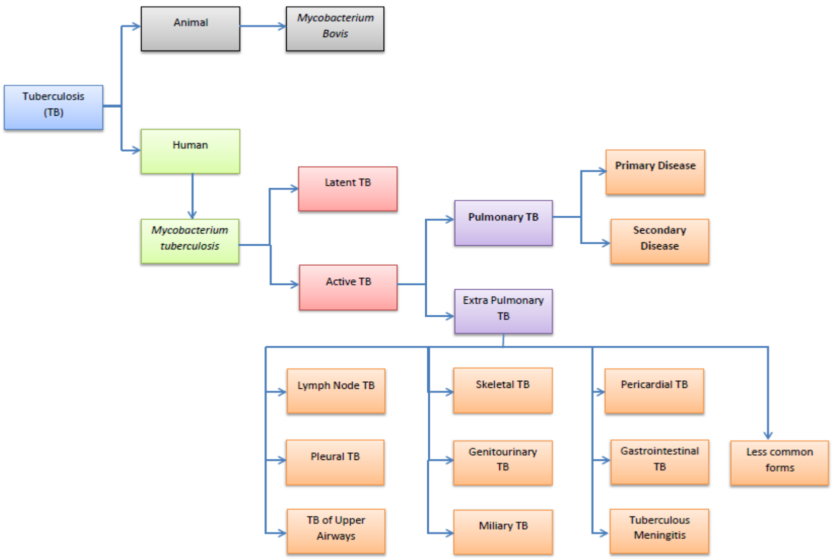

Figure 2.2 Types of Tuberculosis (Centers for Disease Control and Prevention, 1990)

MTB cannot be spread simply by shaking the infected hand, sharing food and drinks with them, sharing toothbrushes and touching bed linens or toilet seats (Centers for Disease Control and Prevention, 2012). MTB bacteria are released into the air from the lungs or throat when the infected host cough, sneeze, speak or sings (American Lung Association, 2020; Centers for Disease Control and Prevention, 2012; Read et al., 2012). Once released from the infected, the bacteria are dispersed throughout the space. Centers for Disease Control and Prevention (1990) stated that since the size of the droplet nuclei is varied from 1 to 5 micrometer, air current in any indoor space can keep this small size MTB bacteria airborne for a very long time. Therefore, people with TB infection are most likely to spread the disease to someone they spend a lot of time with, such as their friends and family members. Cardona (2016) added that to possibly get infected by active TB, a person needs to be in close contact with the sick for at least six hours a day. Cardona (2016) also reveals that the reactivation of TB infection from Latent or Active TB usually happens during the first two years after the first contact and is noted to be almost impossible for it to occur after five years.

Due to a variety of symptoms, TB has not declared a single disease until the 1820s. According to the Centers for Disease Control and Prevention (2012), the symptoms of this illness vary depending on which part of the body the bacteria reside. The early symptoms usually include weakness or fatigue, sudden weight loss, loss of appetite, chills, fever, and even sweating at night. For pulmonary TB, when the infection in the lungs worsens, the patient may experience pain in the chest, a bad cough that last for three weeks or more and even coughing up sputum and/or blood. The symptoms of this disease worsen depending on the immunity of its host, as it may appear more common in those who have weaker immune systems either from suffering other health problems or because of their age. The risk of infection is boosted for those who suffer from other illnesses such as Human Immunodeficiency Virus (HIV) and diabetes mellitus (Swarna Nantha, 2014). It is also said that younger people are more prone to be infected by TB and have higher chances of it being re-infected (Swarna Nantha, 2014).

Centers for Disease Control and Prevention (2012) stated that for people who have the symptoms and may be suspected of TB based on their medical condition and history or the physical exam, there are several ways to diagnose them, which include: TB skin test (TST) and TB blood test. A substance called tuberculin will be injected under the skin for TST, and a blood test called interferon-gamma release assays (IGRAs) will be carried out to identify whether an individual contacted MTB or not. However, these two tests only confirm that a person has contacted TB but do not tell whether a person has latent TB infection (LTBI) or an active TB disease. For an active TB patient to be diagnosed, more tests are needed to be carried out, such as sputum analysis and chest radiographic exam (Centers for Disease Control and Prevention, 2012). TB is known to be treatable, and Barberis et al. (2017) stated that the first vaccine called 'BCG' or *Bacillus of Calmette and Guerin* is the first to succeed in the immunization process against this disease which was discovered by Albert Calmette and Camile Guerin. Later in 1946, antibiotics such as streptomycin stepped in as an effective treatment which made this disease possible to be cured. However, hopes were shattered as the drug-resistant strain, drug-resistant TB (DR TB), was discovered back in the 1980s. Drug-resistant TB is transmitted to other people in the same way as drug-susceptible TB does. The difference between these two is that the treatment of TB is misused or mismanaged, which leads to a person developing drug-resistant TB. Drug-resistant TB may be developed because of the incomplete course of TB treatment, the unavailability of treatment or even poor quality of treatment received.

Therefore, an alternate variety of antibiotics is used to treat TB infections. Different categories of groups will have different prescriptions of drugs according to their current condition. The categories of people are a person with HIV, pregnant women, and children. The few types of antibiotics used during treatment are to increase the effectiveness of the medicine and to prevent the bacteria from becoming resistant to the drug. The most common drugs used for active TB include: Isoniazid (INH), Rifampin (RIF), Pyrazinamide, and Ethambutol (Bhunu et al., 2008; Centers for Disease Control and Prevention, 2012) stated that the treatment using antibiotics might vary from six months up to 24 months and even more. Centers for Disease Control and Prevention (2012) also added that for the latent TB infection, the treatment would be using only one type of antibiotic to prevent the infection from progressing into active TB later in life.

On the flipped side, since the pathogen of TB is dispersed into the air by coughing or sneezing, the bacteria may easily reach and be inhaled by people who present one or meter away from the infected patient (Muller, 2016). According to Huang (2020), during coughing and sneezing, the respiratory droplet can be shot further away, where the droplet may reach up and be inhaled by a bystander who is six meters away. The bacteria called *Mycobacterium tuberculosis* is an aerobe type of bacteria which means oxygen is essential for metabolism processes to take place. Therefore, coughed out, this bacteria can survive outside the host body for up to six months as long as oxygen is present, with poor ventilation procedures and are protected from sunlight (Muller, 2016). Smith (2003) and Schlossberg (2020) stated that the optimum condition for these bacteria to grow is at an oxygen level above 95%, and the temperature of 37°C and pH value ranges from 6.4 to 7.0.