Exploring the Conditions for Increased Viral Persistence in SARS-CoV-2: An Extended SIR Model Framework

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Abstract:

The COVID-19 pandemic has revealed the complex dynamics of SARS-CoV-2, where the virus can evolve into variants that drive both acute and persistent infections. Some lineages, such as the Alpha and Delta variants, have been shown to establish viral reservoirs in non-transmissible organs, potentially leading to the reactivation of symptoms over time. As cases of long COVID increase, understanding the conditions that favor viral persistence is crucial for predicting the long-term trajectory of the pandemic. This study employs an extended Susceptible-Infectious-Recovered (SIR) model to explore the epidemiological conditions under which SARS-CoV-2 may evolve increased persistence. It aims to create a null model with three variable parameters as a start. This preliminary model incorporates variable reproduction numbers for both short-term and persistent infections, as well as an immunity waning rate, to simulate various scenarios at the metapopulation level. Results show that the model captures the dynamics of persistent infections under specific parameter ranges, particularly highlighting critical thresholds for each variable parameter. However, the model's response to higher reproduction numbers for persistent infections indicates potential limitations, suggesting that further refinement is needed to ensure biological realism. Extending upon this metapopulation model and combining it with a within-host model for future research would allow for a more comprehensive understanding of viral persistence across different levels. This can foster public health interventions for prolonged chronic infections, such as long COVID.

Introduction:

Early in the COVID-19 pandemic, there was great optimism about containing the virus through vaccination efforts, social distancing, masking, and through natural immunity. However, after billions of vaccine doses worldwide, the prevalence of SARS-CoV-2 persists, where the virus is now occupying new organ niches (Amer et al., 2024). Reports of infections that lead to symptoms beyond the respiratory system have been identified in patients with long COVID (Zuo et al., 2024). Long COVID is generalized by chronic symptoms (from acute to chronic) that persist after around 12 weeks post-infection and is characterized by persistence and multiple organ tropisms (Davis et al., 2023). These symptoms include but are not limited to cardiovascular complications, neurological issues, and gastrointestinal disturbances (Davis et al., 2023). Figure 1 illustrates the multi-organ tropism of SARS-CoV-2. The distribution of viral infection is largely correlated with the presence of ACE2 receptors, which facilitate viral entry into cells (Liu et al., 2021).

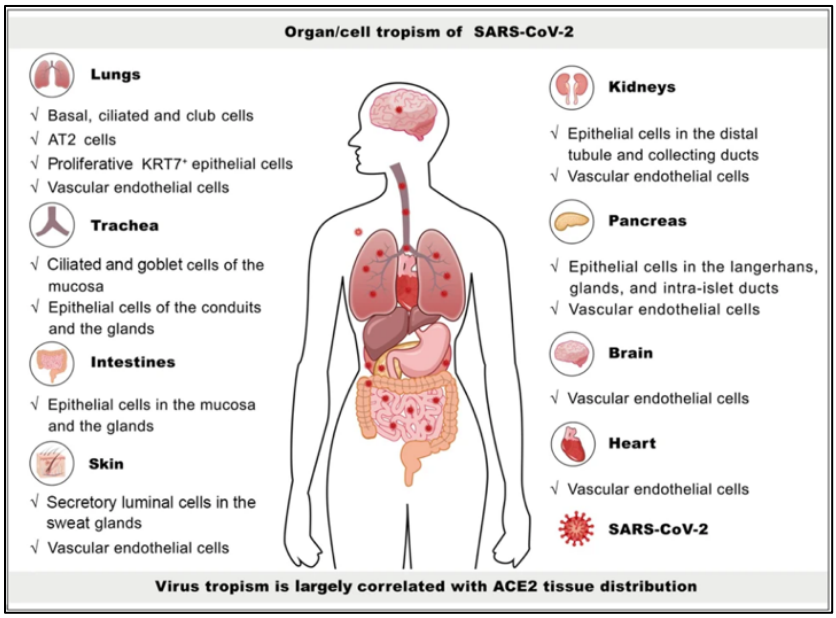

Figure 1: Graphic representation of SARS-CoV-2 organ and cell tropism (Liu et al., 2021).

In this scenario, persistence is defined as the sustained presence of SARS-CoV-2 within a population over an extended period and even potential reactivation mechanisms within the host (Chen et al., 2023). SARS-CoV-2 has been postulated to behave like HIV, where it can remain latent in organ tissue and then reactivate through time (Proal & VanElzakker, 2021). It can be considered an evolutionary stable strategy (ESS), which is a strategy that once established within a population, is resistant to being overtaken by alternative strategies due to its adaptive advantages and inherent stability (Dawkins et al., 2019). Some mechanisms of persistence as an ESS include immune evasion and waning immunity. For instance, SARS-CoV-2's ability to escape the immune system through mutations that can limit antibody binding, appear to be an ESS (Albright et al., 2023). Many strains have taken up this evolutionary advantage, such as XBB and BA.1 after Omicron (Albright et al., 2023). This immune evasion, coupled with the gradual decline of immunity over time, creates a dynamic where the virus can persist and adapt, continually circulating despite widespread immunity and public health interventions (Tea et al., 2021). Understanding these mechanisms is crucial for developing strategies to manage and mitigate the impact of persistent infections.

