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COVID-19 viral - host interaction dynamics and immune response.

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Declaration and Approval

Declaration

I declare that this work has not been previously submitted and approved for the award of a degree by this or any other University. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Approval

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Abstract

Even as the world eases into the COVID-19 pandemic, new variants of the virus keep sprouting and destabilizing normal routines. Initially, to arrest the high transmission of SARS CoV-2, non-pharmaceutical approaches were utilised simply for damage control as other interventions such as development of vaccines were being explored. Fortunately, the urgency to control the crisis prompted the vaccine development process to be expedited. Concurrently, Food and Drug Administration (FDA) approved the use of Remdesivir to treat specific demographics of COVID-19 patients. Despite these measures, progressive studies are still providing fresh knowledge. Quantitative approaches have therefore provided useful insights in understanding key aspects of SARS CoV-2. We developed and analysed a mathematical model to describe the evolution of the virus, its interaction with immune cells, importance of immune response and potential targets for drug development. The well-posedness of the model was determined based on positivity and boundedness of solutions. The model suggests that a greater efficacy of immune cells significantly reduces the viral load. Further, numerical simulation suggests that inhibiting the progression of latently infected cells to productively infected cells is paramount and this can be achieved by using viral transcriptase inhibitors. We suggest that these inhibitors together with the use of approved vaccines and re-purposed antiviral drugs such as Remdesivir and Baricitinib will have a great impact in controlling the severity of the virus in case of subsequent attacks. COVID-19 vaccines confer immunity by primarily utilising the SARS CoV-2 spike proteins. We evaluated the impact of immunization on target and infected cells. Results obtained from the simulations indicate that a lower vaccine efficacy requires booster shots to augment circulating antibodies necessary to nullify the virus. This model of in-host SARS CoV-2 dynamics has therefore provided knowledge useful to encourage the development of antiviral drugs focused on inhibiting transcription hence arresting viral replication.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ACE-2	angiotensin-converting enzyme 2
APCs	antigen presenting cells
CFR	case fertility rate
COVID-19	Coronavirus Disease 2019
CTL	Cytotoxic T-lymphocytes
DAAs	Direct acting antivirals
FAS	furin activation site
FDE	Fractional Differential Equation
HEL	zinc-binding helicase
ICU	Intensive Care Unit
JAMA	Journal of the American Medical Association
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MHC	Major Histocompatibility Complex
mRNA	messenger RNA
NSP	non-structural proteins
ODEs	Ordinary Differential Equations
ORF	Opening reading frame
PAMPS	Pathogen Associated Molecular Patterns
PRRs	Pathogen Recognition Receptors
RBD	receptor-binding domain
RdRp	RNA-dependentRNA polymerase
RNP	Ribonucleocapsid
RTC	replication/transcription complex
SARS	Severe Acute Respiratory Syndrome
SARS CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
scRNA-Seq	single-cell RNA sequencing
sg	sub-genomic
TMPRSS2	Transmembrane protease/serine subfamily member 2

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CHAPTER 1: Introduction

1.1 Background of the study

There have been extensive outbreaks caused by coronaviruses over the last twenty years resulting in major devastating impacts (Harrison et al., 2020). These viruses can affect humans leading to initial mild infection disorders that progress to severe respiratory illness in particular those caused by SARS virus in 2003 in China (Yang et al., 2020), MERS virus in 2012 in the Kingdom of Saudi Arabia (Killerby, Biggs, Midgley, Gerber, & Watson, 2020) and in 2015 in South Korea (Kim, Tandi, Choi, Moon, & Kim, 2017), and now COVID-19 which is a global pandemic.(Tang et al., 2020). Most infections from coronaviruses are mild, however, previous SARS CoV and MERS-CoV epidemics generated more than 10000 cases collectively in the past two decades with MERS-CoV registering higher mortality rates of 37% as against 10% for SARS CoV (Huang et al., 2020; Lu et al., 2020).

COVID-19 was first identified to have emerged from Wuhan, China in December 2019 (Moore & June, 2020). Ever since, the reported cases has risen rapidly to figures above 470 million cases with 6.1 million fatalities (Worldometer, 2021). With tests only purposed to discriminate those with severe complications and excluding asymptomatic infections, the actual cases could be significantly higher than the reported. This possible under reporting could influence the CFR related to COVID-19. Nonetheless, it is evident from recent data on reported cases that CFR of COVID-19 is lower than the other coronaviruses outbreaks (Bean, 2021).

SARS CoV 2, a virus that causes COVID-19, belongs to a group of enveloped Corona viruses with a positive-sense, single stranded RNA and viral particles resembling a crown from where it derives its name, *corona* in latin (Tang et al., 2020). The genomic sequence of SARS CoV-2 shares 80% similarity with SARS CoV and 50% with MERS-CoV (Harrison et al., 2020). The SARS-CoV-2 genome comprises of a capped and polyadenylated RNA. The single stranded RNA contains one large 5 prime ORF and smaller ORFs. Proteolytic activity on the large ORF by viral proteases produce the non-structural proteins (NSP1-NSP16). The smaller ORFs code for structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N) and other polypeptides. Collectively, these proteins form the SARS-CoV-2 proteome (M. Y. Wang et al., 2020).

The entry of the virus to the host cell is facilitated by the interaction of spike protein (S) with the host ACE-2 receptor (Arya et al., 2021). ACE-2 receptors are located on the surface of epithelial cells. The epithelial cells constitute the outer most layer of most organs including the blood vessels and the lungs (Du & Yuan, 2020). The density and distribution of ACE-2 provide indication of potential infection avenues for the virus. It was through single-cell RNA sequencing (scRNA-Seq) approach that researchers discovered high ACE-2 expression in type II alveolar cells of lungs, oesophagus and stratified epithelial cells, absorptive enterocytes from intestines, cholangiocytes, myocardial cells, kidney proximal tubule cells and bladder urothelial cells. These organs were thereby suspected to be highly vulnerable to viral infection (Xu et al., 2020).

TMPRSS2 is a human protease which enhances viral entry as well. This is achieved through priming of the (S) protein. The S protein consists of two sub units: S1 and S2. S1 has the RBD. This RBD has amino acids that play an essential role in protein-

receptor binding (Thomas, 2020). The entry of virus into the cells is facilitated by the conformational alterations of S2 sub-unit resulting from binding of RBD with the ACE2 receptor. TMPRSS2 inhibitors thus could be considered as possible therapeutic targets for drug development (Pradhan & Olsson, 2020). The viral infection can be broadly broken down into two: First, the virus gains entry through the ACE-2 receptors and penetrate the host cells. Later, the virus attacks the host machinery system and the infected cell turns into virus-producing cells. Virions are produced through the eclipse and burst phase (Poduri, Joshi, & Jagadeesh, 2020).

In developing within host mathematical models, two classes of predator-prey models are typically considered. These classes include: (i) *target-cell limited* models in which case the virus is maintained as a predator feeding upon target cell prey and (ii) *immune-control* models where the virus is a prey that is controlled by an immune response predator (De Boer & Perelson, 1998). The epithelial cells with ACE-2 receptors are considered to be target cells (Du & Yuan, 2020). To fully comprehend the *in-vivo* dynamics of SARS COV 2, we need to understand the course and interaction of the virus with the immune responses.

1.2 Life cycle of SARS CoV-2

Knowledge of virus infection is crucial in not only learning the course but also the possible therapeutic intervention points for drug development. In this section, a summary of the key stages and the mechanisms involved in viral progression is provided. Further, figure 1.1 properly illustrates the life cycle of the virus. Cellular invasion can be principally categorized into two phases; *viral entry* steps which include receptor recognition, endocytosis and viral-membrane fusion and *post entry* steps comprising of translation and replication, viral assembly, maturation and exocytosis (Iacob & Iacob, 2020).

1.2.1 Viral entry stages

SARS CoV-2 entry is facilitated by the binding of spike proteins to ACE-2, located on the surface of epithelial cells (Mandal, 2020). Multiple studies carried on the different coronaviruses have indicated that these viruses invade the host cells through either of two distinct pathways:

- via the cells surface following activation by serine proteases such as TMPRSS2,
- via endocytosis within endosomal–lysosomal compartments including processing by lysosomal cathepsins.

The input of each pathway in a particular cell type is majorly determined by proteases expression; when TMPRSS2 is expressed the previous pathway is favourably chosen whereas in the absence of the protease, the latter pathway is preferred (Murgolo et al., 2021). Further studies have shown that the spike protein in SARS CoV-2 belong to class one viral fusion proteins which essentially means the S protein undergoes cleavage through TMPRSS2 to allow activation (Ramarao, Gaurav, & Gowraganahalli, 2020). The spike protein contain two subunits: *S1* subunit (globular domain) that codes for a receptor binding subunit that facilitates viral binding to ACE2 receptor and *S2* subunit

(transmembrane domain) that ensures fusion with the host membrane (Iacob & Iacob, 2020). Upon binding to the ACE2, the S protein is bisected by the TMPRSS2 that acts as the cleaving enzyme (Mandal, 2020). It has been discovered that SARS CoV-2 utilises a furin activation site (FAS) to bind to ACE2 (Ramarao et al., 2020). Furin activates *S2* subunit to ensure fusion or viral protein in addition to enabling cleavage of spike protein. Following fusion, the viral mRNA enters the host cells to initiate infection. This is a crucial step in understanding the viral infectivity.

1.2.2 Post-viral steps

Once inside the host cell, the single-stranded positive sense RNA acts as messenger RNA (mRNA) (Ramarao et al., 2020). It is further translated by the host ribosomes in a series of events that are involved in viral replication to generate new RNA genomes and RNAs which are essential components for the production of new virons (Romano, Ruggiero, Squeglia, Maga, & Berisio, 2020). Viral RNA synthesis takes place in two stages: genome replication and subgenomic mRNAs transcription followed by viral translation and assembly of viral particles. The initial stages are mediated by the replication/transcription complex (RTC) (Iacob & Iacob, 2020). RNA sysnthesis, proofreading of the template and capping as a post modification event are crucial pathways utilised by SARS CoV-2 (Ramarao et al., 2020).

There is a wide range of functional proteins from the N- to C-termini of polyprotein involved in the replication machinery process. These proteins include: RNA-dependent RNA polymerase (RdRp, Nsp12), the zinc-binding helicase (HEL, Nsp13) and those with enzymatic functions related to RNA modifications such as mRNA capping (Nsp14, Nsp16), RNA proofreading (Nsp14), and uridylate-specific endoribonuclease activity (NendoU, Nsp15). The activity of these enzymes is further regulated by the association with other non-structural proteins (Nsp7–Nsp10) which are probably necessary to achieve all of the replication and transcription processes. All of these protein subunits likely associate in a replication transcription enzyme complex anchored to membranes derived from the host cell which drives the synthesis of new genome molecules and also sub-genomic (sg) messenger RNAs.

Different activities are paramount in ensuring the effectiveness of the entire machinery besides the main RNA replication roles. They include: controlling of host gene expression and impeding the innate immune reactions in infected cells enhanced by Nsp1. Further, the nucleocaspid N protein protects the viral genome from host defence mechanisms by packing it into helical ribonucleocapsid (RNP). Also,the N protein must closely bind to the RNA to make it available for replication process despite its exposure during viral infection. The N terminal, through liaison with C terminal, interacts with viral envelope protein M and is associated with genome condensation and packaging of viral proteins (Romano et al., 2020).

