ANALYSIS OF NONLINEAR DYNAMICS OF EPIDEMIOLOGICAL MODELS WITH LOCAL DISPERSAL, REINFECTION AND LIMITED MEDICAL RESOURCES

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by

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N	The total population
S	Susceptible
I	Infected
R	Removal
V	Vaccinated
η	The birth rate
v	The death rate
β	The transmission rate
β_1	The transmission rate for the susceptible group
β_2	The transmission rate of a vaccinated group
ε	The reinfection rate
δ	The recovery rate
γ	The recovered rate of the vaccinated individuals
ρ	The medical resources supplied per unit time
Φ	Half-saturation constant
α	The rate of vaccination of susceptible groups
τ	The treatment control function
ξ	The vaccination control function
$\mathbf{d}$	The diffusion coefficient
λ	Eigenvalue
Ω	Domain
Δ	The Laplacian operator

$\mathcal{R}_0$	The basic reproduction number
$\mathcal{X}$	Banach space
$\mathcal{H}$	Hilbert Space
$\mathcal{J}$	Jacobian matrix
$\forall$	For all
$\in$	Belongs to
∇	Gradient operator

LIST OF ABBREVIATIONS

ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
BRN	Basic Reproduction Number
SIR	Susceptible-Infected-Removal
SIRS	Susceptible-Infected-Removal-Susceptible
SVIR	Susceptible-Vaccinated-Infected-Removal
NBC	Neumann Boundary Condition
DBC	Dirichlet Boundary Condition
HB	Hopf Bifurcation
BP	Transcritical Bifurcation
NPIs	Non-Pharmaceutical Interventions
PIs	Pharmaceutical Interventions
NR	Numerical Range
QNR	Quadratic Numerical Range
CNR	Cubic Numerical Range
DFE	Disease Free Equilibrium
EE	Endemic Equilibrium

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ANALISIS DINAMIK TAK LINEAR MODEL EPIDEMIOLOGI DENGAN PENYEBARAN SETEMPAT, JANGKITAN SEMULA DAN SUMBER PERUBATAN TERHAD

ABSTRAK

Memeriksa dinamik penyebaran penyakit dan langkah kawalannya kekal sebagai cabaran utama dalam epidemiologi. Banyak kajian telah mencadangkan pelbagai faktor yang mempengaruhi penularan penyakit, termasuk keadaan persekitaran, pergerakan penduduk, dan sumber penjagaan kesihatan. Walaupun model yang berbeza telah dirumuskan untuk mengkaji faktor-faktor ini, kurang perhatian telah diberikan untuk memahami bagaimana interaksi jangkitan semula, had sumber perubatan, dan proses penyebaran ruang menentukan hasil wabak. Tesis ini menyiasat dinamik jangka panjang COVID-19 di Malaysia menggunakan sekumpulan model kinetik Susceptible-Infectious-Removed (SIR) yang menggabungkan imuniti sementara, keheterogenan ruang, penyebaran tempatan dan langkah kawalan. Model persamaan pembezaan biasa (ODE) digunakan, dengan parameter dipadankan pada data kes COVID-19 aktif harian di Malaysia, memberikan pemerhatian tentang faktor-faktor yang membentuk dinamik jangkitan. Model ODE berjaya memimik trend jangkitan yang diperhatikan dan menggambarkan kesan melantun yang kritikal serta didorong oleh jangkitan semula dan sumber perubatan yang terhad. Kewujudan dan kestabilan keseimbangan bebas penyakit (DFE) dan endemik (EE) telah dianalisis, dengan nilai titik-titik ambang untuk jangkitan semula, kadar transmisi penyakit dan kadar kecekapan sumber penjagaan kesihatan dikenal pasti. Melintasi titik ambang ini membawa kepada wabak penyakit yang semakin sukar dikawal dan sepadan dengan kejadian pencabangan transkritikal dan Hopf dalam model. Menggabungkan proses penyebaran tempatan ke dalam model ini membawa kepada sistem persamaan pembezaan separa (PDE). Model PDE mendedahkan bahawa keheterogenan ruang dan proses penyebaran boleh menguatkan kelaziman jangkitan di lokasi tertentu, merumitkan usaha kawalan. Pendekatan julat berangka baru, diambil daripada teori operator, telah digunakan untuk menganggarkan spektrum nilai eigen, menawarkan cerapan baharu tentang peralihan kestabilan antara

DFE dan EE dalam sistem PDE. Tambahan pula, kesan strategi kawalan yang berbeza, termasuk vaksinasi dan rawatan, telah diterokai. Strategi bersepadu ditunjukkan lebih berkesan dalam mengurangkan kedua-dua prevalens jangkitan dan tempoh wabak. Walau bagaimanapun, keberkesanan vaksinasi semakin berkurangan dari semasa ke semasa disebabkan oleh jangkitan semula dan imuniti yang semakin berkurangan, menonjolkan keperluan untuk strategi rawatan yang mantap untuk strategi kawalan penyakit. Secara keseluruhannya, kajian ini memberikan sumbangan penting dengan menyepadukan jangkitan semula, kekangan sumber perubatan dan keheterogenan ruang ke dalam rangka kerja pemodelan matematk, menawarkan kedua-dua pandangan teori dan praktikal untuk pengurusan wabak yang berkesan. Had utama kajian ini terletak pada ketersediaan data yang terhad pada kes jangkitan semula COVID-19 dan andaian mengenai strategi vaksinasi, yang mungkin menyekat kebolehgeneralisasian beberapa penemuan. Walau bagaimanapun, kajian ini menekankan kepentingan mengkaji interaksi kompleks antara proses epidemiologi dan dinamik ruang untuk mereka bentuk langkah kawalan yang berkesan dan mampan.

