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Can We Predict the Future? Modelling SARS-Cov-2 Epidemic to Endemic Transition

Krish Agrawal[1] and Arianna Broad[2#]

[1]Genesis Global School, India
[2]Cornell University, USA
[#]Advisor

ABSTRACT

COVID-19, an infectious disease caused by the SARS-CoV-2 virus, is the viral agent responsible for the ongoing pandemic. Various vaccines have been developed for different strains of the virus. This has led to reduction in the number of infections and deaths throughout the world, but the pandemic seems to be far from over due to constant mutations in the structure of the virus and other factors like immunity loss rate and re-infections. However, there is guidance to how we should proceed from a public health standpoint, due to the similar cases of influenza and the Hepatitises. These pathogens started out as epidemics or pandemics, then morphed into an endemic over the course of decades. Therefore, by combining our knowledge of these past epidemic to endemic transitions, we have made similar predictions about the transition of the COVID-19 pandemic into endemicity. A simple epidemiological model called the SIR model has been utilized to predict the course of the pandemic by computation, considering 2 cases – one without vaccination intervention and the other with vaccination intervention. The results indicate that COVID-19 is likely already an endemic, but to maintain a stable state and to mitigate the death toll, there is a serious need for continuous vaccination and regular changes in vaccinations as the virus mutates.

Introduction

The immune system is a complex network of different cell types, proteins, and other defense mechanisms that fight off viruses, bacteria, and other pathogens. This complex immune system is constantly adapting to new stimuli from the environment.[9] For example, when an organism's immune system is exposed to a new pathogen there is two responses that occur: 1) the general immune response and 2) the specific immune response. The general immune response is the first responders of the immune system, quickly jumping into action to degrade any foreign invaders. The specific immune response is a slower one, partly due to the process of retaining memory of the foreign invaders for potential future infections.[9] This process of retaining memory of a foreign invader is how the organism can evade any future invasions from this same pathogen, thus conferring immunity.[9] When a population confers widespread immunity to a pathogen, it imposes an evolutionary selective pressure on the pathogen, preventing the pathogen from infecting and replicating in a new host. However, every time a pathogen replicates its genome, random mutations occur. There are three putative outcomes that can occur when random mutations occur: 1) a silent mutation – where a mutation in the DNA sequence occurs but does not affect the protein sequence, 2) a missense mutation – where a mutation in the DNA sequence causes a single amino acid substitution, this may or may not cause a change in the protein structure, and 3) a nonsense mutation – where a mutation in the DNA sequence causes a premature stop codon in the protein, resulting in a non-functional protein. [14] The most powerful mutations for a pathogen struggling to overcome this conferred immunity by the host organism is a missense mutation that results in a protein structure change. Because immunity is a complex association between antibodies and antigens, changing the protein structure of the antigen typically

prevents the antibody from recognizing the pathogen, thus evading host organism immunity. A prime example of a virus that has shown to continually mutate to evade the host immune system is that of SARS-CoV-2, the virus responsible for the COVID-19 pandemic.

The first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China in December 2019.[7] SARS-CoV-2 spreads through the respiratory pathway via lung mucus droplets that contain particles of the virus. Common symptoms include fever, cough, loss of taste and smell, breathing difficulties, headaches, fatigue, etc. and may begin 1-14 days post infection.[7] However, epidemiological studies have shown that asymptomatic infections are common as well.[16] This commonality of asymptomatic cases has posed a surmounting challenge epidemiologically, to get this pandemic under wraps. From the end of 2019 to the end of 2021, the SARS-CoV-2 viral outbreak has proven to be the most devastating global pandemic since the 1818 influenza outbreak. Not only is the SARS-CoV-2 outbreak a public health crisis, but also an economic and socio-political crisis. The outbreak of this virus has led to the swift development of new vaccines and treatments through robust collaboration in the scientific community.

Regardless of the robust collaboration and measures to work together to mitigate the virus' effects, experts have deemed the elimination of SARS-CoV-2 a near impossible probability. That is why current efforts have been placed on mask mandates and vaccination programs, to help mitigate active SARS-CoV-2 infections. Current vaccination programs have high efficacy rates, but immunity loss and re-infections are also prevalent. Therefore, at this stage it becomes important to think about the course of COVID-19 transitioning from an epidemic to an endemic at the national level, and what this means in terms of further actions to prevent spikes of infections.