Despite significant advancements in understanding SARS-CoV-2 transmission and immunity, several gaps remain. One major gap is the comprehensive understanding of the long-term dynamics of immune evasion and waning immunity. Current research has primarily focused on short-term responses to emerging variants, but the mechanisms that

enable the virus to sustain its presence over extended periods are not fully elucidated. Additionally, the interaction between short-term and long-term infections and their combined impact on viral persistence at the metapopulation is not well understood. Addressing these gaps requires detailed modeling of the virus's behavior in different epidemiological scenarios.

This study utilizes an epidemiology model to uncover what conditions would cause the evolution of increased persistence at the metapopulation level. A foundational extended SIR (Susceptible, Infectious, Recovered) model was implemented. By incorporating factors such as intrinsic reproductive numbers for both short-term and persistent infections, and the immunity waning rate, this model aims to simulate various epidemiological scenarios. The objective is to identify the key parameters and conditions that enable the virus to maintain its presence within a population over extended periods, despite public health interventions and widespread immunity. The model can be considered as a null model, serving as a baseline framework that assumes minimal complexity to provide a reference point for understanding the dynamics of viral persistence. Overall, if the number of long-term/persistent infections increase over an extended period, then persistence is being selected for as an ESS.

Determining the conditions that favor the selection of persistence can help predict the trajectory of persistent infections and the virus's evolution. If the model accurately predicts an increase in persistent infections under specific conditions, real-time monitoring can validate its accuracy by comparing trends in studies that either support or contradict the model's predictions.

Methods:

Model Schematic and Framework:

To evaluate the conditions for persistence infections at the metapopulation level, an extended SIR model was implemented. The two-strain model includes four compartments represented by ordinary differential equations (ODEs): Susceptible ($\boldsymbol{S}$), Short-term Infectious ($\boldsymbol{I_s}$), Long-term Infectious ($\boldsymbol{I_p}$) and Recovered ($\boldsymbol{R}$). Figure 1 shows a visual schematic of the four compartmental model, where transitions between them are influenced by the infection rates of both strains, their recovery rates, and natural immune waning. The model was generated based on the four ordinary differential equations (ODEs) and solved using the R package 'deSolve'. A User-Interface was created though the "shiny" package for population dynamics graphs. The R script is provided as a supplementary file.

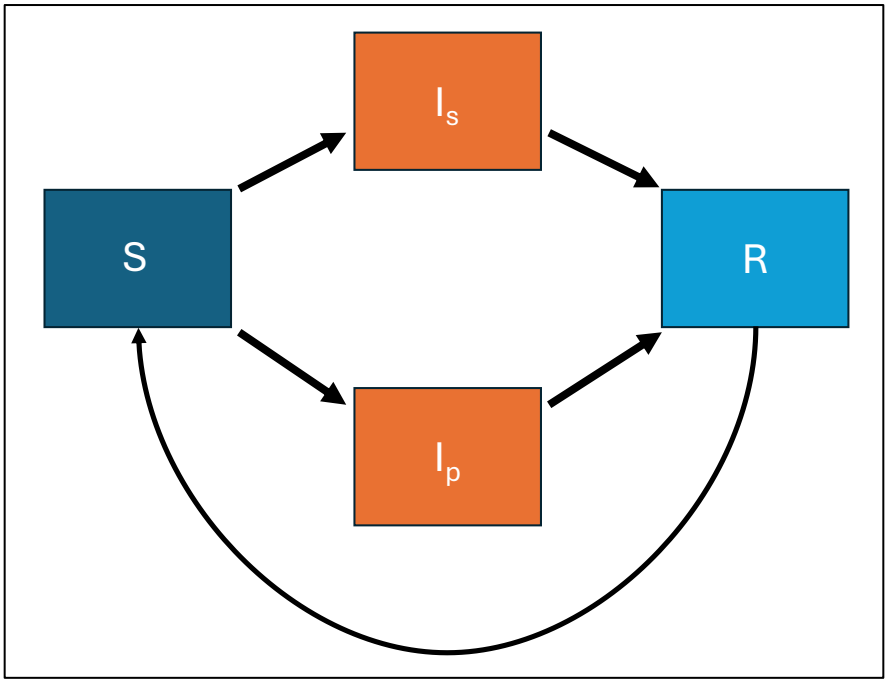

Figure 2: Schematic of extended SIR framework. Four compartments with distinct attributes. The susceptible population is represented by the navy-blue compartment, the infected individuals are represented by orange compartments, and the recovered population are shown in blue. The susceptible compartment ($\boldsymbol{S}$) represents individuals who are at risk of infection. The Short-term Infectious compartment ($\boldsymbol{I_s}$) includes individuals who are recently infected and can either recover or transition to the Persistent Infectious compartment ($\boldsymbol{I_p}$). $\boldsymbol{I_s}$ consists of individuals who have progressed to a chronic stage of infection. The Recovered compartment ($\boldsymbol{R}$) includes individuals who have recovered from the infection but can lose immunity and return to the susceptible state.