ANALYSIS OF NONLINEAR DYNAMICS OF EPIDEMIOLOGICAL MODELS WITH LOCAL DISPERSAL, REINFECTION AND LIMITED MEDICAL RESOURCES

ABSTRACT

Examining the dynamics of disease spread and its control measures remains a main challenge in epidemiology. Numerous studies have proposed various factors influencing disease transmission, including environmental conditions, population movement, and healthcare resources. While distinct models have been formulated to examine these factors, less attention has been given to understanding how the interplay of reinfection, medical resource limitations, and spatial dispersal processes determines epidemic outcomes. This thesis investigates the long-term dynamics of COVID-19 in Malaysia using a group of deterministic Susceptible-Infectious-Removed (SIR) kinetic models that incorporate temporary immunity, spatial heterogeneity, local dispersal, and control measures. Ordinary differential equation (ODE) models were first employed, with parameters fitted to daily active COVID-19 case data in Malaysia, providing observations into how these factors shape infection dynamics. The ODE models successfully mimic observed infection trends and highlight critical rebound effects driven by reinfection and limited medical resources. The existence and stability of disease-free (DFE) and endemic (EE) equilibria were analysed, with threshold values for reinfection, transmission rate, and healthcare resource efficiency identified. Crossing these thresholds leads to disease outbreaks that are increasingly difficult to control and corresponds to the occurrence of transcritical and Hopf bifurcations in the models. Incorporating a local dispersal process into these models leads to systems of partial differential equations (PDEs). The PDE models reveal that spatial heterogeneity and dispersal can amplify infection prevalence in certain locations, complicating control efforts. A novel numerical range approach, drawn from operator theory, was used to estimate the eigenvalue spectrum, offering new insights into the stability transitions between DFE and EE in PDE systems. Furthermore, the impacts of different control strategies, including vaccination and treatment, were explored. Integrated strategies were shown to be more

effective in reducing both infection prevalence and epidemic duration. However, vaccination effectiveness diminishes over time due to reinfection and waning immunity, highlighting the need for robust treatment strategies to sustain control. Overall, this thesis provides significant contributions by integrating reinfection, medical resource constraints, and spatial heterogeneity into a unified mathematical modelling framework, offering both theoretical and practical insights for epidemic management. The main limitation lies in the limited data availability on COVID-19 reinfection cases and simplifying assumptions regarding vaccination strategies, which restrict the generalisability of some findings. Nevertheless, the work demonestrates the importance of capturing the complex interplay between epidemiological and spatial dynamics to design effective and sustainable control measures.

CHAPTER 1

INTRODUCTION

1.1 Epidemiological Background

Infectious diseases have historically posed significant challenges to societies, with the COVID-19 pandemic serving as a recent example of their threats [1–5]. Beyond substantial mortality rates and disease burden, the COVID-19 endemicity profoundly disrupted modern societal structures, leading to lasting transformations in healthcare systems, economic frameworks, and social policies [6, 7]. Therefore, understanding the transmission dynamics of infectious diseases is crucial for safeguarding public health and developing effective intervention strategies. However, such an understanding remains difficult due to the intricate interplay of biological, epidemiological, and environmental factors. These are in fact the main concern of this thesis.

Given our current understanding of these epidemiological and biological factors, the joint influences of reinfection [8, 9], limited medical resources [10], environmental heterogeneity [11], and local dispersal on disease transmission dynamics remain largely unknown [11, 12]. Understanding these interdependencies using mathematical modelling techniques is crucial for developing more effective intervention strategies and predictive models to mitigate the spread of infectious diseases [13–16].

As the virus spreads, infected individuals contribute to sustained transmission, particularly in regions where limited healthcare capacity constrains timely treatment. Conversely, the increasing burden of disease and mortality triggers adaptive public health responses, prompting the implementation of both pharmaceutical (PI) and non-pharmaceutical interventions (NPI). These measures reshape transmission dynamics by altering population mobility, contact rates, and infection susceptibility, leading to shifts in both local and global outbreak patterns. Furthermore, the interplay between reinfection dynamics and medical resource scarcity can exert selective pressures on the virus, potentially influencing its evolutionary trajectory and long-term persistence [13].

Understanding this intricate feedback loop is critical for anticipating disease recurrence and optimising intervention strategies.

Upon detecting a new epidemic threat, policymakers and health authorities deploy a combination of pharmaceutical and non-pharmaceutical interventions aimed at mitigating or containing its spread. Pharmaceutical strategies typically involve vaccination campaigns or anti-viral treatments, but these solutions are often unavailable in the early stages of an emerging disease due to the time required for development. Consequently, NPI play a critical role in early containment efforts. These interventions can be broadly classified into measures that reduce the frequency of interpersonal contact such as lockdowns and quarantine and those that minimise transmission likelihood during contact, such as mask mandates and improved hygiene protocols [17–19]. Beyond direct transmission reduction, NPIs also influence population structure by modifying susceptibility patterns. For instance, targeted strategies such as isolating high risk groups or implementing test-trace-isolate (TTI) protocols help reduce disease prevalence by identifying and quarantining infectious individuals before they contribute to further spread [20–24]. Collectively, these interventions share a common objective: to lower the basic reproduction number of disease and curtail its transmission within the community.

1.1.1 The Epidemiology of COVID-19

The global community faced an emerging infectious disease characterised by high transmission capacity, moderate fatality risk, asymptomatic transmission, and a rapidly evolving pathogen (SARS-CoV-2). These factors collectively posed significant challenges to containment efforts, which were further exacerbated by logistical constraints and the proliferation of misinformation across successive epidemic waves. During the pandemic, researchers conducted tests by introducing respiratory samples into human airway epithelial cells, as well as Vero E6 and Huh7 cell lines, leading to the isolation of a new respiratory virus. Genome analysis revealed this virus to be a novel coronavirus closely related to SARS-CoV, and it was subsequently named severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is classified as a betacoronavirus within the sarbecovirus subgenus. The global spread of SARS-CoV-2 and the substantial number of deaths attributed to coronavirus disease (COVID-19) prompted the World Health Organisation to declare a pandemic on March 12, 2020. To date, this pandemic has exacted a heavy toll worldwide in terms of human lives lost, economic consequences, and increased poverty [25]. Figure 1.1 illustrates the structural representation of a coronavirus, showing key proteins and genomic RNA essential for viral function.