Disease Endemicity and Modelling

An endemic refers to a disease that is constantly present within a population, at a usual prevalence level and in a stable state.[7] An epidemic can turn into an endemic in one or both of the following cases :

(a) Progressive elevation of specific antibody titres in the affected population by repeated infections or regular vaccinations. This refers to an increase in the immunity of organisms against the virus due to repeated exposure to the virus (which confers natural immunity) or induction of antibodies by vaccination. This decreases the susceptibility of the population towards infection and also decreases the severity of infection in the individual.

(b) Loss of virulence of the pathogen. This refers to decrease in pathogenicity of the virus, which could either make it less infective or less fatal or both. [1]

This makes the infection or disease clinically stable and less apparent among the population. Over time, pandemic viruses typically mutate and evolve into an endemic disease that circulates at lower, more manageable levels, common examples include Influenza and Hepatitises. There are various mathematical algorithms to model infectious disease epidemiology in discrete time. One such approach is the Susceptible, Infected, and Recovered (SIR) model. The SIR model is of a population that is partitioned into three classes: Susceptible (S), Infectious (I), and Recovered (R). Individuals who become infected proceed from class S to class I at a rate which depends on the infectiousness of the virus and the prevalence of infection. Infectious individuals either die or move to the recovered class (R). People in the R class have an immunity to the infection which can either last lifelong or wane over time, depending on the immunity loss rate of the antibodies (*Figure 1*).

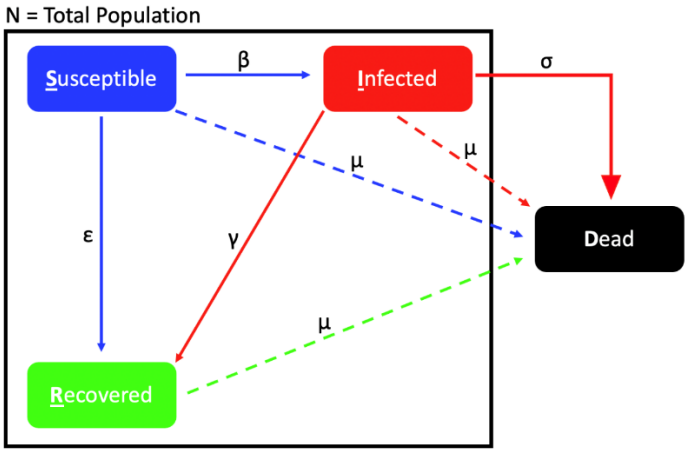

Figure 1. SIR Model Flowchart. Figure depicts flow of individuals in a population based on their level of viral exposure and/or recovery or death. Dashed arrows indicate the normal death rate that is equal between all populations, represented by the value μ. Solid arrows indicate flow of individuals into different categories based on the status of infection. β is the transmission rate, σ is the disease death rate, γ is the recovery rate, and ε is the vaccine efficacy rate. Each iteration of the SIR algorithm takes into consideration life cycling, the dead population leaves the N(t) total population, births are added to each SIR category at a defined birth rate α.

Epidemic to Endemic Transition Case Studies: Hepatitis B and Influenza A

Hepatitis B Endemic Case Study

Hepatitis B is a liver infection caused by the Hepatitis B virus (HBV), a partially double-stranded DNA virus of the Hepadnaviridae family.[6] HBV causes inflammation of the liver but in severe cases, it can also cause hepatocellular carcinoma (HCC), cirrhosis and even premature death. It transmits via the transfer of body fluids from an infected individual to a susceptible individual. This can happen through horizontal transmission, which includes sexual contact, sharing needles, syringes, or other drug-injection equipment, or through vertical transmission, from mother to fetus at birth. [5]

Hepatitis B virus (HBV) infection is a worldwide public health crisis. HBV is the most common blood-borne infection with 350 million chronic hepatitis B virus (HBV) carriers worldwide.[12] Vaccination is the most effective way to control HBV incidence worldwide. In many countries, after the introduction of mass immunization campaigns, the prevalence of HBV notably changed, resulting in a decrease of the HBsAg carrier rate and HCC incidence. [6]

HBV has an interesting epidemiological profile, displaying epidemic-endemic cycling in many countries.[10] Because the HBV virus keeps on circulating within the population like an endemic, with brief stochastic epidemic spikes, the HBV epidemiological profile undergoes many periods of epidemic to endemic transition.[15] To model this epidemic to endemic transition, the HBV modified SIR model displays the cumulative human population at any instant of time t represented by N(t) is categorized in five different classes, namely S(t) the susceptible individuals, L(t) the latently HBV infected individuals, I(t) the individuals with acute HBV infection, C(t) the chronic infected individuals, and R(t) the individuals that have been recovered. Figure 2 represents the flow chart of the model which represents the flow compartments of all the variables taken from the population.