1.2.3 Viral release

Following post mRNA modifications, virons are released from the corrupted cell via budding, exocytosis or cell death. For immature virion particles, budding occurs. During this event, the N protein, whose primary role is to allow proper alignment for virion budding, interacts with host membrane and enable the release. Fully developed viruses

that have matured at the Golgi apparatus or endoplasmic reticulum are released via exocytosis. Through this, the cell integrity is breached by lysosome production resulting in cell death and ultimate release of viral particles (Ramarao et al., 2020).

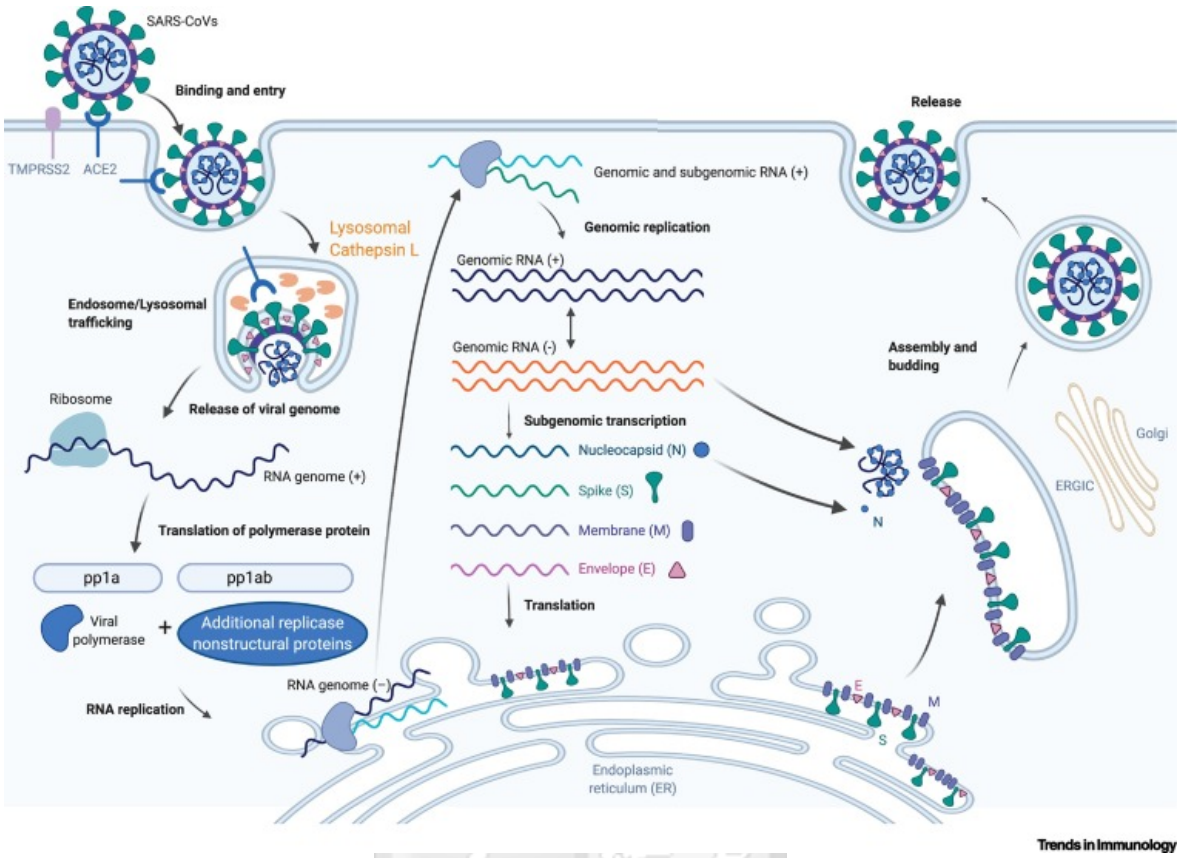


Figure 1.1: Schematic representation of SARS COV-2 life cycle.
Source: Harrison et al. (2020)

1.3 Variability in COVID-19 Severity Across Patient Populations

With the expansion of research scope and accomplishments acquired by researchers globally, the differences in COVID-19 severity across the populations has triggered plenty of analysis. The scale of corona virus infection and progression has been shown to vary among different genders and age.

1.3.1 Age-associated Preference of SARS CoV-2

According to data from Centers for Disease Control and Prevention, the highest SARS-COV-2 severity and mortality falls into the middle-aged and elderly groups, with majority of the COVID-19 mortality cases being 55 and older in the United States of America (CDC, 2020). In addition, data published by the China CDC to Journal of the American Medical Association (*JAMA*), which summarizes the distribution characteristics of COVID-19 patients, showed that 87% of SARS Cov-2 patients are between 30-79 years (Wu & McGoogan, 2020).

With the ongoing research on COVID-19, speculations have been made to explain

the high susceptibility of elderly demographic to SARS COV-2. Indeed it is widely accepted that infectious diseases are more prevalent to elderly people. With regards to COVID-19, statistics show a greater morbidity and admittance to Intensive Care Unit (ICU), high fevers and sizeable mortality rates on the aged bracket (Harrison et al., 2020). This increased vulnerability is due to *immunosenescence*. This is the gradual decline of immune system brought about by normal age advancement. This phenomenon increases susceptibility to other conditions including malignancies and autoimmune disorders. Both innate and adaptive immune responses deteriorate with age. Investigations claim the possibility of impaired barrier provided by the mucosa cells and the diminished adaptive immune response among the elderly could be the reason for increased susceptibility to infectious microorganisms. Furthermore, the reduced effectiveness of the adaptive immune response is a result of the decline in generation of naive T lymphocytes due to *thymic involution*. Age-associated thymic involution is marked by continuous decline in thymus size and structure. These deteriorating conformational changes is closely related to immunosenescence, particularly due to its effects on T-cell composition (Gui, Mustachio, Su, & Craig, 2012). Aging renders both the naive T and B cells dysfunctional but the memory T and B cells function is maintained (Cunha, Perazzio, Azzi, Cravedi, & Riella, 2020).

Surprisingly, recent findings have pointed out rising reported cases of SARS COV-2 among children who previously were considered to not belong to prone subgroups. Children contract the virus mainly from family gatherings. Children constitute a unique group relative to other age groups due to their close family contacts which make them susceptible to cross-infection. From existing epidemiological data, 56% of COVID cases among children are from family gatherings, with 43% from exposure to SARS COV-2 (She, Liu, & Liu, 2020).

1.3.2 Gender-associated severity of SARS-CoV-2

Initial reported data shows that larger number of males were infected by the novel coronavirus (SARS-CoV-2) than females. While this is the case, the molecular mechanisms supporting this remain unclear. Studies have indicated delayed viral RNA clearance in males with SARS COV-2 infection. The main host receptor of SARS-CoV-2 is ACE2, which is a gene located on the X chromosome hence could be quite detrimental in males compared to females who have two copies of the X chromosome. While females have been shown to respond better to vaccination due to high antibody reaction to vaccines they, however, show higher adverse reactions including pain, fever and inflammation to vaccines (Pradhan & Olsson, 2020).

After the initial outbreak of SARS-CoV in 2002-2003, experiments carried out by Stanley Perlman from the University of Iowa found that male mice exposed to SARS coronavirus are more susceptible to infection than female mice. Male mice also exhibited a lower immune response and adverse effects including more severe lung damage and higher mortality rate. Female mice became more likely to die when blocking estrogen or removing ovaries, whereas blocking testosterone in male mice had no such effect. From the results of this experiment, estrogen could play a role in mitigating coronavirus infections to some extent (Channappanavar et al., 2017).
Furthermore, ACE-2 has been reported to be widely expressed in the ovary, uterus, vagina and placenta. This study demonstrated the potential damage of SARS-CoV-2 to female reproductive system and consequently, fertility. Therefore, in addition to contact

transmission via contaminated droplets, investigations of whether vertical transmission of mother-child or sexual transmission are been carried out (Jing et al., 2020).

1.3.3 Behavioural factors

A study conducted in China showed that men (67%) were highly predisposed to SARS COV-2 than women. This sex predisposition could be associated with higher smoking rate in Asian men compared to women although no strong association can be drawn to elicit a conclusion (Cai, 2020).

1.3.4 Co-morbidity-related Severity of SARS CoV-2

The prevalence of underlying conditions also affects the degree of infection of men and women with COVID-19. Type-2 diabetes remains a vital co-morbidity to SARS COV-2. However, the association of type-2 diabetes with severity and mortality of COVID-19 patients still remains unclear. A study carried out in China showed patients with type 2 diabetes required a greater attention with a higher mortality rate and associated multiple organ failure. Thereby optimal blood glucose control could play a crucial role in the prognosis of COVID-19 treatment. Also it showed that patients with type 2 diabetes were facing more pressure when fighting against the invasion of SARS-CoV-2 (Zhu et al., 2020).

In patients with cardiovascular conditions and hypertension, the level of plasma ACE2 is high and they experience severe implications from the viral infection with a high risk of multiple organ failure due to uncontrolled amplification of cytokine production (Liu, Blet, Smyth, & Li, 2020).

1.4 Immune System and Viral Infections

The immune system is a network of complex biological processes that helps repel disease causing organisms referred to as pathogens (Perdue & Humphrey, 2020). Immunity is broadly divided into two cooperative classes: innate and adaptive systems. The innate confers non-specific protection to pathogens equally while the specific adaptive system develops to attack particular foreign microorganisms. The innate system provides the first line of defense from pathogens. It comprises of a group of cells including macrophages, monocytes, dendritic cells and granulocytes which directly eradicates the pathogens as well as linking up and stimulating the adaptive system through the antigen presenting cells (APCs). The innate system detects the invasion of pathogens through the Pathogen Recognition Receptors (PRRs) which identify particular molecular patterns referred to as Pathogen Associated Molecular Patterns on the pathogen. This results in transcription of innate immune genes and induction of cytokines.

During respiratory, viral infection such as SARS COV-2, a cascade of events take place via mediation of innate responses and the epithelial cells with $ACE2$ receptors. The detection and recognition of viral RNA by the endosomal PRRs results in activation of various transcription factors which in turn triggers the expression of type 1 and type 3 interferons. Interferons release molecules that call upon and amplifies the innate immune system. These molecules also alert the neighbouring epithelial cells of an invasion. The normal cells stimulate anti-viral immunity to prevent attack from the virus. Despite this, little is known about the interaction between the innate system and

SARS COV-2. Recent findings however indicate an increased neutrophils to monocytes ration in the lungs of infected patients particularly among the middle aged group of patients (O'Connell & Aldhamen, 2020).

The adaptive immune, in contrast, takes longer to be established. In addition to its specificity it produces memory cells which provides immunity in case of re-infection. The adaptive system is mobilized when the pathogen overwhelms the innate system. The dendritic cells migrate to the lymph and stimulates the activation of the adaptive system. The adaptive system is divided into cell-mediated immune response, which is carried out by T cells, and the humoral immune response, which is controlled by activated B cells and antibodies. Similarly, both T and B cells recognize the antigen via a complimentary receptor followed by self-maturation to specifically bind to the particular antigen of the infecting pathogen.