ODEs:

$$\boldsymbol{B_s = R_{0,s} \bullet \gamma_s}$$

$$\boldsymbol{B_p = R_{0,p} \bullet \gamma_p}$$

The transmission rates for the short-term and persistent strains are represented by $\boldsymbol{B_s}$ and $\boldsymbol{B_p}$ respectively. These transmission rates are calculated using the basic reproduction numbers of each strain along with their corresponding recovery rates. $\boldsymbol{R_{0,s}}$ and $\boldsymbol{R_{0,p}}$ are the intrinsic reproduction numbers of the short-term strain and persistent strains respectively, while $\boldsymbol{\gamma_s}$ and $\boldsymbol{\gamma_p}$ are their corresponding recovery rates.

The four ODEs are summarized below:

$$\frac{dS}{dt} = \mu N - \beta_s \frac{SI_s}{N} - \beta_p \frac{SI_p}{N} - \mu S + \rho R$$

$$\frac{dI_s}{dt} = \beta_s \frac{SI_s}{N} - \gamma_s I_s - \mu I_s$$

$$\frac{dI_p}{dt} = \beta_p \frac{SI_p}{N} - \gamma_p I_p - \mu I_p$$

$$\frac{dR}{dt} = \gamma_s I_s + \gamma_p I_p - \rho R - \mu R$$

Susceptible individuals (S) can become infected by either the short-term strain, transitioning into the I_s compartment or the I_p compartment. Infected individuals in both I_s and I_p can recover and move to the R compartment. The R compartment includes all individuals who have recovered from either strain of the infection. Over time, recovered individuals in R may lose their immunity and return to the S compartment. The model assumes a constant population size, with the birth rate equal to the death rate, and excludes co-infection possibilities. Additionally, disease-related deaths are not considered in this model. All these assumptions are made to simplify the null model.

Parameters:

Table 1: Fixed parameters used in the model.

Symbol	Parameter Name	Value	Units
μ	Birth and Death Rate	0.000027	1/person/day
N	Population Number	2,794,356	Individuals
γ_s	Recovery rate for short-term infections	0.048	1/day
γ_p	Recovery rate for long-term infections	0.0056	1/day

The birth and death rate ($\boldsymbol{\mu}$) of Toronto was obtained from Statistics Canada. The population number ($\boldsymbol{N}$) is the population of Toronto as of 2021 according to Statistics Canada. Toronto was selected as the population for this simulation due to its high population count. The recovery time for short-term and persistent infections were about 14 days and 180 days respectively (Tamiru et al., 2023 & Mizrahi et al., 2023). The recovery rates ($\boldsymbol{\gamma_s}$ and $\boldsymbol{\gamma_p}$) were calculated using the inverse of these recovery times.

Table 2: Variable parameters used in the model.

Symbol	Parameter Name	Value	Units
$\boldsymbol{R_{0,s}}$	Intrinsic reproductive number (short-term)	5-10	Individuals
$\boldsymbol{R_{0,p}}$	Intrinsic reproductive number (persistent)	0-4	Individuals
$\boldsymbol{\rho}$	Immunity waning rate	0.001 – 0.01	1/day

The intrinsic reproductive number varies for short-term ($\boldsymbol{R_{0,s}}$) and persistent ($\boldsymbol{R_{0,p}}$) infections (Liu & Rocklov, 2022 & Du et al., 2022). The persistent reproductive number range is an arbitrary range, where it must be lower than the short-term. The immunity waning rate ($\boldsymbol{\rho}$) ranges from 0.001-0.01 1/day to encompass healthy individuals to the more immunocompromised individuals (Borchering et al., 2021)

Initial Conditions:

For the initial conditions of the model, the $\boldsymbol{S}$ population is the total population ($\boldsymbol{N}$) minus the initial infected individuals and the recovered individuals. $\boldsymbol{I_s}$ was initialized to start at 1000 individuals, while $\boldsymbol{I_p}$ was initialized to start at one individual. $\boldsymbol{R}$ was set to 0, implying no recovered individuals at the start of the simulation. Initializing $\boldsymbol{I_p}$ to 1 allows for analyzing persistent infection dynamics, where the potential spread and long-term impact can be analyzed. The simulation occurs over a 5-year (1825 days) span to observe long-term population dynamics. Variable parameters were varied within realistic ranges to observe specific conditions for SARS-CoV-2 to persist in the population.