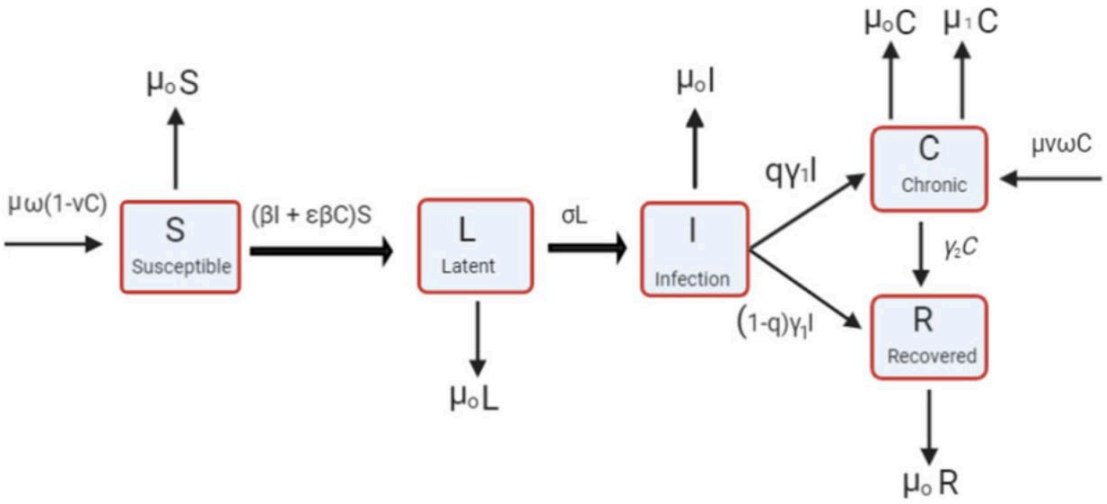

Figure 2. HBV Modified SIR Model Flowchart. The susceptible population is generated by the newborn children at the rate of μ, birth proportion without vaccination at the rate of ω. The parameter ν shows the proportion of children who are un-immunized born to those mothers who are chronic. The factors μωνC accounts for the children who are newborn unsuccessfully immunized to the infected mothers. ϵ and β are the disease transmission rates relative to infected individuals in I(t) and C(t) classes respectively. The rate of natural mortality is μ0. The latent individuals move to the acute (infection) stage at the rate σ, to the chronic compartment at the rate qγ1, recovered stage at rate (1−q)γ1. Hepatitis B virus related morality rate is μ1 and recovery at the rate γ2.[11]

Influenza A Endemic Case Study

Another prime example of epidemic to endemic transition is the Influenza A virus. Influenza A viruses are negative strand RNA viruses of the genus Orthomyxoviridae.[2] The first severe influenza pandemic caused by this viral agent was in 1918. It has been estimated that one-third of the world's population may have been clinically infected during the pandemic.[2] The pandemic lasted about 18 months and ended after either majority of the people had been exposed to the virus and gained immunity, or the virus adapted to be less lethal to maintain in the population through antigenic drift, the evolutionary accumulation of amino acid substitutions in viral proteins selected by host adaptive immune systems as the virus circulates in a population.[13] Therefore, the 1918 Influenza A strain never disappeared, rather it randomly mutated under the selective pressure of too many deaths resulting in the decrease in transmission, essentially resulting in an endemic.