Naive T cells express either CD4 or CD8 cells on their surface and accordingly classified as $CD4^+$ or $CD8^+$ cells. Naive $CD4^+$ cells binds to the antigen presenting cells(APC) to stimulate the maturation to T helper cells which stimulate the differentiation and maturation of B cells which secretes cytokines. Naive $CD8^+$ cells differentiate to cytotoxic T cells which are directly involved in the eradication of the pathogens. Current investigations on middle aged COVID-19 patients have noted the reduction in type 3 interferon($IFN\gamma$) which is stimulated by the $CD4^+$ cells. Striking difference appears where $CD8^+$ cells have been shown to be hyper-activated and exhausted concurrently.

There are two categories of immune responses generated by immune system during viral infections: lytic and non-lytic mechanisms. The previous involves killing of infected cells while the latter applies mechanisms to hinder viral replication by using soluble mediators. Cytotoxic T lymphocytes are highly involved in killing corrupted cells though antibodies too play a fundamental role in deactivating free virus resulting in inhibition of infected cells (A. Chatterjee, Basir, Almuqrin, Mondal, & Khan, 2021).

Over the years, coronaviruses have evolved and developed mechanisms to evade immune system. These mechanisms have been observed in the previous betacoronaviruses outbreaks and recent findings suggest SARS CoV-2 is no exception (Harrison et al., 2020). The key target for evasion is the interfon pathway due to rapid and potent viral infection elimination. Coronaviruses avoid immune recognition through:

(i) the formation of DMVs that "hide" viral nucleic acid from recognition by PRRs.

(ii) directly "shuts down" immune signaling molecules functionality by viral proteins

1.4.1 Mechanisms of action of COVID-19 vaccines

Vaccines are biological suspensions administered by injection, orally or nasally. They contain agents that resemble disease-causing microorganisms formed from weakened, killed or fragmented forms of the microbes, its toxins, antibodies or lymphocytes aimed at disease prevention.

Vaccines can confer both active and passive immunity. In active immunity, it triggers the immune system to attack the antigen and create memory B-cells that remain responsive to future attacks from the foreign agent. The vaccines may also provide antibodies already created by the animal or human donor conferring passive immunity (Brunson,

2018). The bottom line mechanism of action of vaccines is exposing the body to target pathogen to stimulate an immune response, however the route of exposure varies.

Currently, several authorized front runner companies have rolled COVID-19 vaccines and Kenya is among the countries undertaking large scale vaccinations to the public. After vaccination, it takes a few weeks to produce T-lymphocytes and B-lymphocytes, hence a person could be infected with SARS CoV-2 virus just before or after vaccination and get sick. There are three types of COVID-19 vaccines that have been approved, recommended and have shown to not give COVID-19. they categories include: *mRNA* , protein sub-unit and vector vaccines. (CDC, 2021).

a. **mRNA vaccines**

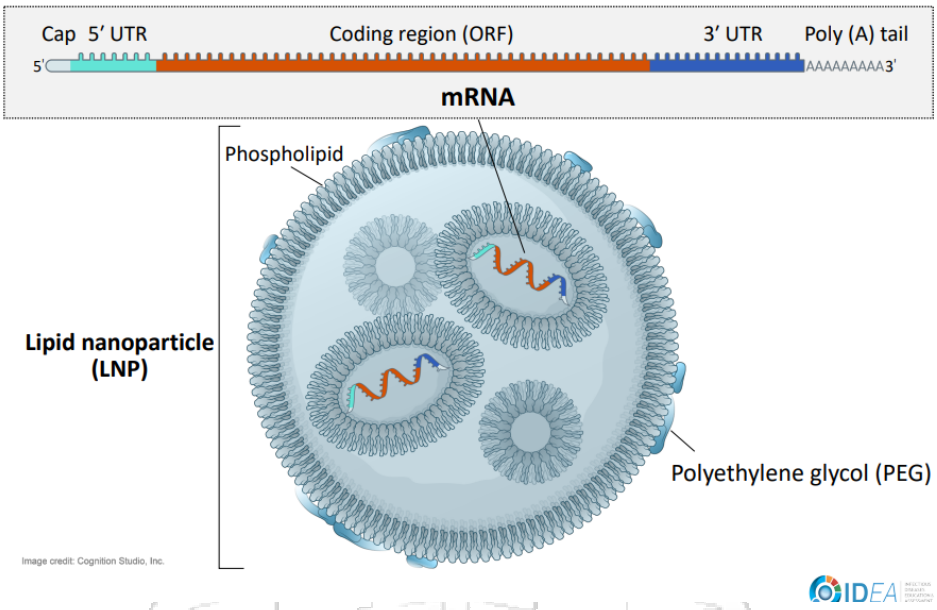


Figure 1.2: Structure of mRNA vaccines

Source: SARS COV-2

These vaccines fall under nucleic acid vaccines, DNA and RNA vaccines, that use genetic material from COVID-19 to trigger immune response against it (Gavi, 2020a). Covid-19 vaccines mRNA consists of mRNA, with the Cap 5' and 3' UTR elements to enhance stability and translation of the nucleic acid, enclosed in lipid nanoparticle (LNP) which offers protection from degradation as well as facilitate cellular uptake of mRNA. The open reading frame (ORF) is the coding region with genetically engineered sequence that encodes the SARS CoV-2 spike protein. After administering through intramuscular injections, the mRNA enters the cell cytoplasm where its translated by the ribosomes to form SARS COV-2 spike proteins that are transported to the cell surface and presented to the immune system. Moderna COVID-19 Vaccine (mRNA-1273) and Pfizer-BioNTech COVID-19 (BNT-162b2) uses this relatively new technology to produce vaccines. Each of the above vaccines require two doses. (Spach, 2020).

b. **Protein Sub-unit Vaccines**

They belong to sub-unit vaccines that uses harmless pieces of proteins and/or polysaccharides from SARS CoV-2 rather than injecting the whole pathogen (CDC, 2021). The protein fragments are attentively studied to identify combinations that are highly likely to produce the least harm and strong immune response to the respondent. These vaccines are relatively cheap and easy to produce and more stable than those utilizing whole organism. However, the antigens used to stimulate an immune reaction may lack PAMPs therefore not recognised as danger signals by the immune cells consequently eliciting a weaker response (Gavi, 2020b).

c. **Vector Vaccines**

Viral vector-based vaccines contain a modified virus which serves as a vector to deliver the genetic code for the antigen (COVID-19 spike proteins) into the human cells. (Gavi, 2020c). Enclosed in the modified virus is the antigen that causes SARS CoV-2 CDC (2021). There are two main types of viral vector-based vaccines, non-replicating and replicating vector vaccines. COVID-19 vaccines uses non-replicating vaccines which only produce the vaccine antigen rather than manufacturing new viral particles. In contrast, replicating vector vaccines produce new viral particles in cells they infect, which infect new cells that make the vaccine protein (Gavi, 2020c). Inside the cells, the genetic materials provides cellular instructions to produce proteins unique to the COVID-19 virus. The cells make copies of the proteins prompting an immune reaction and resulting memory cells for future viral attacks (CDC, 2021). AstraZeneca , which is being used in Kenya, is a viral vector-based vaccine.

1.5 Problem Statement

With the continuing COVID-19 pandemic caused by SARS COV-2, efforts are been made to attenuate the transmission to manageable levels. With the successful development of vaccines, fully vaccinated population in Kenya (23.59%) is comparatively low to the global stage (62.08%) (our world in data, 2021). After enrollment of the vaccines, the Kenyan government highly encouraged the masses to be vaccinated besides adopting non-pharmaceutical strategies to mitigate the spread. The measures set in place included proper hand washing, mandatory wearing of masks, self isolation to those with COVID-19 like symptoms, encouraging social distancing, imposing curfew hours and limiting large crowds in social gatherings. Several epidemiological models have been developed to provide insights in the transmission rates of the pandemic as well as advise the government on how to relax the measures set in place.

In-host mathematical models have prospered over the last few decades, and have been used to describe the intricate dynamics of various infectious diseases such as HIV, Ebola or even malaria parasite. The low number of within host mathematical models of SARS COV-2 could be attributed to limited experimental information available about the virus. Concerted efforts are underway to understand the advancement of the disease and the interaction with the immune responses. Comparisons have been drawn from the

previous corona viruses pandemics, SARS COV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), to deduce possible patterns that would point the research and experiments in the right direction. Appreciating the interactions of COVID-19 with the immune system will provide potential targets for drug development and inhibit the propagation of the virus.

As we continually receive fresh information about the virus, so are advanced models being developed. The cornerstone for majority of these models is the target-cell limited model. In these models, the virus attacks and infects naive susceptible cells. Most in-host SARS CoV-2 models have modified this model to suit their objectives. A great proportion of the models have maintained the basic components of target-cell limited models with the aim of describing the evolution of the virus in the host, while others have incorporated the immune system which interacts with the virus. However, majority of these models fail to capture the eclipse phase. During this phase, the cell undergoes the various stages of infection such as uncoating, translations, transcriptions and virion assembly. The model also introduces the intervention by immune cells either towards free circulating virus or during infection of epithelial cells. Further, our model shows that the immune system is heightened when the virus is introduced. Additionally, this model looks at the impact of vaccines to the epithelial cells. These inputs have been incorporated in this model to represent a biologically feasible premise.

1.6 Research Objectives

- **General Objective**
  The main objective is to develop a mathematical model for the in-vivo interaction between SARS COV-2, host, and the immune system.
- **Specific Objectives**
  1. To describe the progression of the virus in the host cells through a deterministic model.
  2. To analyze the importance of the immune cells on the virus, and the infected cells.
  3. To identify potential targets for drug development against the virus.

1.7 Justification

Although little, as yet, is known about the COVID-19 dynamics within the host levels, progressive studies are continually being developed to boost the understanding. Recent studies have attempted to model the dynamics using known biological mechanisms between the immune cells and previous corona viruses (SARS CoV and MERS). This has provided useful insights of the virus and how it affects the immune system. In this study, our focus is to capture the progression of the virus in the host. The life cycle of SARS CoV-2 provides useful information to formulate a model to be used in this project. Also, from examination of previous research carried out on beta coronaviruses interaction with the immune system, the model proposes to explore the significance of immune responses on the viral dynamics. The current enrolment of vaccines have prompted the need to recognize probable targets in the virus course that would have a remarkable effect in its destruction. Accordingly, the model intends to identify these

possible targets for drug development that would have maximum effect. The model further attempts to relate the impact of vaccines and to what extent they evoke the immune cells. Improvements can be made based on the information to demonstrate how the progression could explain the severity of the virus in specific demographics particularly those who with co-morbidities. Most importantly, the research is timely as the world is still undergoing the pandemic hence it will provide a better comprehension of the dynamics of the virus within the host.

CHAPTER 2: Literature Review

2.1 Introduction

Mathematical models have been productive for obtaining insightful understanding into the in vivo dynamics of viral infections. Viral infectious diseases have been, and continue to be, a global health concern as is evident by the pandemics of Middle East Syndrome, Ebola virus disease and most recently, SARS CoV-2, among others. The viral epidemics have provided a socio-economic problem that has both short and long term costs for disease diagnosis and treatment. The results of these pandemics underline the importance of a proper analysis of viral-host interactions, which would help understand the mechanisms of the diseases and develop interventions. Dynamic mathematical modeling has improved the understanding of in-vivo viral dynamics, pathogenesis of the virus, transmission patterns and disease progression. Additionally, the models have assisted to identify drug targets which in turn forecasts disease duration and help reduce treatment costs (Zitzmann & Kaderali, 2018a).