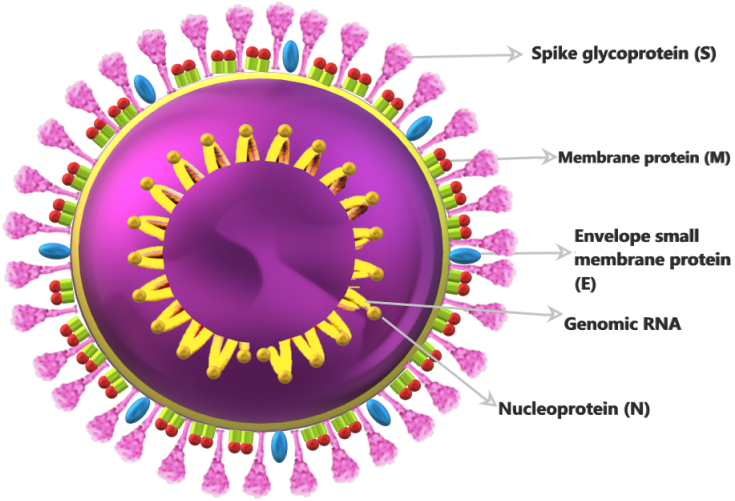

Figure 1.1: Structural representation of COVID-19.

Figure 1.2 illustrates the structure of a SARS-CoV-2 (COVID-19) virion which is distinguished by its spherical morphology adorned with spike glycoproteins emanating from its surface. The infectious agent is comprised of genomic material, specifically single-stranded RNA in this instance, enclosed within a phospholipid bilayer membrane. This lipidic casing is decorated with spike glycoproteins that confer upon the pathogen its distinctive crown-like morphology, hence earning the designation "coronavirus." These spike glycoproteins serve a pivotal function in adhering to and penetrating host cells, particularly those located in the respiratory tract. Housed within the viral lipid envelope, the RNA genome harbors the genetic directives imperative for viral replication and the generation of new viral entities upon entry into a host cell. A

comprehensive comprehension of the intricate configuration of the COVID-19 virion is imperative for the development of efficacious vaccines and antiviral treatments targeting this worldwide health crisis [26].

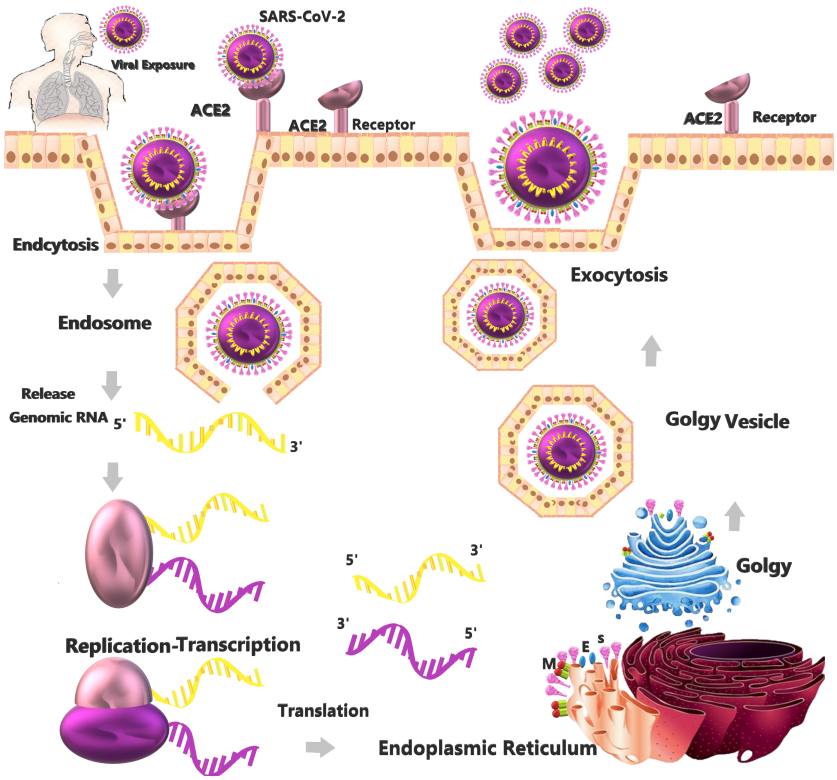

Figure 1.2: Structure of COVID-19 particles

1.1.2 Reinfection

Reinfection remains a significant challenge in the epidemiology of infectious diseases, particularly for pathogens capable of evading host immunity through genetic variation. While initial infection often confers temporary immunity, the duration of this immunity can vary widely depending on the pathogen and individual host factors. For instance, immunity following recovery from COVID-19 has been shown to wane within months, rendering previously infected individuals susceptible to reinfection [13, 27]. Reinfection not only sustains the chain of transmission but also complicates efforts to achieve herd immunity, necessitating continuous monitoring and adaptation of public health strategies. Moreover, the emergence of new variants, often driven by selective pressures from partial immunity and vaccination efforts, further

exacerbates reinfection risks and undermines long term disease control [12, 28]. These challenges highlight the need for robust surveillance systems and dynamic intervention strategies capable of addressing evolving epidemiological landscapes.

1.1.3 Limited Medical Resources

The availability of medical resources plays a crucial role in determining the outcomes of infectious disease outbreaks, especially during periods of heightened transmission. Limited access to healthcare facilities, diagnostic tools, and therapeutic interventions can significantly increase morbidity and mortality rates, particularly among vulnerable populations [29]. The strain on healthcare systems during the COVID-19 pandemic exemplified how resource shortages can exacerbate the severity of outbreaks, leading to overwhelmed hospitals, delayed treatments, and compromised patient outcomes. Mathematical models incorporating resource constraints have demonstrated that timely allocation of available resources can mitigate the impact of outbreaks and prevent healthcare system collapse [30]. Thus, integrating resource availability into epidemiological modelling is essential for designing effective, realistic intervention strategies that consider both disease dynamics and healthcare capacity.

1.2 Modelling Background

Mathematical modelling is widely recognised as one of the most powerful approaches to understand the complex dynamics of infectious disease transmission. This particular formulation offers a structured framework for denoting disease trajectory, estimating intervention efforts, and projecting potential outbreak scenarios [31, 32]. Mathematical models are known as key tools, which allow researchers to translate biological assumptions and epidemiological observations into measurable numerical formulations, and simulate real-life scenarios, identify crucial thresholds at which diseases are controlled, and shape evidence based public health decisions.