Almost all cases of influenza A and subsequent flu pandemics, have been caused by descendants of the 1918 virus. These descendants circulate the globe, infecting millions of people each year i.e., various strains of the Influenza virus circulate among populations and cause seasonal endemics every year (mainly in the winter in temperate climates). This has resulted from an increasingly widespread elevation in antibody titre in progressively larger segments of the population, which, in turn, has been the result of endemic infection. To rephrase, as population immunity rises, an increasing proportion of infections become clinically inapparent.[1] However, Influenza A viruses constantly evolve by the mechanisms of antigenic drift and shift. They should be considered emerging infectious disease agents, perhaps “continually” emerging pathogens. Antigenically novel virus strains emerge sporadically as pandemic viruses, causing a more severe outbreak. [2]

Today, about 8% of the U.S. population becomes sick with the seasonal influenza every year and about 12,000-52,000 people die due to it yearly. [2] But every few years, due to constant antigenic mutation, a more severe influenza epidemic occurs, causing a boost in the annual number of deaths past the average, with 10,000

to 15,000 additional deaths. [2] To summarize, influenza has become a scattered sporadic disease i.e., influenza epidemics occur when a novel virus is introduced to the population, and between these epidemics the virus continues to circulate between populations in an endemic fashion producing infection that is clinically less apparent or unrecognizable, thus making it a prime endemic candidate.[1]

To simulate an influenza epidemic using the SIR model, one infected individual (I) is introduced into a closed population where everyone is susceptible (S). Each infected individual (I) transmits influenza, with a certain probability, to each susceptible individual (S) they encounter. The number of susceptible individuals decreases as the incidence (i.e., the number of individuals infected per unit time) increases. At a certain point, the epidemic curve peaks, and subsequently declines, because infected individuals recover and cease to transmit the virus.[3] By varying the modulation of the basic SIR model via factors such as seasonality, influenza epidemics can be shown to have sustained cycles (Figure 3).

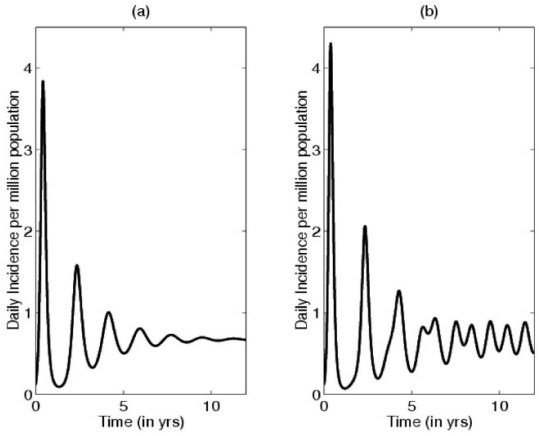

Figure 3. Daily incidence for an influenza outbreak calculated using an SIR model. (a) With constant transmission rate. (b) With small seasonal variation in transmission rate. For a constant transmission rate, after an initial transient period, the system approaches an endemic level (that is, equilibrium) by damped oscillations. If a small amount of seasonal variation in transmission is introduced oscillations are sustained rather than damping out, and the system eventually tends to an annual cycle.[4]

Results

Due to the extensive research on epidemic to endemic transition on other viruses such as Hepatitis B and Influenza, we can draw parallels between those known viruses and emerging viruses. In this study, we combined our knowledge in Hepatitis B and Influenza, in principle and in computation, to model the future of the SARS-CoV-2 pandemic. We modelled an SIR population for the next 50 years based on parameters collected in March 2022, with and without vaccination intervention, to get a better idea how necessary it will be to maintain vaccination programs in the coming decades. While there are many algorithms to utilize, depending on the parameters available, for this study we have adapted an algorithm from Ma et al. (2013) that includes life cycling as we modelled the SARS-CoV-2 over the course of 50 years.[17,18]

$$S(t+1) = S(t) + \Lambda - \frac{\beta S(t) I(t)}{N(t)} + \omega R(t) - (\mu + \varepsilon) S(t) + \alpha S(t)$$
$$I(t+1) = I(t) + \frac{\beta S(t) I(t)}{N(t)} - (\mu + \sigma + \gamma) I(t) + \alpha I(t)$$
$$R(t+1) = R(t) + \gamma I(t) + \varepsilon S(t) - \mu R(t) + \alpha R(t)$$
$$D(t+1) = D(t) + (\mu + \sigma) I(t) + \mu S(t) + \mu R(t)$$
$$N(t+1) = S(t+1) + I(t+1) + R(t+1) - D(t+1)$$

Equation 1. SIR model algorithms utilized to model SARS-CoV-2. S=susceptible, I=infected, R=recovered, D=deceased, and N=total population. "Λ"=constant recruitment rate, β=transmission rate, ω=immunity loss rate, ε=vaccination efficacy rate, γ= recovery rate, σ=disease death rate, μ=normal death rate, and α=normal birth rate.