Du and Yuan (2020) applied mathematical modeling to investigate the impact of innate and adaptive immune responses on the progression of the disease. They made modifications on target-cell limited model incorporating the different immune systems on the model. They validated their model using influenza virus then later compared between the two viruses. According to the study, there exists a timing mismatch between the two divisions of the immune system with the adaptive system highly probable to arrive before the peak of the viral load in COVID-19 patients. In contrast, the opposite takes place in influenza patients. This difference in adaptive response timing results in delayed depletion of vulnerable epithelial cells in the lungs in COVID-19 patients while enhancing viral clearance for influenza patients. Based on their analysis, delaying the onset of the adaptive immune response during the early phases of infections could be a potential treatment for severe COVID-19 patients.

Wanga, Mondal, Samui, Chatterjee, and Yusuf (2022) proposed a mathematical model to describe the interaction between the SARS CoV-2 virus and the epithelial cells of the human lungs. Further, they explored optimal control strategies representing antiviral drug treatment effects. They employed the Pontryagin's maximum principle to clarify the optimal control strategies. Based on their numerical simulations, efficiency and cost-effectiveness analysis, they concluded that a time-dependent antiviral drug with other control mechanisms would reduce the viral load and control the infection process.

A. N. Chatterjee and Al Basir (2020) proposed and analyzed a mathematical model to investigate the effect of Cytotoxic T-lymphocytes(CTL) responses over the viral mutation to control viral infection when a post-infection immunostimulant drug is administered at regular intervals.

Previous studies have reviewed the in-host viral dynamics. Zitzmann and Kaderali (2018b) analysed the target cell-limited models applied for various large-scale viruses including Zika virus, Dengue virus, Ebola virus, Hepatitis virus, Influenza A virus and HIV. Further, they evaluated different extensions of the target cell-limited models incorporating antiviral interventions, immune responses and a multi-scale age-based models for direct acting antivirals (DAAs). They employed these adjunct models to understand the dynamics of the mentioned viruses. They noted that the target cell me-

diated models focused only on the essential players in viral-host interaction, disregarding the intracellular processes. These models however, formed the rudimentary backbone for other modifications. To combine the effects of immune reactions, particularly the innate immune responses, on viral dynamics, they integrated key aspects of the immune responses which hinder the viral life cycle. Additionally, they included the effect of immune system (both innate and adaptive immune responses) into the model.

Nath, Chu, and Sarmah (2021) mathematically evaluated earlier work from Chentong, Jinhu, Jiawei, and Yicang (2020), focusing on assessing the properties of the model such as boundedness and non-negativity of solutions. Also, they calculated the basic reproduction number and examined the stability analysis of the system. From the earlier work done by Chentong et al. (2020), a within-host viral dynamic model was used to describe the SARS CoV-2 kinetics within a host. They drew comparisons between SARS Cov-2 and MERS via the chest radio graph score data which was used to estimate the parameters. The results showed a higher death rate of COVID-19 than MERS. Also the death rate was larger than the clearance rate thereby indicating the virus can be cleared directly by the immune system. Further, the R_0 of SARS CoV in severe patients was lower relative to MERS virus. MERS had a higher virulence rate to infect the pulmonary epithelial cells than SARS CoV explaining why the former had a higher mortality and a shorter incubation period. Using chest radio graph score posed a major drawback as the data was not real.

In a similar fashion, Lee et al. (2009) developed a mathematical model to forecast immune reactions to influenza A (H1N1) infection. In addition to describing the viral-immune cells interaction, it also captures the different immune response situations with key emphasis on a couple of variables including viral pathogenicity, role of antigen-presenting cells and concentration of B-cells and T-cells responding to the invasion. The model puts forward that protracted viral infection hinders T-cell production and inhibits antigen presentation to immune cells. The outcome also suggested that antiviral therapy is most effective within two days of viral infection. The researchers used delay differential equations to explain time delays between viral infection, immune cell activation and movement of immune effector cells between tissue and the lymph.

A report by Xiulan (2014) provides a general summary of the interaction between virions and the host immune system. Prior to invasion, the virus has a short extracellular span compared to the intracellular period. During the latter, replication takes place. The immune cells can target the virus in either of these two stages, however, it is in the course of viral assembly that antigens are presented on the membrane of infected cells that immune system is triggered in response. Various components of the innate and adaptive immune systems are aimed towards inhibiting different stages of viral life cycle as discussed earlier on. They also went ahead to describe how CD8+ cytotoxic T lymphocytes migrated using chemotactic movement during a viral attack. In this, they used a reaction diffusion model with chemotaxis. From their discovery, they established that while chemoattractive movement did not destabilize the positive steady state of the model, chemorepulsion did, as the chemotactic sensitivity increased, due to HIV infection.

Another variation of the basic viral-host interaction was exploited by Dai, Ma, Song, and Wang (2014) in which they concentrated on modifying the infection rate in an attempt to capture a more biologically feasible system. In their argument, they claimed

that most experiments on microparasitic infections suggested that infection rate was nonlinear thereby disregarding the assumption that infection rate was conditioned on mass-action principle.

Fractional Differential Equation (FDE) has been a crucial addition in mathematical modeling according to A. Chatterjee et al. (2021). This tool uses a fractional derivative operator to describe the intrinsic memory property in a biological system. The equation also reduces errors from neglected parameters in usual models. The researchers used this technique to explore the interaction between SARS CoV-2 and the cytotoxic T cells. Two immune responses were incorporated: lytic and non-lytic immune reactions. They also included the effect on antiviral treatment in an optimal control-theoretic approach. To describe the interaction, they introduced an inhibition term $(1 + pC)$ on the transmission rate β due to the non-lytic property of immune response.

Additionally, Hattaf and Yousfi (2020), surmised the lytic and non-lytic immune responses in the interaction of the virus, host epithelial cells and the cytotoxic T lymphocyte cells. The proposed model factored in two modes of transmission: virus-to-cell infection and cell-to-cell transmission.

Esteban, Hernandez, Jorge, and Velasco (2020) put forward an in-vivo mathematical model of SARS CoV-2 and the interaction with the immune system. The model adapted a minimalistic model to capture the immune cells response to the virus. In their model, virus replication incorporated a logistic function with the carrying capacity K. The immune T-cells reaction was heightened in the presence of virus and was represented by $rT(\frac{V^m}{V^m+K_T^m})$. They observed that the virus presence prompted a gradual T-cell response against the virus. During the first days post infection, low inflammation levels may have been promoted by the slow immune responses.

Vabret et al. (2020) provided a summary of what is known as yet of immune responses promoted during SARS CoV-2 invasion as well as the immunological pathways which may contribute to disease severity. They evaluated both the innate and T-cell sensing when the virus attacks as well as the S protein as the target for vaccine development. Further, they investigated the various evasion methods utilised by the virus to elude the innate system. They used different predictors to analyze the severity of COVID-19 such as immunological and susceptibility and risk bio markers.

Target cell limited models form a firm framework for most within host SARS CoV-2 mathematical models. Majority of these models highlighted in the above review have modified the target cell limited models to accommodate what is known of the viral dynamics, and the relationship with immune system. The model proposed maintains the foundation of the target cell limited model while adapting the various extensions obtained from the earlier models. This model borrows ideas on the transmission inhibition by the immune cells, the use of non-lytic mechanisms by immune activity as well as how the immune cells are triggered during the introduction of the virus in the host. The model does not consider the specific immune cells or the distinct branch of the immune system involved. It however puts forward the knowledge on the eclipse phase during viral progression which most models did not consider. Integrating this phase broadly captures the various stages of the virus life cycle before maturation.

CHAPTER 3: SARS CoV-2 Invivo Model

3.1 Model Formulation

To describe the interaction between the immune system and SARS CoV-2, a five states compartmental model was applied. The model majorly incorporates the target-cell limited model. These models belong to a sub-class of the prey-predator model. In a target-cell limited model, the virus is considered as the predator. It attacks and corrupts the cell which is the prey. This model has been used mostly in *in-vivo* modeling of viral infections. The other sub-class is the immune-control models. In these models, the virus which is the prey, is controlled by an immune response predator.

The model assumes a group of uninfected target epithelial cells, denoted as E_S, are generated at a rate Λ in the body with a carrying capacity of K_1 and a natural death rate μ_1. Through interaction of the virus (V) with the uninfected target cells (E_S), the target cells become infected. This infection is limited in the presence of host immune response, represented as $\frac{\beta}{1+\alpha_1 N}$, where β is the infection rate and α_1 represents the efficacy of immune system intervention. The infection results in the transition of the uninfected cells to latently infected cells, E_{IL}. At this stage, the virus attains a state of dormancy as it undergoes the various stages of viral infection including translation of the viral RNA by using the host machinery system which leads to formation of enzymes that are involved in viral replication, and consequently generation and assembly of new viral particles. These dormant cells remain undetected by the hosts immune system through processes like down-regulation of the Major Histocompatibility Complex (MHC) and inhibiting the apoptotic pathway but can die naturally at a rate of μ_2.

Subsequent to the dormancy state, the infected cell progresses to a productive state (E_{IP}) which involves viral shedding. Similarly, this progression is limited by the interaction with the host immune response hence represented as $\frac{\gamma}{1+\alpha_2 N}$, where γ is the progression rate and α_2 represents the intervention by immune cells. Virion release from the infected cells occur primarily through budding, exocytosis or cell death. In most cases, virus attack destroys the host machinery system resulting in the release of lysosomes which leads to cells death and release of the virions. In contrast to dormant infected cells, these productive cells are recognized by the immune system and mechanisms are initiated to destroy them. The number of virions released by the death productive infected cells is represented by κ. The virions die naturally or due to destruction by the immune cells at a rate δ and ν respectively. The immune cells are produced at a rate of Π with a carrying capacity K_2. Following a viral infection, the host immune system is induced to produce more immune cells which is presented in a log sigmoid concept as $\epsilon N(t)(\frac{V(t)}{\zeta+V(t)})$, where ϵN is the maximum rate of immune cells production and ζ represents a Michaelis-Menten constant that depicts when the rate of interaction between the immune cells and virus is half the maximum rate. The immune cells die naturally at a rate σ.

3.1.1 Model Assumptions

(i) The SARS COV-2 selectively attacks the epithelial cells with $ACE2$ receptors.

(ii) The uninfected epithelial cells, E_S are constantly being produced in the body until they reach the carrying capacity.

(iii) There exists natural death rates for cells and virions.

(iv) The latent cells are undetected by the immune system and any interventions directed to these cells are non-lytic which only limits viral replication. Non-lytic activity of immune cells inhibits viral replication via soluble molecules. These molecules are responsible for attracting immune cells as well as regulatory and signaling roles.

(v) Production of the virons occurs solely due to lysis of the infected cells. The lytic effectors kills the infected cells. It is assumed that, at this stage, the cytopathic effect of the virus has been experienced and any attempt to destroy the cells would result in virion production.

(vi) The virus levels induce the production of the immune response cells. The introduction of the virus expands the immune response besides the general elimination of antigens in the host. The increase in response is thereby proportional to the level of virions present.

(vii) The model does not differentiate between the various components of the immune system such as cytotxic T-cells and antibodies. In principle, the immune system should neutralize the virus antigen hence analyzing which branch has the most contribution will not be objective on this project.