Mathematical models used in epidemiology can be broadly classified into three categories: deterministic, statistical, and stochastic models. Additionally, each type has distinct characteristics, and the choice of model depends largely on the nature of the disease, the specific research objectives, and the availability of empirical data. Deterministic models, like the classical Susceptible-Infectious-Recovered (SIR) model proposed by Kermack and McKendrick [33], represent the overall dynamics of disease spread in a population and are based on systems of ordinary differential equations (ODEs). These models are built based on homogeneous mixing and continuous population dynamics, accounting for population-level, long-term trajectory effects, which can be quite useful.

In contrast, statistical models analyse epidemiological data to search for patterns and associations using regression based methods to infer transmission parameters and predict the trajectory of the spread of the disease [34]. When detailed surveillance data are available, these models are useful for predicting current and future areas at risk for infection. In contrast, stochastic models also account for random variation in the transmission dynamics; therefore, they are often fitted for small populations, early stages of epidemic outbreaks, as well as possibilities that the outcomes are heavily dependent on chance [35]. Stochastic frameworks account for the stochastic nature of infection and recovery processes, and offer more realistic estimates of outbreak variability and extinction probabilities.

The primary objective of any epidemiological model is to describe the underlying processes governing disease transmission. These processes can be summarised as follows: (i) when infected individuals are introduced into a susceptible population, the pathogen spreads through established transmission routes, often facilitated by close contact between individuals; during the initial infection stage, some individuals may remain asymptomatic and still transmitting the disease, while others develop clinical symptoms, becoming identifiable as active infection cases; (ii) a disease outbreak occurs when the number of cases surpasses the typical baseline level within a short period,

while an epidemic is characterised by the rapid spread of infection across a large segment of the population; and (iii) the recovery of infected individuals depends primarily on two factors the strength of their immune system and the availability of effective medical interventions. Following recovery, individuals may acquire temporary or long-lasting immunity, although immunity can wane over time, as observed with COVID-19 [36]. The progression of an epidemic typically halts when the pool of susceptible individuals is sufficiently depleted, reducing the effective reproduction number ($\mathcal{R}_0$) below the critical threshold of one. As the transmission rate declines, the outbreak gradually diminishes, ultimately resulting in a complete eradication of the disease from the population. This dynamical interaction between infection, immunity, and recovery indicate the importance of mathematical models to capture the non-linear nature of the disease spread and identifying optimal intervention strategies.

Diseases prevalent within a specific population or region are classified as endemic diseases, with their prevalence defined by the proportion of active cases relative to the total population at a given time referred to as the endemic equilibrium. Notable examples include influenza and other respiratory illnesses caused by pathogens such as Respiratory Syncytial Virus (RSV) or Human Rhinovirus (HRV). Around this endemic equilibrium, these diseases impose a implicitly accepted due to familiarity and manageable impact despite the paradox that the cumulative cost of managing them frequently exceeds the cost of eradication during their initial epidemic phase [37]. Fluctuations in the endemic equilibrium often exhibit seasonal patterns, driven by temporal variations in pathogen persistence and population contact behaviours [38, 39]. From a dynamical systems perspective, the endemic equilibrium corresponds to a fixed point, and its stability and potential bifurcations provide valuable insights for epidemiological risk assessment [17, 40, 41]. In contrast, diseases that are newly introduced to a population are termed "emerging," while those previously eliminated from a region but reappearing are classified as "re-emerging." Epidemic diseases typically pose greater threats than endemic ones, prompting an immediate societal response aimed at curbing their spread [37]. Prominent examples include Ebola, Marburg virus disease, and COVID-

19. Furthermore, emerging diseases can arise through zoonosis, wherein pathogens affecting non-human species mutate to infect humans, or when pathogens endemic to isolated regions are introduced into new populations. Regardless of their origin, emerging diseases, unlike endemic ones, prompt substantial societal efforts to contain outbreaks before they can significantly impact the population [37,41]. Mechanistically, these mitigation efforts can be integrated into epidemiological models as feedback loops, leading to complex long-term dynamics, including high-periodic wave patterns, period-doubling cascades, and chaotic behaviours [42–45].

Mathematical models are an essential tool that enables the assessment of the efficiency of (non-)pharmaceutical interventions, for example vaccination and anti-viral treatments, social distancing and quarantine measures. They allow scenario based analyses for policy makers to predict the potential consequences of various control strategies and the efficient allocation of resources. Modelling frameworks also aid in identifying key epidemiological thresholds for emerging and reemerging infectious diseases, including the basic reproduction number $\mathcal{R}_0$, which determines whether an outbreak will propagate or eradicated [36].

1.3 Problem Statement

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a major global impact since its emergence in December 2019 in Wuhan, China. As of April 2024, the virus has resulted in over 704 million confirmed cases and more than 7 million deaths worldwide [46]. This unprecedented health crisis has highlighted the critical need for accurate and robust epidemiological models to inform public health strategies and policy decisions, given the endemicity situation of COVID-19.

Traditional compartmental models, such as the Susceptible-Infectious-Recovered (SIR) framework, have proven their importance in understanding disease dynamics [9,33,47]. These models operate under the assumption of homogeneous mixing within a population, where individuals have equal chances of contact and transmission [48–50].

However, this assumption often fails to capture the complexities of real world social structures, where interactions occur in heterogeneous enviroments and contact rates vary among individuals across a spatial scales. These simplified models may lead to inaccurate predictions regarding the spread and control of infectious diseases.

Moreover, standard SIR models typically do not account for critical factors such as reinfection [13, 51] due to waning immunity and the constraints posed by limited medical resources [9,47]. Reinfection, a phenomenon observed in diseases like COVID-19, challenges the notion of permanent immunity and necessitates the inclusion of dynamic susceptibility in modelling efforts [52, 53]. Additionally, healthcare systems worldwide have faced significant strain during the pandemic, with resource limitations impacting patient outcomes and disease progression [54, 55]. Ignoring these elements can lead to oversimplified models that fail to accurately reflect the outbreak trajectories and the efficiency of intervention strategies.

Another limitation of traditional models is the assumption of closed populations without migration. In reality, human mobility has a critical role in the spread of infectious diseases, as individuals frequently move between regions, facilitating transmission across geographical boundaries [12, 56–58]. Incorporating spatial dynamics and migration patterns into epidemiological models is essential for capturing the full scope of disease spread and informing targeted intervention strategies.