Based off our relatively simple SIR model algorithm and the current parameters of the SARS-CoV-2 virus, we found these observations on the 50 iterations of the SIR code. In the simulation without any further vaccination intervention, we found that within ~2 years the susceptible population exponentially grows and surpasses the recovered population. At about ~27 years the death toll due to the virus exceeds the recovered population. Meanwhile, the infected population remains stable the entire duration, indicating that based off these parameters from March 2022, COVID-19 is likely already an endemic (*Figure 4*). In the simulation with vaccination intervention, we observe the recovered population exponentially increasing and maintaining the status as the highest populated category. However, around 30 years the susceptible population begins to exponentially increase. This is due to the relatively high immunity loss rate of SARS-CoV-2 antibodies. Soon after the susceptible population exponentially increases, the death toll also exponentially increases. Meanwhile, the infected population remains stable the entire duration of the simulation (*Figure 5*). This is indicative of a stable endemic with no spikes of infectious populations. However, this also means that the death toll is directly correlative to the size of the susceptible population. Because this stochastic model takes into consideration antigenic drift but does not consider vaccine adaptivity it is likely that this simulation demonstrates the need for ever changing vaccines as the virus mutates. Therefore, it is imperative that continuous vaccination occurs and that vaccines are modified to be effective against new strains to mitigate the death toll due to SARS-CoV-2.

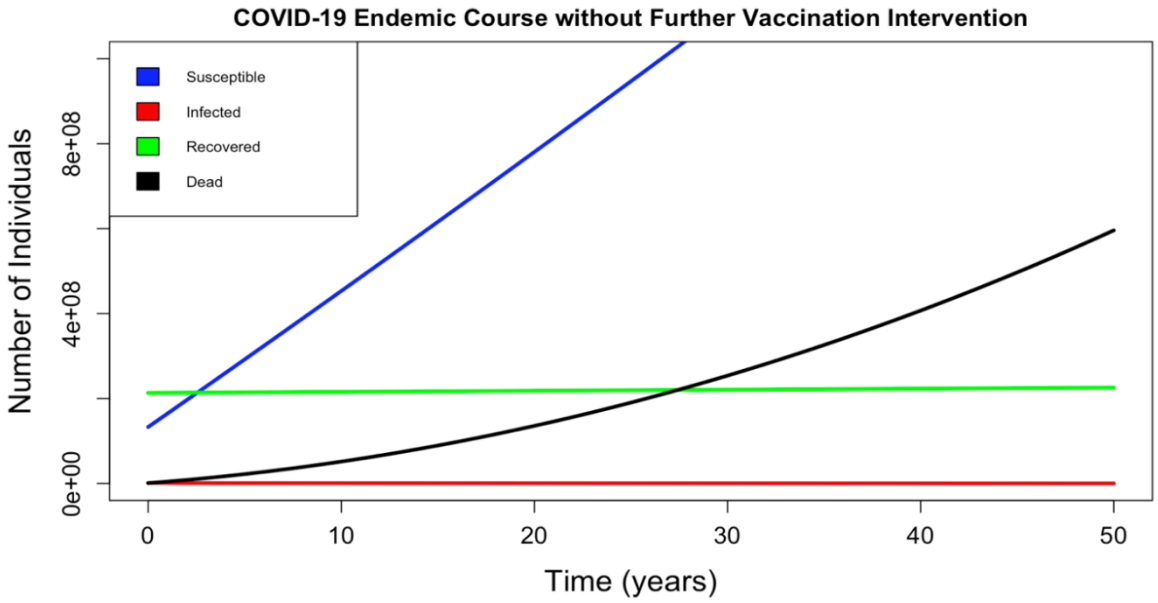

Figure 4. COVID-19 endemic course without further vaccination intervention. This graph displays a sharp linear rise in the susceptible population, exceeding the recovered population after only ~2 years. The recovered population remains mostly stable, with a slight decline in population. The death toll has a slight exponential increase starting from year one, and the deceased population exceeds the recovered population at about ~27 years. Meanwhile, the infected population remains stable throughout the course of the iterations.