3.1.2 Model Parameters

Table 3.1: Description of parameters for the model

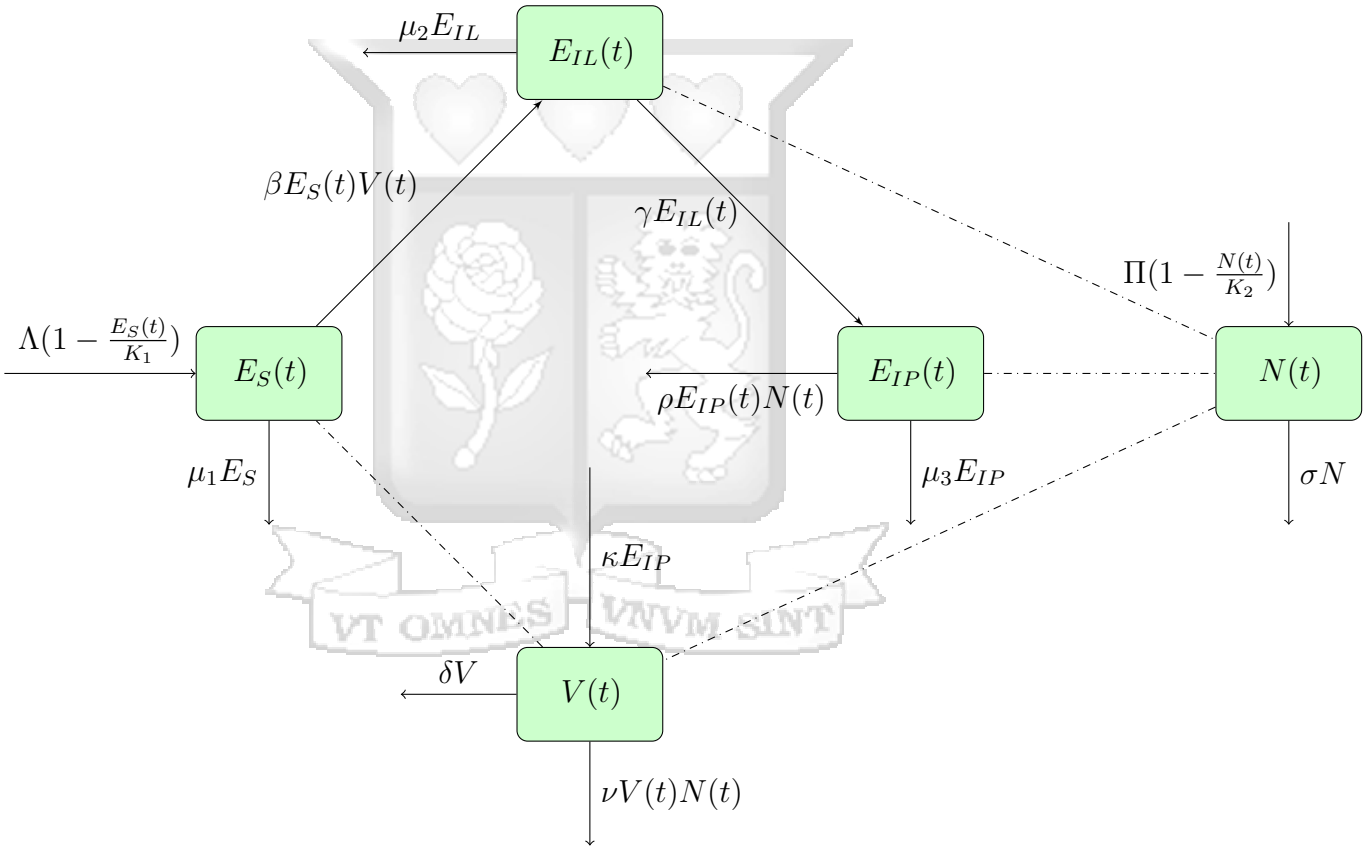
Parameter	Description
Λ	Number of uninfected epithelial cells produced
K_1	Carrying capacity of the epithelial cells
K_2	Carrying capacity of the immune cells
μ	Natural death rate of epithelial cells
δ	Natural death rate of virus
σ	Natural death rate of immune cells
β	Rate of infection
ρ	Removal rate of the infected epithelial cells due to interaction with immune cells
Π	Number of immune cells produced
ν	Removal rate of the virus due to interaction with immune cells
κ	Number of virons produced from infected cells
γ	Transition rate of latent epithelial cells
α_1	Intervention rate by the immune cells to virus infection
α_2	Intervention rate by the immune cells to transition of latent epithelial cells
ζ	Michaelis-Menten constant-measure of cytokines production
ϵ	Recruitment rate of immune cells due to viral invasion

Table 3.2: Model variables

Variable	Description
$E_S(t)$	Susceptible epithelial cells
$E_{IL}(t)$	Latent epithelial cells
$E_{IP}(t)$	Productively active Infected epithelial cells
$V(t)$	Virions
$N(t)$	Immune cells

3.2 Model Framework

A compartmental representation of the SARS CoV-2 *in-vivo* dynamics as shown in Figure 3.2 below:



3.3 Model Equations

Using the model description in 3.1 and the flow diagram in 3.2, the SARS CoV-2 model is presented as follows:

$$\left.\begin{aligned}
\frac{dE_S(t)}{dt} &= \Lambda\left(1-\frac{E_S(t)}{K_1}\right) - \frac{\beta}{1+\alpha_1 N(t)}E_S(t)V(t) - \mu_1 E_S(t),\\
\frac{dE_{IL}(t)}{dt} &= \frac{\beta}{1+\alpha_1 N(t)}E_S(t)V(t) - \mu_2 E_{IL}(t) - \frac{\gamma N(t)}{1+\alpha_2 N(t)}E_{IL}(t),\\
\frac{dE_{IP}(t)}{dt} &= \frac{\gamma N(t)}{1+\alpha_2 N(t)}E_{IL}(t) - \mu_3 E_{IP}(t) - \rho E_{IP}(t)N(t),\\
\frac{dV(t)}{dt} &= \kappa E_{IP}(t) - \nu V(t)N(t) - \delta V(t),\\
\frac{dN(t)}{dt} &= \Pi\left(1-\frac{N(t)}{K_2}\right) + \epsilon N(t)\left(\frac{V(t)}{\zeta+V(t)}\right) - \sigma N(t).
\end{aligned}\right\} \tag{3.1}$$

subject to the following initial conditions:
$E_S(0) \geq 0, E_{IL}(0) \geq 0, E_{IP}(0) \geq 0, V(0) \geq 0, N(0) \geq 0.$

3.4 Model Properties and Analysis

3.4.1 Positivity of Solutions

We show that all state variables are non-negative and that the solution of the system 3.1 with positive initial values remain positive for all $t \geq 0$.
From the first equation in system (3.1):

$$\begin{aligned}
\frac{dE_S(t)}{dt} &= \Lambda(1-\frac{E_S(t)}{K_1}) - \frac{\beta}{1+\alpha_1 N(t)}E_S(t)V(t) - \mu_1 E_S(t),\\
\frac{dE_S(t)}{dt} &\geq -\frac{\beta}{1+\alpha_1 N(t)}E_S(t)V(t) - \mu_1 E_S(t).
\end{aligned} \tag{3.2}$$

Assuming no contribution from the immune system, equation (3.2) becomes:

$$\frac{dE_S(t)}{dt} \geq -(\beta V(t) + \mu_1)E_S(t). \tag{3.3}$$

Using separation of variables and applying initial conditions in equation (3.3):

$$\begin{aligned}
\int \frac{dE_S(t)}{E_S} &\geq \int -(\beta V(t) + \mu_1)dt,\\
\ln E_S &\geq \int_0^t -(\beta(\tau) + \mu_1)d\tau,\\
E_S &\geq e^{\int_0^t -(\beta V(\tau)+\mu_1)d\tau}.
\end{aligned} \tag{3.4}$$

Thus

$$E_S(t) \geq E_S(0)e^{\int_0^t -(\beta V(\tau)+\mu_1)d\tau} > 0.$$

Similarly for the second equation in 3.1:

$$\frac{dE_{IL}(t)}{dt} = \frac{\beta}{1+\alpha_1 N(t)} E_S(t)V(t) - \mu_2 E_{IL}(t) - \frac{\gamma N(t)}{1+\alpha_2 N(t)} E_{IL}(t),$$
$$\frac{dE_{IL}(t)}{dt} \geq -(\mu_2 + \gamma N(t))E_{IL}(t). \tag{3.5}$$

Using separation of variables and applying initial conditions in equation (3.5):

$$\int \frac{dE_{IL}(t)}{E_{IL}} \geq \int_0^t -(\mu_2 + \gamma N(\tau))d\tau,$$
$$\ln E_{IL} \geq \int_0^t -(\mu_2 + \gamma N(\tau))d\tau,$$
$$E_{IL} \geq e^{\int_0^t -(\mu_2+\gamma N(\tau))d\tau}. \tag{3.6}$$

Thus

$$E_{IL}(t) \geq E_{IL}(0)e^{\int_0^t -(\mu_2+\gamma N(\tau))d\tau} \geq 0.$$

For the third equation in 3.1:

$$\frac{dE_{IP}(t)}{dt} = \frac{\gamma N(t)}{1+\alpha_2 N(t)} E_{IL}(t) - \mu_3 E_{IP}(t) - \rho E_{IP}(t)N(t),$$
$$\frac{dE_{IP}(t)}{dt} \geq -(\mu_3 + \rho N(t))E_{IP}(t). \tag{3.7}$$

Using separation of variables and applying initial conditions in equation (3.7):

$$\int \frac{dE_{IP}(t)}{E_{IP}} \geq \int_0^t -(\mu_3 + \rho N(\tau))d\tau,$$
$$\ln E_{IP} \geq \int_0^t -(\mu_3 + \rho N(\tau))d\tau,$$
$$E_{IP} \geq e^{\int_0^t -(\mu_3+\rho N(\tau))d\tau}. \tag{3.8}$$

Thus

$$E_{IP}(t) \geq E_{IP}(0)e^{\int_0^t -(\mu_3+\rho N(\tau))d\tau} \geq 0.$$

For the fourth equation in 3.1:

$$\frac{dV(t)}{dt} = \kappa E_{IP}(t) - \nu V(t)N(t) - \delta V(t),$$
$$\frac{dV(t)}{dt} \geq -(\nu N(t) + \delta)V(t). \tag{3.9}$$

Using separation of variables and applying initial conditions in equation (3.9):

$$\begin{aligned}\int \frac{dV(t)}{V} &\geq \int_0^t -(\nu N(\tau)+\delta)d\tau,\\ \ln V &\geq \int_0^t -(\nu N(\tau)+\delta)d\tau,\\ V &\geq e^{\int_0^t -(\nu N(\tau)+\delta)d\tau}.\end{aligned} \tag{3.10}$$

Thus

$$V(t) \geq V(0)e^{\int_0^t -(\nu N(\tau)+\delta)d\tau} \geq 0.$$

For the fifth equation in 3.1:

$$\begin{aligned}\frac{dN(t)}{dt} &= \Pi\left(1-\frac{N(t)}{K_2}\right)+\epsilon N(t)\left(\frac{V(t)}{\zeta+V(t)}\right)-\sigma N(t),\\ \frac{dN(t)}{dt} &\geq -\sigma N(t).\end{aligned} \tag{3.11}$$

Using separation of variables and applying initial conditions in equation (3.11):

$$\begin{aligned}\int \frac{dN(t)}{N} &\geq \int -\sigma dt,\\ \ln N &\geq -\sigma t + C,\\ N &\geq Ce^{-\sigma t}.\end{aligned} \tag{3.12}$$