To address these issues, this thesis proposes the development of analysis of selected mathematical models that integrate critical factors such as reinfection, limited medical resources, and local dispersal. Utilising both ordinary differential equations (ODEs) and partial differential equations (PDEs), these models aim to provide a more comprehensive representation of disease dynamics. Furthermore, by applying techniques from dynamical systems and bifurcation theory, the analysis will explore the stability of disease-free and endemic equilibria, as well as the conditions under which distinct bifurcations may occur, leading to changes in disease dynamics. Additionally, the incorporation of optimal control theory will contribute to the evaluation of different

mitigation strategies.

1.4 Research Questions

The research questions for this study are:

i. What optimal solutions can be extracted from the formulated modelling frameworks to help in curbing the transmission of COVID-19 and how these findings can help in enhancing our public health response and preparedness strategies?

ii. How local dispersal of individuals determine the spread of COVID-19 in spatially extended systems?

iii. From modelling and dynamical systems viewpoints, how distinct bifurcation (or epidemiological tipping) points emerge in these systems and shape the transmission dynamics of COVID-19?

1.5 Research Objectives

The main research objective of the thesis are:

i. To assess the transmission dynamics of COVID-19 by evaluating the ordinary differential equations (ODE) models that incorporate reinfection and limited medical resources scenarios, using the techniques from dynamical systems and bifurcation analysis.

ii. To formulate extended deterministic models with optimal control theory by considering the effects of pharmaceutical interventions and perform extensive numerical simulations, which can generate insights that inform the planning of effective control strategies for COVID-19 mitigation.

iii. To predict the impacts of spatial dispersal process and environmental heterogeneity on disease dynamics using the partial differential equations (PDE) systems

and generate the stability analysis of the PDE using the numerical range method from the operator theory and functional analysis.

1.6 Scope of the Study

The scope of this study encompasses the dynamical systems analysis of infectious disease transmission through mathematical modelling, with a particular focus on the SIRS (Susceptible-Infected-Recovered-Susceptible) and SVIR (Susceptible-Vaccinated-Infected-Recovered) models. These models have been chosen based on their capacity to capture critical aspects of disease dynamics, including reinfection, limited medical resources, and pharmaceutical interventions. These factors are related to the epidemiology of COVID-19.

In this study, the SIRS model is employed to investigate the transmission dynamics of infectious diseases in heterogeneous environments with local dispersal, subject to homogeneous Neumann boundary conditions (NBC). This approach is particularly relevant to diseases such as COVID-19, where the recovered cases lose their immunity against the virus over time, leading to reinfection. In contrast, existing models such as the SEIR [57, 59] or SQIER [60] frameworks incorporate an exposed compartment, which accounts for a latent period but does not directly capture the reinfection dynamics characteristic of COVID-19. Therefore, the SIRS model was chosen as a more suitable approach.

The decision to focus on the SIRS and SVIR models, rather than other frameworks such as SEIR or SQIER, was based on the specific characteristics of COVID-19 and the objectives of the study. The absence of an actual data of exposed cases COVID-19 cases makes the SEIR framework less applicable, while the SQIER model, which includes quarantine compartments, would complicate the analysis without providing additional insights relevant to the goals of the study. The SIRS and SVIR models, by contrast, strike an appropriate balance between model complexity and epidemiological relevance, enabling a more targeted investigation of reinfection dynamics, vaccination

strategies, and pharmaceutical interventions.

The study explores a spectrum of mathematical models, ranging from ordinary differential equations (ODEs) to partial differential equation (PDE) formulations. Equilibrium points of the SIRS model were computed and the stability of each point was analysed. Through the application of XPPAUT and bifurcation analysis, critical bifurcation points were identified, marking threshold values where qualitative shifts in disease dynamics occur. To further understand the long-term behaviour of the epidemic, numerical simulations were conducted in MATLAB using parameter values estimated based on real COVID-19 case data.

In this study, parameter estimation was conducted to ensure the models accurately reflect real-world epidemiological conditions. The infection rate and recovery rate were estimated using active COVID-19 case data provided by the Ministry of Health (MOH) Malaysia. The birth and death rates were derived from previous epidemiological studies to maintain biological realism. Other parameters, including the reinfection rate, the medical resources supplied per unit time, and the half-saturation constant, were set hypothetically under various scenarios to investigate their influence on disease dynamics. This combination of data-based estimation and hypothetical scenarios provides a comprehensive framework for analysing disease dynamics and evaluating public health policies.

To further investigate the impact of pharmaceutical interventions, optimal control theory was applied to the SIRS model, incorporating two key control variables (vaccination and treatment). Vaccination serves as a preventive measure to enhance immunity and ensuring long-term protection against infection, thereby reducing the susceptible population and limiting disease transmission. Treatment, on the other hand, involves the administration of anti-viral drugs or other medical interventions aimed at mitigating disease severity, reducing infection duration, and preventing further complications. By integrating these controls, the model provides a framework for identifying optimal intervention strategies that minimise disease burden while balancing cost-effectiveness and

resource availability. Furthermore, this approach can be extended to incorporate both pharmaceutical (e.g., novel therapeutics) and non-pharmaceutical (e.g., social distancing, quarantine) interventions, making it an adaptable tool for epidemic management and policy decision-making.

In addition to the SIRS model, the SVIR model was also analysed, in the form of partial differential equation (PDE) system with local dispersal in homogeneous environment and homogeneous Neumann boundary conditions. This model was chosen to assess the impact of vaccination of disease mitigation policies. The inclusion of a vaccinated compartment provided a more realistic framework for evaluating the effectiveness of vaccination campaigns in controlling the infectious diseases. Furthermore, an advanced approach utilising the cubic numerical range was applied to the stability analysis of the SVIR model. The estimation of the eigenvalue spectrum for the PDE system provided deeper insights into the conditions under which the disease could either persist or be eradicated. By employing this novel approach, the investigation of stability phenomena in the SVIR model was improved, overcoming challenges often associated with traditional methods.

1.7 Significance of the Research (Contribution)

This research contributes to the field of mathematical epidemiology by advancing the understanding of infectious disease dynamics through the development of analysis of selected mathematical models that address critical limitations in traditional approaches. By integrating reinfection dynamics, limited medical resources, and pharmaceutical interventions into the modelling frameworks, this study offers valuable insights for both theoretical epidemiology and practical public health strategies.