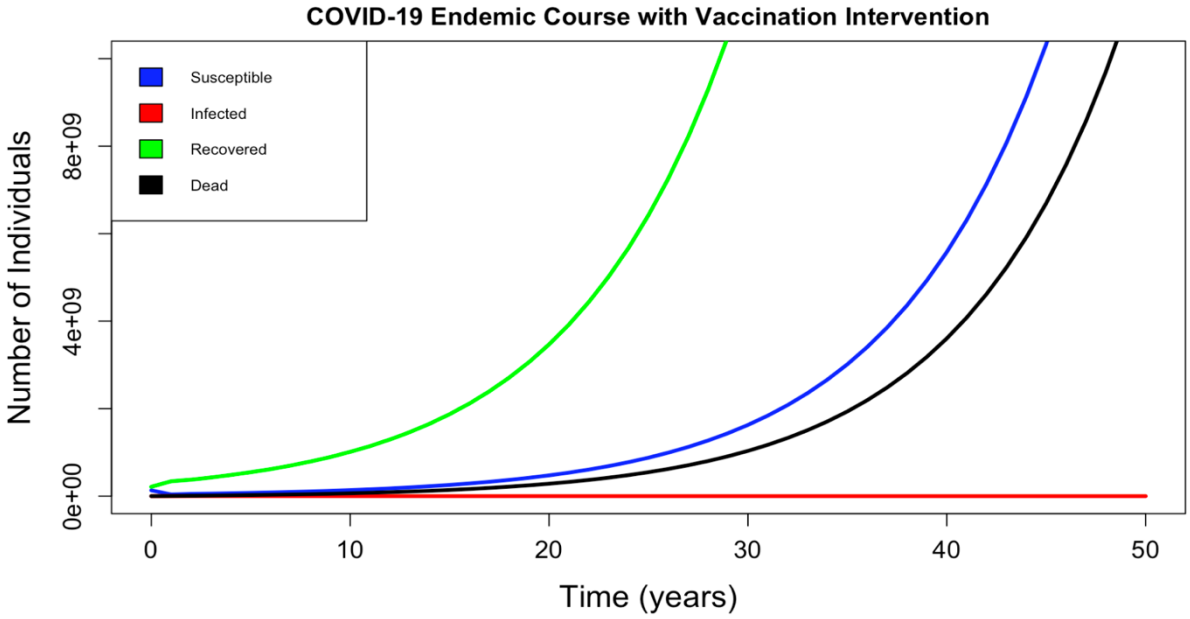

Figure 5. COVID-19 endemic course with vaccination intervention. The graph displays a sharp exponential growth of the recovered population. Followed by a sharp growth of the susceptible population after ~10 years due to the immunity loss rate of SARS-CoV-2 antibodies. Shortly after the susceptible population exponentially increases, the death toll exponentially increases. Meanwhile, the population of infected people is stable within the whole population throughout the iterations.

Discussion

Pathogens and their hosts are subjected to population cycling, just as there are cycles of population bursts between predator and prey in an ecosystem, the host and the pathogen cycle through which is more prevalent.[9] When one adapts to a new change in their defense (host) or offense (pathogen), the other has a spike in prevalence until the other adapts to a newer change once again. This proposes a constant evolutionary arms race between pathogens and their hosts.[9]A recent example of this is the current evolutionary arms race between *Homo sapiens* and the SARS-CoV-2 virus, the pathogen that is responsible for the ongoing COVID-19 pandemic. It is a respiratory disease with symptoms including cough, fever, breathing difficulty etc.[7] Various vaccinations have been developed to confer immunity against the virus which has led to a reduction in the death toll as well as the number of infections, but due to the high immunity loss rate of nascent and/or acquired antibodies, in addition to the high mutation rate of the spike protein in the SARS-CoV-2 virion, complete elimination of the virus seems to be improbable. Due to SARS-CoV-2's improbability for elimination, it is likely that this virus already is or will become an endemic.