Thus

$$N(t) \geq N(0)e^{-\sigma t} \geq 0.$$

3.4.2 Boundedness of the Solutions

The total population of epithelial cells is given by:

$$E_T = E_S + E_{IL} + E_{IP}$$

Substituting the derivatives in system (3.1), we have

$$\begin{aligned}\frac{dE_T(t)}{dt} &= \Lambda - \frac{\Lambda E_S(t)}{K_1} - \mu_1 E_S(t) - \mu_2 E_{IL}(t) - \mu_3 E_{IP}(t) - \rho E_{IP}(t)N(t),\\ \frac{dE_T(t)}{dt} &\leq \Lambda - \mu E_T(t),\\ \frac{dE_T(t)}{dt} &+ \mu E_T(t) \leq \Lambda.\end{aligned} \tag{3.13}$$

The integrating factor for (3.13) is given by:

$$I.F = e^{\mu t}. \tag{3.14}$$

Multiplying (3.13) by the integrating factor given in (3.14) we have

$$E_T(t)e^{\mu t} \leq \frac{\Lambda}{\mu}e^{\mu t} + C,$$
$$E_T(t) \leq \frac{\Lambda}{\mu} + Ce^{-\mu t}.$$

Applying the initial condition in (3.1), we obtain

$$E_T(t) \leq \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + E_{T0}e^{-\mu t}$$

Clearly, there exists a bounded positive invariant region for the epithelial cells, that is

$$0 \leq E_T \leq \frac{\Lambda}{\mu}.$$

Similarly, for the immune cells:

From system (3.1), we have

$$\begin{aligned}
&\frac{dN(t)}{dt} = \Pi - \frac{\Pi N(t)}{K_2} + \epsilon N(t)\left(\frac{V(t)}{\zeta + V(t)}\right) - \sigma N(t),\\
&\frac{dN(t)}{dt} \leq \Pi - \sigma N(t),\\
&\frac{dN(t)}{dt} + \sigma N(t) \leq \Pi. \qquad (3.15)
\end{aligned}$$

The integrating factor for (3.15) is given by:

$$I.F = e^{\sigma t}. \qquad (3.16)$$

Multiplying (3.15) by the integrating factor given in (3.16) we have

$$N(t)e^{\sigma t} \leq \frac{\Pi}{\sigma}e^{\sigma t} + C,$$
$$N(t) \leq \frac{\Lambda}{\mu} + Ce^{-\sigma t}.$$

Applying the initial condition in (3.1), we obtain

$$N(t) \leq \frac{\Pi}{\sigma}(1 - e^{-\sigma t}) + N_0e^{-\sigma t}.$$

Clearly, there exists a bounded positive invariant region for the immune cells, that is

$$0 \leq N(t) \leq \frac{\Pi}{\sigma}.$$

3.4.3 Equilibrium Analysis of the Model

The next generation matrix method was applied to derive the basic reproduction number, R_0. The system has a disease-free equilibrium point when there is no infection in the body and is obtained by setting the infected class to zero, that is, $E_{IL} = E_{IP} = V = 0$. We obtain:

$$E_0 = \left(\frac{\Lambda}{\mu_1}, 0, 0, 0, \frac{\Pi}{\sigma} \right).$$

The reproduction number is given by $R_0 = \rho(FV^{-1})$, where ρ is the spectral radius of the next generation matrix. F represents the expected number of new cases while V is the rate of transfer of the infections. Thus,

$$R_0 = \frac{\beta\gamma\kappa\Lambda\Pi}{\left(\frac{\alpha_1\Pi}{\sigma} + 1\right)\sigma\left(\delta + \frac{\nu\Pi}{\sigma}\right)\mu_1\left(\frac{\Pi(\alpha_2\mu_2+\gamma)}{\sigma} + \mu_2\right)\left(\mu_3 + \frac{\Pi\rho}{\sigma}\right)}. \tag{3.17}$$

R_0, given by (3.17), describes the average number of newly infected cells produced by an infected cell during an infectious period. Hence, this ratio determines whether the virus persists within the host or becomes extinct. If R_0 is above unity, an infection is initiated.

CHAPTER 4: Numerical Simulation

This section presents numerical results of system (3.1) using parameter values obtained from literature to describe epithelial and viral dynamics given the value of R_0, outlines the significance of immune cells on virions and infected cells, and the most attractive targets for drug development.

3.1 Parameter Estimation

Limitations arising from experimental data on *in-vivo* dynamics of SARS CoV-2 resulted in use of parameter values from cross-checking multiple works. Other values were assumed from literature based on their biological feasibility. Table 3.1 summarizes all the parameter values.

Table 3.1: Parameter values for invivo COVID-19

Parameter	Value	Range	Source
π	1×10^4	$1 \times 10^4 - 1 \times 10^5$	Assumed
β	0.0072	0-1	Hattaf and Yousfi (2020)
γ	0.2	0-1	Assumed
κ	500	88-580	Hattaf and Yousfi (2020)
Λ	5000	57.757 - 12000	Hattaf and Yousfi (2020)
μ_3	0.4	0.088-0.58	Hattaf and Yousfi (2020)
σ	0.67	0.05-1	Hattaf and Yousfi (2020)
μ_1	0.01	0-1	Assumed
α_1	0.000574	0-1	Hattaf and Yousfi (2020)
δ	0.8	0-1	Assumed
ν	0.6	0-1	Assumed
ρ	0.00119	0-1	Lee et al. (2009)
α_2	0.03	0-1	Assumed
μ_2	0.33	0.088-0.58	Hattaf and Yousfi (2020)
ϵ	0.1	0-1	Hattaf and Yousfi (2020)
ζ	1.26×10^5	$1 \times 10^3 - 7.94 \times 10^7$	Esteban et al. (2020)
K_1	4×10^7	$1.27 \times 10^7 - 4 \times 10^8$	Esteban et al. (2020); Hattaf and Yousfi (2020)
K_2	1×10^7	$1 \times 10^7 - 1 \times 10^8$	Assumed

3.2 Sensitivity Analysis of R_0 with respect to the Model

Using parameter values in Table 3.1, we identified how respective input parameters affect the reproduction number R_0, of the model as shown in Figure 3.1 and Table 3.2.

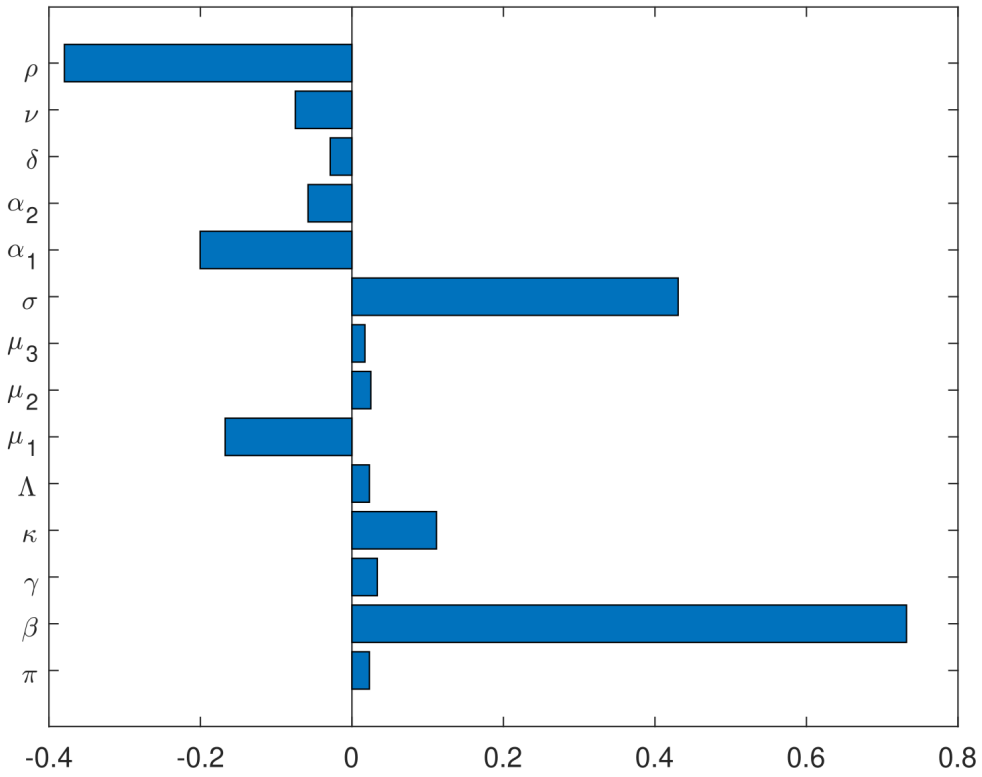


Figure 3.1: Tornado plots of in-vivo COVID-19

Table 3.2: PRCC values of Parameters

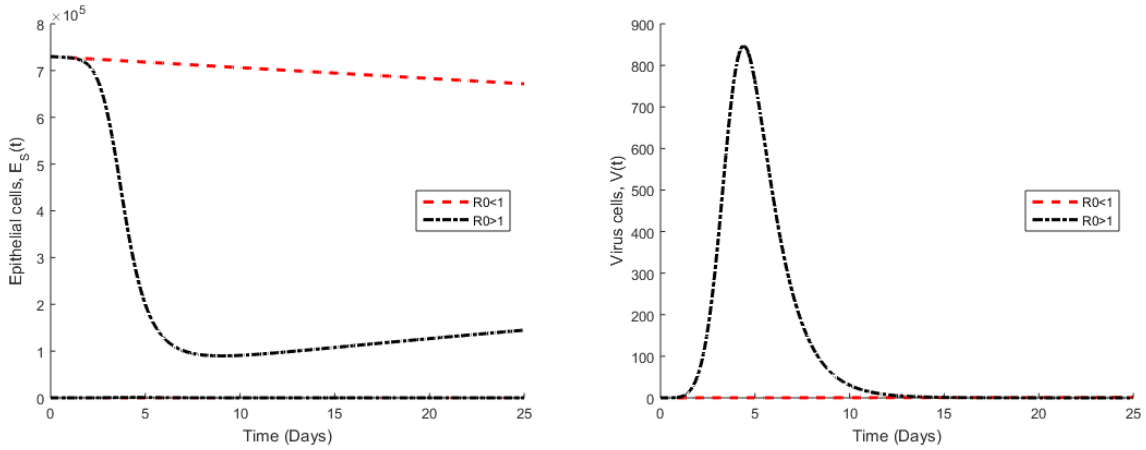
Parameter	PRCC Value
π	0.03194
β	0.7335
γ	0.02062
κ	0.1304
Λ	0.03194
μ_3	0.02101
σ	0.4784
μ_1	-0.1911
α_1	-0.2176
δ	-0.0136
ν	-0.1309
ρ	-0.381
α_2	-0.08863
μ_2	0.02208

Selected parameters are significant in influencing the R_0 value. A lower R_0 would be attained by reducing the transmission rate (β), the most sensitive parameter. To combat this viral menace, different approaches have been employed including non-pharmaceutical interventions, vaccine development and exciting new techniques such as monoclonal antibodies and viral inhibitors. As depicted from Figure 3.1, curbing viral transmission plays a paramount role in providing prophylactic solution. Although this is a somewhat unexplored method, the use of fusion inhibitors have been earlier proposed as an alternative approach to tackle corona viruses. Given the close genetic make up between the already encountered corona viruses, these fusion inhibitors may ensure a worthy alternative in future attacks in arresting the virus at viral entry stages. Therefore, we could have broad-spectrum fusion inhibitors which target the binding or the membrane fusion steps in the viral entry process. Fusion inhibitors can broadly be categorized into small molecules, antibodies and peptides inhibitors. Small molecules and antibodies target the receptor-binding domain in the S1 unit of S protein. Their effectiveness is limited because the RBD is a highly mutable region. The use of peptide inhibitors is the most recent area of research focused on hindering the membrane fusion through targeting the heptad-repeating region 1 (HR1) on the S2 sub unit (Cormier, 2020; X. Wang, Xia, Zhu, Lu, & Jiang, 2021). The greatest benefit for this approach is that the S2 is a highly conserved region therefore it is insusceptible to mutation. Peptide drugs would thus have a larger impact in impeding viral entry when compared with small molecules (X. Wang et al., 2020). In general, each class of fusion inhibitors has its merits in contrast with the others. The neutralizing antibodies are safe, stable and possess high efficacy. Small molecules can be administered orally, easy to transport, cheap to manufacture and well acceptable to patients. Peptide inhibitors have relatively low immunogenicity, since they attack a greatly conserved region, their inhibition is virtually guaranteed, safer, and have fewer side effects (Cao et al., 2020; X. Wang et al., 2021; Xia, Zhu, & Liu, 2020).