One of the primary contributions of this research lies in the analysis of the dynamical systems of the SIRS model formulated in terms of ordinary differential equations (ODEs). The study examines the ODE formulation of the SIRS model to capture reinfection dynamics and limited medical resources. Through stability and bifurcation

analysis, critical epidemiological thresholds were identified, including conditions under which disease-free and endemic equilibria become unstable, leading to oscillatory outbreaks. This theoretical framework provides a deeper understanding of how reinfection rates and the availability of medical resources interact to influence long-term disease persistence.

Extending this analysis to partial differential equations (PDEs), the study further investigates disease transmission in heterogeneous environments. The PDE-based SIRS model incorporates local dispersal under homogeneous Neumann boundary conditions, capturing spatial variations in infection spread. Additionally, the SVIR model was analysed in a homogeneous environment under similar boundary conditions, enabling a focused assessment of vaccination strategies. These models were chosen for their epidemiological relevance, particularly in capturing the combined effects of reinfection, limited medical resources, and vaccination policies key factors influencing the control of COVID-19 and similar diseases.

A significant contribution of this study is the application of bifurcation theory to the SIRS model, both analytically, and numerically. This analysis identified critical thresholds, such as the basic reproduction number and bifurcation points, that determine the stability of disease-free and endemic equilibria together with the emergence of oscillatory dynamics. By illustrating the solution trajectories of the models through numerical simulations, the study provided a detailed understanding of how changes in epidemiological parameters influence disease persistence and control in a long run.

Moreover, this research introduced the use of optimal control theory to evaluate pharmaceutical interventions, specifically vaccination and treatment strategies in both ODE and PDE models. By formulating and solving optimal control problems, the study identified cost effective strategies for mitigating disease spread while minimising the burden on healthcare systems. This approach bridges the gap between theoretical modelling and practical decision making, offering policymakers actionable insights for resource allocation during outbreaks.

Another important contribution is the application of the numerical range and cubic numerical range methods for the stability analysis of the SVIR model. This novel approach enabled the estimation of the eigenvalue spectrum for the PDE system, providing a more robust understanding of stability conditions. By employing this advanced mathematical tool, the study offers a unique perspective on the long term behaviour of infectious disease models, which is often challenging to achieve using conventional stability analysis methods.

Furthermore, the reliance of the study on real world COVID-19 data for parameter estimation enhances the practical relevance of the findings. By calibrating the models based on active case data, the study ensures that the results are not merely theoretical but reflective of realistic epidemiological scenarios. This approach strengthens the validity of the proposed models and their potential application to future outbreaks.

1.8 Limitation of the Study

Although this study offers a comprehensive analysis of the nonlinear dynamics of epidemiological models incorporating local dispersal, reinfection, and limited medical resources, certain limitations must be acknowledged. While several epidemiological parameters, such as the infection rate and recovery rate, were estimated from real active COVID-19 case data in Malaysia, the availability of detailed and longitudinal datasets for other aspects of the model was limited. In particular, accurate and up-to-date data on reinfection rates remain scarce, leading to reliance on assumptions and literature-based approximations that may not fully capture the variability of actual reinfection dynamics. Similarly, the lack of comprehensive information on vaccination strategies including implementation schedules, coverage rates, and long-term efficacy posed challenges for precise model calibration. These constraints may affect the generalisability of the findings to other contexts or disease settings. Nevertheless, the modelling framework developed in this study is robust and adaptable, and its predictive capacity can be enhanced as richer and more specific context epidemiological data become available.

1.9 Outline of the Thesis

This thesis is outlined as follows. In Chapter 2, a general overview is provided of selected models of epidemiological systems and local dispersal processes in both homogeneous and non-homogeneous environments. This chapter includes the derivation of several deterministic models to address the reinfection phenomenon and the constraints imposed by limited medical resources. The effects of local dispersal in homogeneous environments are introduced, along with the modelling of pharmaceutical interventions, using optimal control theory. Additionally, diffusion models in heterogeneous environments are explained, followed by a detailed linear stability analysis of ODE models. The chapter also explores bifurcation theory in dynamical systems to analyse the qualitative behaviour of the epidemiological models. Finally, a review of previous works and developments in modelling frameworks relevant to this study is presented.

Chapter 3, investigates the transmission dynamics of COVID-19 using an extended SIRS model, emphasising the effects of reinfection and limited medical resources. Through mathematical analysis and bifurcation techniques, the study identifies critical thresholds for reinfection, highlighting conditions under which the epidemic may exhibit persistent oscillations or stabilising trends. The findings demonstrate that resource constraints significantly influence disease progression, with inadequate medical supplies will sustain ongoing outbreaks. Additionally, the chapter explores the role of waning of immunity, reinfection patterns, and vaccination efficacy, drawing insights from epidemiological studies. Policy implications highlights the necessity of timely resource allocation, coordinated public health strategies, and sustained non-pharmaceutical interventions to prevent epidemic resurgence.

Chapter 4 focuses on the role of pharmaceutical interventions in controlling the spread of COVID-19 through an optimal control framework. It introduces an SIRS epidemiological model incorporating vaccination and treatment as time-dependent control variables. The mathematical formulation and theoretical analysis demonstrate how

these interventions can minimise infection levels while optimising resource allocation. Numerical simulations illustrate the effectiveness of early and targeted intervention strategies in flattening infection curves, reducing healthcare burdens, and mitigating reinfection risks. The chapter also examines the implications of medical resource constraints and provides insights into designing cost-effective public health policies.

In Chapter 5, a dynamical systems analysis of a reaction-diffusion SIRS model with optimal control is conducted, focusing on the spatial spread of COVID-19. This chapter examines the dynamical behaviour of a PDE-based SIRS model, assessing the effects of reinfection and limited medical resources in a spatially structured population. Additionally, optimal control theory is applied in the context of vaccination and treatment strategies, demonstrating how effective control measures can reduce the severity of disease outbreaks.

In Chapter 6, a novel approach is presented for investigating the stability analysis and dynamics of a reaction–diffusion SVIR epidemic model. The stability and dynamics of a PDE-based SVIR model are examined, with particular attention to infection-recovery rates and vaccination effects. The study identifies disease-free (DFE) and endemic (EE) equilibria under varying parameter conditions. Numerical (NR) and cubic numerical ranges (CNR) are utilised for the stability analysis of the PDE system, with CNR providing a robust estimation of the eigenvalue spectrum to better understand the long-term behaviour of the system.