An endemic refers to a disease which is constantly present in a population, at a certain prevalence level. Common examples of endemic diseases include Influenza A and Hepatitis B. Influenza A started out as a pandemic in 1918, infecting an estimated 1/3 of the population, which led to the development of antibody immunity, and eventually herd immunity within the population.[2] With herd immunity present in the population, the virus randomly mutated under the selective pressure of too many deaths resulting in the decrease in transmission, resulting in a less lethal influenza A strain, ultimately transitioning the influenza A epidemic into an endemic.[2]Even though influenza is an endemic, seasonal epidemic spikes within the population still occur. These spikes in infections help maintain its prevalence in the population, by increasing the chances of infecting immunocompromised persons, the virus is primarily carried by them in the population during non-seasonal periods.[1] Similarly, Hepatitis B also keeps on circulating as an endemic in various countries, periodically displaying epidemic spikes.[15]These epidemic spikes can be due to socioeconomic influences, such as recessions increasing horizontal transmission via illegal drug use and needle sharing. Or epidemic spikes can be due to an increase in vertical transmission from mother to fetus.[5] Both transmission types increase the risk of infection to healthcare workers, which overall increases the infection rate within the entire population. Considering what is known about the epidemic-to-endemic transitions and epidemic cycling of Influenza A and Hepatitis B, we wanted to utilize this knowledge to synthesize predictions regarding the SARS-CoV-2 pandemic-to-endemic transition.

The goal of this study was to answer two questions: 1) is the SARS-CoV-2 pandemic already an endemic? And 2) will SARS-CoV-2 exhibit epidemic spikes throughout its endemicity? A rudimentary SIR model was used to model the endemicity of SARS-CoV-2. It includes the division of the population into 3 classes – Susceptible (S), Infected (I), and Recovered (R). Two cases have been considered – one with vaccine intervention and one without vaccine intervention. Results of both the cases indicate that COVID-19 is likely already an endemic, based on the parameters collected in March 2022. However, based on the exponential growth of the susceptible and dead populations in the later years of the with vaccination model, it is clear that there is a need for constant vaccinations to maintain a stable endemic state.

Conclusions

Based on the results of this study, we can conclude that SARS-CoV-2 is likely already an endemic. To further understand the endemicity of SARS-CoV-2, we can build upon the current SIR model by modifying it to include other measures which were undertaken to control infection, like isolation and quarantine. It could also be modified to include different parameters based off the characteristics of different strains of the virus and the efficacy

of different vaccines created to combat them. Another way to better understand SARS-CoV-2 endemicity would be to model a projected evolution simulation. Here we would include parameters such as random mutation rate, effective mutation rate, and the mutated immunity loss rate. This study projecting the evolution pattern of the SARS-CoV-2 virus, could help to deepen the understanding of the progression of the infection as time progresses and this would also be vital for developing vaccines against new mutations of the virus to maintain a stable endemic state.

Limitations

Limitations for this study include the limited studies and parameters available to model an endemic of a current pandemic. Furthermore, certain papers on Hepatitis B and influenza were inaccessible due to Cornell University not holding a subscription to their journal.

Methods

Literature Curation and Data Collection

Cited literature in this study was curated from scientific literature platforms such as Elsevier, National Center Biotechnology Information (NCBI), BioMedCentral, National Institutes of Health (NIH), and Google Scholar. Data collection for parameters were obtained through the Centers for Disease Control COVID-19 Tracker.

COVID-19 SIR Modelling Code Summary

All computational models and graphs were made using R studio. No packages were used to generate these plots, only base code. The algorithm for the SIR model was implemented by adapting a for looping mechanism to iterate transmission probabilities over a course of 50 years.

COVID-19 SIR Modelling Parameters Table

Table 1. Names, values, and sources of the parameters collected and used for the SIR model of SARS-CoV-2.

Name of Parameter	Value of Parameter	Source of Parameter
Transmission rate (β)	3.1828e-07	Rahman et al 2021
Birth rate (α)	0.011338212	2020 US Census Report
Normal death rate (μ)	0.01027	2020 US Census Report
Disease death rate (σ)	0.011795566049452	CDC COVID-19 Tracker
Constant recruitment rate (Λ)	1	Rahman et al 2021
Immunity loss rate (ω)	0.147843942505133	CDC COVID-19 Tracker
Recovery rate (γ)	0.02	Rahman et al 2021
Vaccination efficacy rate (ε)	0.95	Pfizer reported efficacy

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