3.3 Simulation Results

In this subsection, we discuss the results obtained from running simulation on model (3.1). The results focus on the specific objectives of this work; describing the dynamics of virions pivoted on R_0 value, the impact of immune cells on the concentration of virus and infected cells and potential targets for drug development. The initial conditions applied to these simulations were assumed based upon previous work thus contrasting dynamics may be observed with different set of initial conditions.

3.3.1 Epithelial and virus cells dynamics considering the value of R_0



(a) (b)

Figure 3.2: Dynamics of (a) *epithelial* and (b) *virus* cells when R_0 is less than or greater than 1.

For $R_0 > 1$ (see Figure 3.2), the population of epithelial cells initially declines as the number of virions increases due to the viral invasion as indicated by the black dotted line. It can be observed that very low concentration of epithelial cells coincides with high viral levels between 5-7 days. At these low epithelial cells levels, we would expect the infection to be severe often associated with abnormal increase in creatinine and lactose dehydrogenase levels, signalling kidney and livers dysfunctions respectively. Further, a low lymphocyte count is the most prevalent marker for SARS CoV-2 severity among unusually low haemoglobin levels and increased ferritin levels (Qu et al., 2021). This severity could be strongly linked to immuno-compromised patients. From Figure 3.2a, there is a gradual increase in epithelial cell count from day 15 which could be due to cell regeneration. Evidence has been shown through the revival of olfactory epithelial cells in the nasal cavity but the rationale is still indeterminate (Urata et al., 2021). One avenue SARS CoV-2 trigger cell death mechanism is through apoptosis. It was discovered that SARS CoV-2 ORF3a induces apoptosis thereby proposing a connection between high apoptotic rate with high viral load (see Figure 3.2b) (Donia & Bokhari, 2020).

When $R_0 < 1$, the concentration of target epithelial cells gradually decreases stabilizing at levels lower than initial as shown by the red dotted line in Figure 3.2a. This suggests the individual is immuno-competent and can effectively neutralize the virus without interventions such as vaccines.

3.3.2 Effects of immune cells on virus dynamics

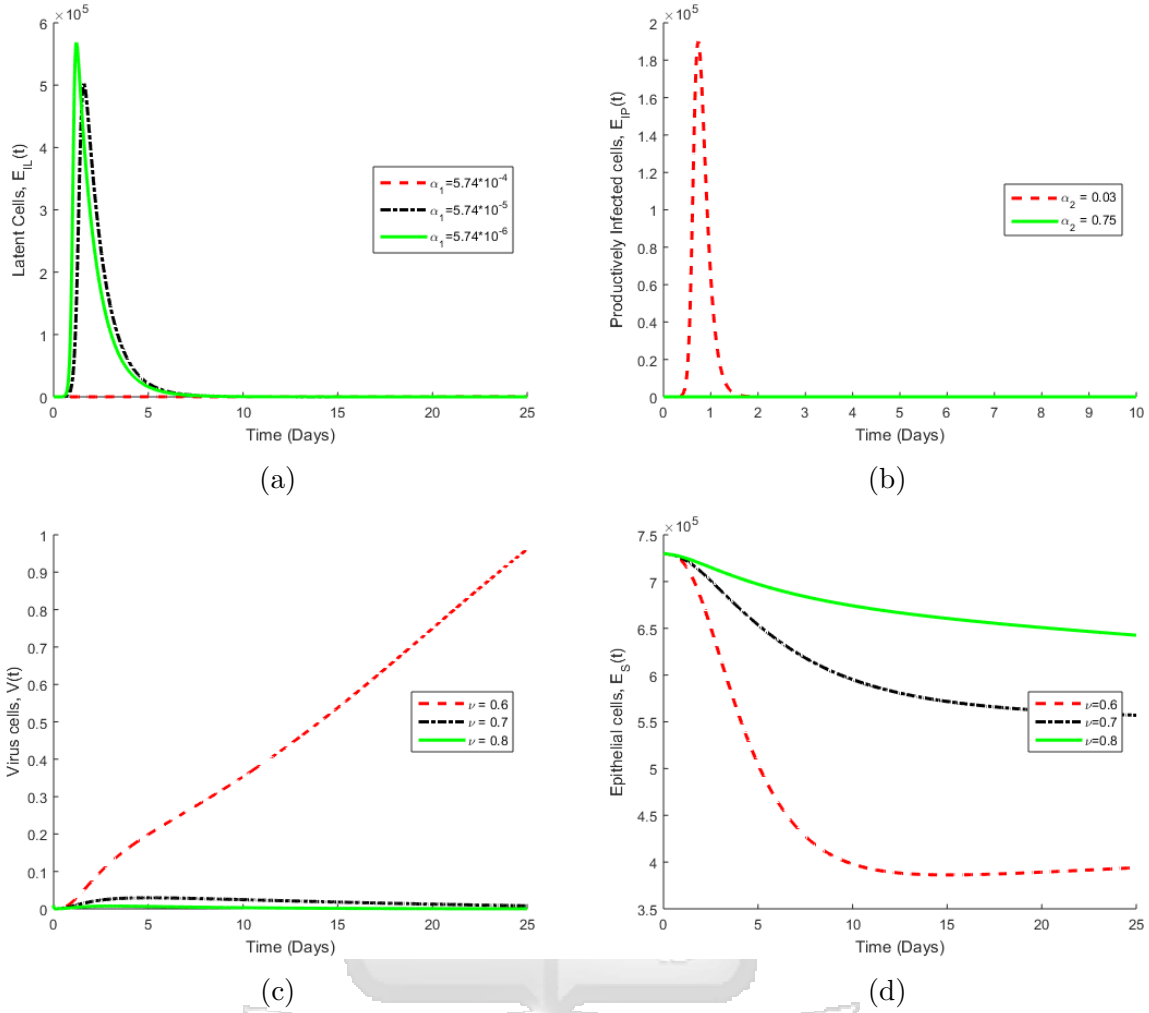


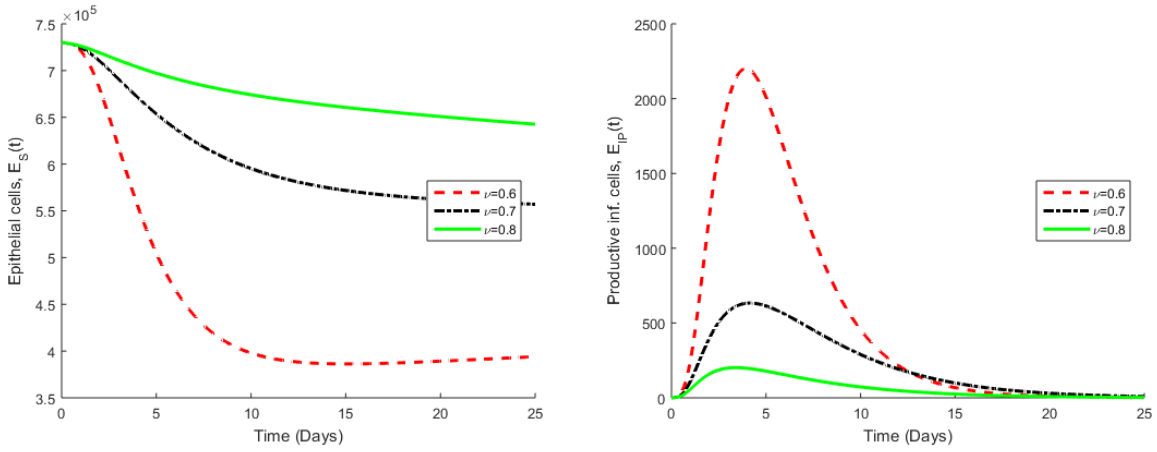
Figure 3.3: Effects of immune responses on virions and infected cells

The immune system influence viral dynamics through increasing death rate of infected cells via lytic effector mechanisms, and inhibiting binding and replication of the virus through non-lytic effector mechanisms. The lytic effector responses utilise cytotoxic T cells while non-lytic mechanisms use antibodies to neutralise the virus (A. Chatterjee et al., 2021; Wodarz, Christensen, & Thomsen, 2002). When the viral replication is greater than cytopathogenic effect of the virus then both lytic and non-lytic mechanisms are crucial (Kaifa, J., & F., 2014).As shown by Figure 3.3, a greater efficacy of immune cells significantly reduces the virion and infected cells, and curbs the depletion of epithelial cells. From this model, the immune activity impedes infection, and progression of the virus in infected latent cells, α_1 and α_2 respectively, as well as deactivation of the virus ν. Viral infection can be inhibited via neutralizing antibodies. These neutralizing antibodies prevents binding event by mimicking the lung ACE-2 receptor in a jigsaw-puzzle fashion. The virus, covered by antibodies, attract each other to form large clusters which, unlike free virus, are easily recognized by immune cells (Sebastian, 2020; Zoppi, 2020). Interferons are responsible for mediating antiviral and anti-growth of infected cells. This inhibit viral replication and can further activate other components of innate and adaptive immunity (Felgenhauer et al., 2020; Sallard, Lescure, Yazdanpanah,

Mentre, & Peiffer-Smadja, 2020).

Impact of vaccination on epithelial cells

SARS CoV-2 is a highly infectious disease caused by combined transmission from asymptomatic and symptomatic individuals (Speiser & Bachmann, 2020). To curb the devastating effects of the virus, vaccine development was primordial. The urgency for interventions to control pathogenicity of SARS CoV-2 accelerated vaccine development without compromising crucial aspects such as efficacy and toxicity monitoring. Heavy investments from big pharmaceutical companies as well as simultaneous testing of different techniques to be employed significantly shortened the period that would typically take years. The task was to create antibodies with high affinity that would neutralize the virus. The more preferred approach was utilizing the viral spike protein as the antigen because it was the only surface protein hence would be easily accessible to antibodies. However, respective companies opted for different methods such as using mRNA, viral vectors, inactivated form of the virus and protein sub-units to formulate their vaccines (Mascellino, Di Timoteo, De Angelis, & Oliva, 2021). Given that SARS CoV-2 vaccines induce memory T and B-cells to combat future attacks and consequently boost immunity (CDC, 2021), Figure 3.4 shows the effects of vaccination in enhancing the host immunity. It has been observed that vaccine immunity wanes, however, the longevity of protection and the degree to which vaccine induces immunity still remains undetermined (Juno & Wheatley, 2021). From Figure 3.4, a vaccine with a higher efficacy will significantly prevent the depletion of naive epithelial cells subsequently resulting in a lower population of actively productive infected cells. Vaccine booster shots would thus be used in cases where the efficacy is relatively low as shown by red dotted line. As the efficacy increase, as shown by the black and green dotted lines, less additional shots are required. These additional shots raise the number of circulating antibodies thus a higher immune response. A relationship is therefore maintained between high vaccine efficacy and increased immunogenecity.