In Chapter 7, the thesis is concluded by summarising several important insights, followed by suggestions for possible directions of future work.

CHAPTER 2

LITERATURE REVIEW AND MATHEMATICAL CONCEPTS

2.1 Introduction

In this chapter, provides a review for the key terminologies, fundamental principles, and concepts from dynamical systems theory and epidemiological modelling. These foundational aspects are crucial in the next chapters as were various models related to infectious diseases dynamics shall be explored.

2.2 Epidemiological Models

Epidemiological models are mathematical frameworks that are used to describe the spread of infectious diseases within a population. These models aim to capture the dynamics of disease transmission, predict future outbreaks, and evaluate control strategies such as vaccination or quarantine measures. Commonly employed models, such as the Susceptible-Infected-Recovered (SIR) model, categorise the population into compartments based on disease status and track the rates of change between these compartments over time. By incorporating factors like transmission rates, recovery rates, and population demographics, epidemiological models provide valuable insights into public health planning and disease control strategies.

Mathematical modelling of infectious diseases typically follows three primary approaches [2]:

1. **Statistical models:** These models are highly data-driven and are designed to address specific datasets [61, 62]. The advantages of statistical models are extensively utilised in epidemiology and public health research. While the disadvantages of the statistical models depend on large samples of data for effective analysis.

2. **Deterministic models:** These models commonly are formalised using differential and difference equations in various forms [8, 33]. A key assumption is that the sizes of the susceptible and infectious populations are continuous functions of time. These models illustrate the dynamic interactions between the rates of change and the sizes of the populations.

   The advantages of mathematical theories for this type of modelling are more developed compared to stochastic models. The derivation of mathematical models is less reliant on data than statistical models, making them well-suited for predictive purposes. While the disadvantages of these models are not expected to be valid if the population sizes are very small, in which case stochastic disturbances become non-negligible.

3. **Stochastic models:** These models commonly are formalised using differential and difference equations in various forms [29, 35]. A key assumption is that the sizes of the susceptible and infectious populations are continuous functions of time. These models illustrate the dynamic interactions between the rates of change and the sizes of the populations.

   The advantages in this type of model, disease transmission is treated as a stochastic process, capturing the dynamic relationships among its probability distributions. While the disadvantages, the mathematical analysis of stochastic models is challenging due to the limited mathematical tools available. Therefore, the evaluation of these models largely depends on observations from a vast number of numerical simulations.

In situations where data availability is limited, deterministic models often serve as valuable tools for making inferences about disease dynamics. Unlike statistical models, which heavily depend on large datasets for accurate predictions, deterministic models rely on underlying mathematical structures to describe the interactions between susceptible, infected, and recovered populations. By leveraging differential equations, these models provide a systematic framework to understand disease spread, even when

empirical data is sparse. While they may not capture random fluctuations inherent in real-world outbreaks, their predictive capabilities and well-established mathematical foundations make them useful for generating insights, guiding public health interventions, and formulating hypotheses that can later be refined with additional data. Therefore, in this thesis focuses on deterministic models of infectious diseases. This chapter, provides review and introduces key concepts related to these models.

2.3 Deterministic Models: Compartmental Approaches

This section, will explore the compartmental approaches to deterministic models of infectious diseases. This method divides the population into distinct compartments based on disease status, allowing for a systematic analysis of disease dynamics and the interactions between different compartments over time. For a simple infectious disease, possible compartments consists of:

S : susceptible group, I : infected group, and R : recovered (removal) group.

Figure 2.1 demonstrate the schematic transmission proces compartments. The term "removal" includes loss of individuals out of compartment through death or recovered. The purpose of the model is to monitor the number of hosts in each of the three

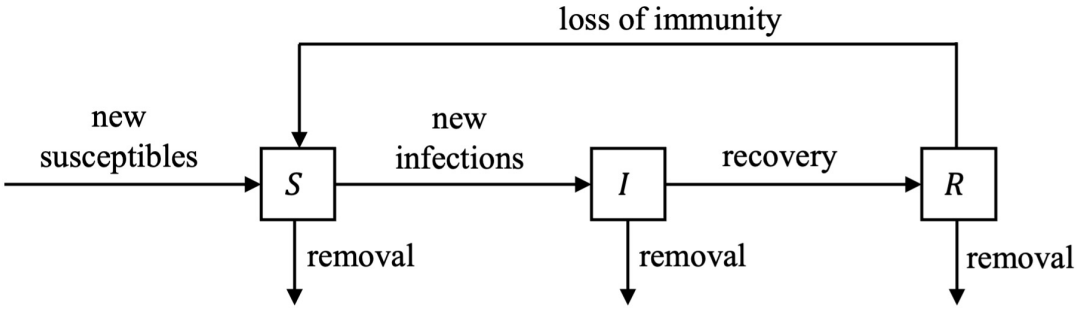

Figure 2.1: Transfer diagram for an SIRS compartment model [2].

compartments at any time t, denoted as $S(t)$, $I(t)$, and $R(t)$, respectively. To construct the compartmental model, a small time interval $[t, t + \Delta t]$ will be used to examine and assess the net change in the number of individuals within each compartment. In

the transfer diagram (Figure 2.1), arrows indicate the direction of movement between compartments. The net change in the number of hosts in a compartment is calculated as the difference between the number entering and the number leaving during the time interval. Applying this approach to each compartment yields the following equations:

$$\begin{aligned}
\Delta S(t) &= \boxed{\text{new susceptible}} + \boxed{\text{transfer from } R} - \boxed{\text{new infections}} \\
&- \boxed{\text{removal from } S}, \\
\Delta I(t) &= \boxed{\text{new infections}} + \boxed{\text{transfer into } R} - \boxed{\text{removal from } I}, \\
\Delta R(t) &= \boxed{\text{transfer from } I} + \boxed{\text{transfer into } S} - \boxed{\text{removal from } R}.
\end{aligned} \tag{2.1}$$

By dividing both sides of equations (2.1) by Δt and assume $\Delta t \to 0$, the left-hand side becomes the derivatives $S'(t)$, $I'(t)$, and $R'(t)$, as

$$\frac{\Delta S(t)}{\Delta t} = \frac{S(t+\Delta t) - S(t)}{\Delta t} \to S'(t), \text{as } \Delta t \to 0,$$

similarly for $I'(t)$, and $R'(t)$:

$$\frac{\Delta I(t)}{\Delta t} = \frac{I(t+\Delta t) - I(t)}{\Delta t} \to I'(t), \text{as } \Delta t \to 0,$$

and

$$\frac{\Delta R(t)}{\Delta t} = \frac{R(t+\Delta t) - R(t)}{\Delta t} \to R'(t), \text{as } \Delta t \to 0,$$

The terms on the right-hand side will represent instantaneous rates of incidence, recovery, and removal. To obtain the following differential equations:

$$\begin{aligned}
S'(t) &= \boxed{\text{influx of new susceptible}} + \boxed{\text{transfer rate from } R} - \boxed{\text{incidence rate}} \\
&- \boxed{\text{removal rate from } S}, \\
I'(t) &= \boxed{\text{incidence rate}} + \boxed{\text{transfer rate into } R} - \boxed{\text{removal rate from } I}, \\
R'(t) &= \boxed{\text{transfer rate from } I} + \boxed{\text{transfer rate into } S} - \boxed{\text{removal rate from } R}.
\end{aligned} \tag{2.2}$$

By expressing all the terms on the right-hand side as functions of $S(t)$, $I(t)$, and $R(t)$, a system of differential equations for $S(t)$, $I(t)$, and $R(t)$, has been derived which constitutes the mathematical model. It is crucial to note that the formulation of these terms as functions of $S(t)$, $I(t)$, and $R(t)$ is guided by our underlying assumptions

regarding the biological mechanisms of disease transmission and the dynamics of population movement across compartments. Consequently, different assumptions will lead to distinct forms of the model, potentially yielding varying outcomes. If empirical data are available to validate the model's predictions, the model can be employed to assess the accuracy of our hypotheses on the disease transmission process. The next section, will illustrate how fundamental assumptions can be applied to derive one of the classical epidemic models.

2.3.1 Kermack–McKendrick Model

In the 1927, A. G. McKendrick and W. O. Kermack [33] presents a mathematical framework for modelling the spread of infections, focusing on discrete time intervals where transmission occurs at the transition between intervals. Key variables such as the number of infected individuals, the rate of removal (due to recovery or death), and population density are central to understanding epidemic dynamics. The authors employ integral and differential equations to describe the relationships between susceptible, infected, and removed individuals over time, incorporating assumptions of constant infectivity and population density to simplify the model. The analysis reveals the existence of a threshold population density, below which an epidemic cannot occur, and demonstrates how small increases in infectivity can lead to significant outbreaks when the population density exceeds this threshold. The study concludes that epidemics typically subside before the susceptible population is fully depleted, highlighting the complex interplay between infection rates and population dynamics.

To illustrate how the rates in Equation (2.2) may be influenced by $S(t)$, $I(t)$, and $R(t)$, the following assumptions shall be applied concerning the transmission dynamics of the infectious disease and its host population:

1. The transmission occurs horizontally through direct interaction between hosts.
2. The mixing of individual hosts is homogeneous, adhering to the Law of Mass Action: the frequency of interactions between hosts from different compartments

is solely dependent on the number of hosts in each compartment. Specifically, the incidence rate, defined as the number of new infections per unit time, can be represented by $\beta I(t)S(t)$, where β denotes the transmission coefficient.

3. The rate of transfer from a compartment is directly proportional to the population size within that compartment. For example, the transfer rate from compartment I to compartment R, representing the recovery rate, can be expressed as $\delta I(t)$, where δ is a constant rate parameter.

4. Infected individuals become infectious immediately upon infection, without any latency period.

5. There is no loss of immunity, nor is there any possibility of reinfection. This indicates that the transfer rate from compartment R back to compartment S is zero.

6. There is no addition of new susceptible and no removal from any compartments. The influx of new susceptible is zero, and the removal rates from all compartments are also zero.

7. The total host population is constant, a consequence of the preceding assumption; however, this point is explicitly articulated here to underscore its importance. The dynamics of epidemic models can become more complex when the total population fluctuates over time.

While these assumptions may seem quite limiting, they are reasonably plausible for the spread of disease within a campus student population, where interactions primarily occur in settings such as classrooms, cafeterias, libraries, and other communal areas. Based on these assumptions, the transfer diagram for the conceptual model depicted in Figure 2.1 can be transformed into a concrete model as illustrated in Figure 2.2.

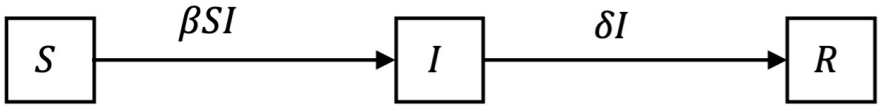

Figure 2.2: Transfer diagram for an simple SIR model [2].

By substituting all terms in Equation (2.2) with the mathematical representations, the following system of differential equations has been derived [2, 33]:

$$\begin{aligned} S_t &= -\beta SI, \\ I_t &= \beta SI - \delta I, \\ R_t &= \delta I, \end{aligned} \tag{2.3}$$

with initial conditions:

$$S(0) = S_0 > 0, I(0) = I_0 > 0, \text{ and } R(0) = R_0 > 0.$$

In the model, functions $S(t)$, $I(t)$, and $R(t)$ are variables. Since they denote the number of people, they are expected to take nonnegative values. Constants β and δ are model parameters, and they are assumed to be nonnegative since they denote rate constants. If the values of the model parameters β and δ are known, then for each set of initial conditions S_0 and I_0, model (2.3) has a unique solution $(S(t), I(t), R(t))$ that produces a prediction for the time course of the epidemic for $t > 0$. Here, $t = 0$ marks the beginning of the epidemic.

2.3.2 SIR Model with Demography

Often mathematical models of epidemics assume that the total population is constant, making the mathematical analysis easy. However, in real life scenarios, the population is not static but dynamic due to birth, disease induced mortality, and natural death. A discussion on how the demographic factors can be included in the SIR model is provided, giving a more accurate picture not only of the spread of infection but also of the long term behaviour of the population.