(a) (b)

Figure 3.4: Impact of vaccination on epithelial cells

The results supports the current sensitization on the use of vaccines and the general public should feel encouraged to be vaccinated. Kenya is still comparatively behind the curve as only 23.59% of the population has been fully vaccinated (our world in data,

2021). Reports further indicate that 18.6 million doses of various approved vaccines have been administered. Notably, 31.57% of the Kenyan population has at least received one dose. These numbers are strikingly low against the global figures of 62.08% and 67.59% for the fully vaccinated and those who have received at least one dose respectively. As yet, 12.3 billion vaccine doses have been administered (CDC, 2022).

3.3.3 Potential targets for drug development against the virus

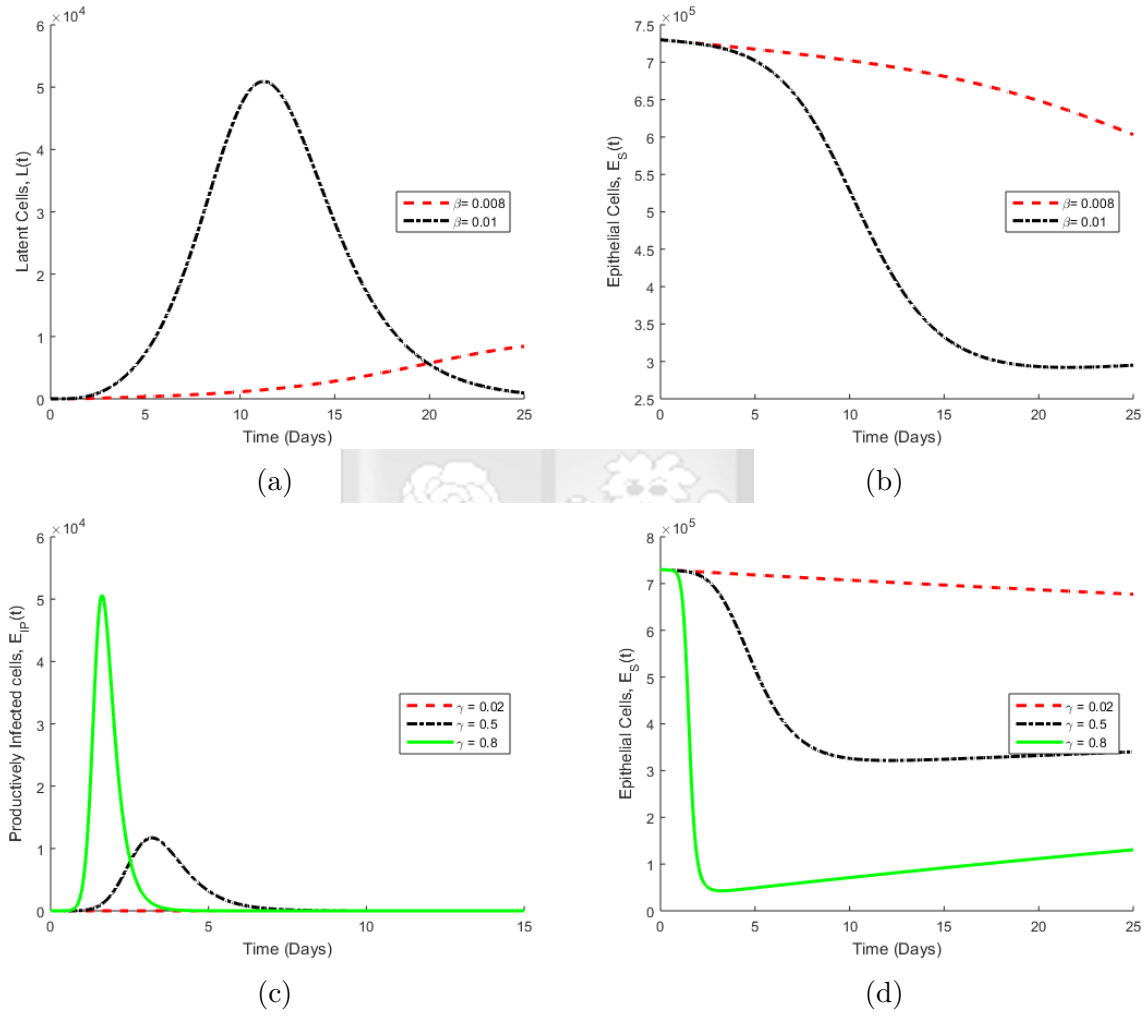


Figure 3.5: Impact of fusion and transcriptase inhibitors on infected and susceptible epithelial cells

In this period, where the world is still hit by the COVID-19 pandemic, timely intercessions are critical in managing and controlling the virus. Nations have placed measures to restrain the spread and maintain quality of health among the citizens (Ayouni et al., 2021). Reducing viral transmission has a major impact as both a non-pharmaceutical and within-host measure. The previous has been explored through the use of masks and social distancing among others. We sought to evaluate the most attractive stage between inhibiting infection through fusion inhibitors or preventing progression to productive stage through a transcriptase inhibitor, that would yield a huge impact in arresting the virus. According to Figure 3.5, hindering viral transcription within the

host will more effective in controlling the virus (see Figure 3.5c and 3.5d). There is a higher depletion of epithelial cells under fusion inhibitors (see Figure 3.5a) compared to the use of antiviral drugs (see Figure 3.5b). SARS CoV-2 virus is able to evade the fusion inhibitors as shown by the gradual increase in latently infected from day 10 in Figure 3.5a. Through mutations of the receptor-binding domain in S1, the fusion inhibitors are rendered less effective. Further, these fusion inhibitors have a shorter half-life thus longevity of their activity is reduced (X. Wang et al., 2020, 2021).

CHAPTER 5: Conclusion and Recommendation

This project presents a mathematical model that thematically describes the progression of SARS CoV-2, interaction between virus and the immune cells and possible targets for drug development. To investigate biological feasibility, well-posedness of the model was established in terms of positivity and boundedness of solutions. To analyze the equilibrium of the model, basic reproduction number R_0 was used as a threshold parameter. When the R_0 is greater than one, biologically this means the infection persists otherwise it goes to extinction.

The behaviour of target and viral cells is dependent on the model R_0. An R_0 value greater than one results in an increased decay of vulnerable epithelial cells during which infection is persistent. These cells enter an eclipse phase of infection before they begin to actively produce virions. Similarly, this R_0 value results in an increase in population of virions with a decline noticed later during the course of infection. Naturally, the lowest concentration of epithelial cells around day 5 to day 7 corresponds to the highest viral cells population. This is commonly closely related to immuno-compromised patients. Mathematically, the rapid depletion of target cells would pose a vantage-point in a quick elimination of virions, yet in reality this may open up serious risks for COVID-19 patients.

Through non-lytic and lytic mechanisms, the immune cells eradicated the virus by impeding viral binding and replication or killing infected cells, respectively. An assessment of the impact of immune cells from the model provides that a greater efficacy matches a higher decline in infected cells as well as virion population. Also, there is less depletion of epithelial cells in case of an virus attack in an immuno-competent individual. Based on the model blocking the viral progression from latently infected cells to productively infected cells seems to be the more efficient approach to control the virus. This may be enhanced by transcription inhibitors. These transcriptase inhibitors are crucial in blocking the formation of replication/transcription complex (RTC) which is crucial in viral replication.

Lack of experimental data in this formulated model has proven to be the key setback thereby caution is advised. The experimental data would shed light on key aspects which are necessary in describing how the virus evolves. Such areas would include studying the functional antibodies released during an infection, protective antibody levels, infectivity of those re-infected and the rate of waning immunity.

The intention of this work is not to fit the model to any particular set of data, but rather being able to describe the broad features of SARS CoV-2 infection. Extensions on this work may however be interested in applying real data and evaluate the performance of the model. Another development of this project would be to consider how the various immune system compartments contribute to neutralizing the virus.

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APPENDICES

Appendix A: Similarity Report

Curiginal

Document Information

Analyzed document	Signed Thesis (1).docx (D138623006)
Submitted	2022-05-31T09:31:00.0000000
Submitted by	
Submitter email	Charles.Kaumbutha@strathmore.edu
Similarity	3%
Analysis address	library.strath@analysis.urkund.com

Sources included in the report

W	URL: http://www.maths.qmul.ac.uk/~ig/MTH5118/Notes11-09.pdf Fetched: 2020-11-13T15:01:27.4430000	1
SA	**Group 2, Project Work.docx** Document Group 2, Project Work.docx (D44267851)	18
SA	**BBA_Covid19_T_Taj.pdf** Document BBA_Covid19_T_Taj.pdf (D112827221)	3
W	URL: https://journals.tubitak.gov.tr/cgi/viewcontent.cgi?article=2579&context=biology Fetched: 2022-05-31T09:30:46.0830000	1
W	URL: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html Fetched: 2020-03-09T02:13:03.8600000	1
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7592233/ Fetched: 2020-11-10T18:49:18.4730000	1
SA	**Review - Manuscript (covid19).docx** Document Review - Manuscript (covid19).docx (D71361742)	1
W	URL: https://www.news-medical.net/news/20211216/T-cell-responses-remain-broadly-robust-against-Omicron-variant-of-SARS-CoV-2.aspx Fetched: 2022-01-22T00:39:22.8730000	1
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102615/ Fetched: 2020-04-07T15:36:46.4530000	1
SA	**Bachelor research project -- Mahmoud Alahmad Beig S4079035.pdf** Document Bachelor research project -- Mahmoud Alahmad Beig S4079035.pdf (D100651858)	1
SA	**Idris-1-genetic variants os SARS-CoV-2.docx** Document Idris-1-genetic variants os SARS-CoV-2.docx (D111968608)	1
W	URL: https://www.frontiersin.org/articles/10.3389/fimmu.2020.570927/full Fetched: 2020-11-03T11:32:35.1500000	2

Appendix B: Ethics Review Report

Strathmore UNIVERSITY

31st May 2022

Mr Kaumbutha Charles,
Charles.Kaumbutha@strathmore.edu

Dear Mr Kaumbutha,

RE: COVID-19 viral - host interaction dynamics and Immune response.

This is to inform you that SU-IERC has reviewed and **approved** your above **SU Masters'** research proposal. Your application reference number is **SU-IERC1358/22.** The approval period is **31st May 2022 to 30th May 2023.**

This approval is subject to compliance with the following requirements:

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by SU-IERC.
iii. Death and life-threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to SU-IERC within 48 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to SU-IERC within 48 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to SU-IERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology, and Innovation (NACOSTI) https://research-portal.nacosti.go.ke/ and obtain other clearances needed.

Yours sincerely,

for: **Dr Ben Ngoye,**
Secretary; SU-IERC

Cc: Prof Fred Were,
Chairperson; SU-IERC