Results:

Impact of Increasing $R_{0,p}$ to Observe Model Behaviour:

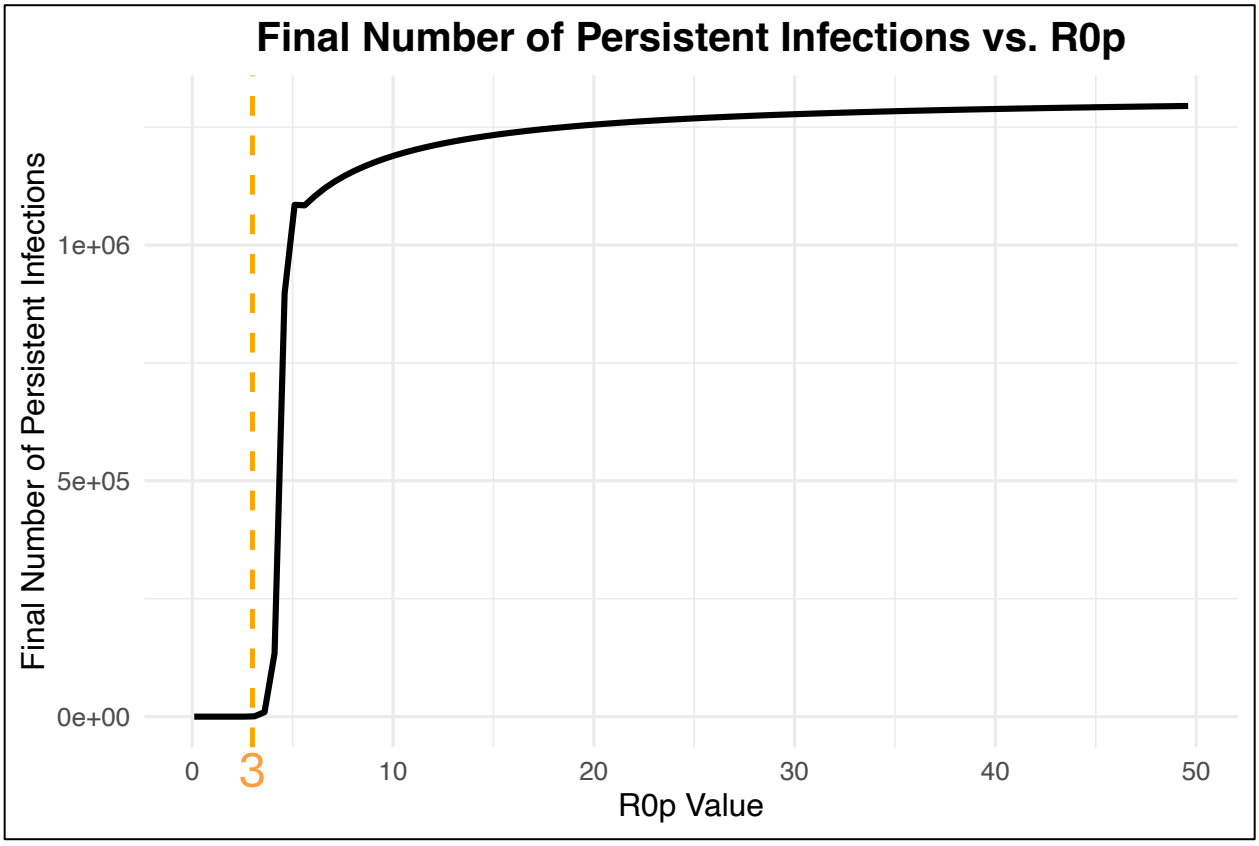

Figure 3: Final Number of Persistent Infections vs. $R_{0,s}$. When $R_{0,p}$ is below 3, the number of persistent infections remains negligible. However, once $R_{0,p}$ surpasses the threshold of 3, there is a rapid and substantial increase in persistent infections. The dashed orange line marks the critical threshold at $R_{0,p}$ = 3. Constants were $R_{0,s}$ = 8 and ρ = 0.005.

Figure 3 shows that as $R_{0,p}$ increases, the number of persistent infections also increase. A striking observation is the exponential increase between $R_{0,p}$ values of 3 and 5.

Below this threshold, the number of persistent infections remains relatively low. However, as $R_{0,p}$ surpasses the threshold value, the number of persistent infections escalates rapidly, indicating that higher $R_{0,p}$ values significantly contribute to the persistence and spread of the infection. After a value of 5, the number of persistent infections increase gradually.

Population Dynamics (Realistic Vs. Unrealistic Conditions):

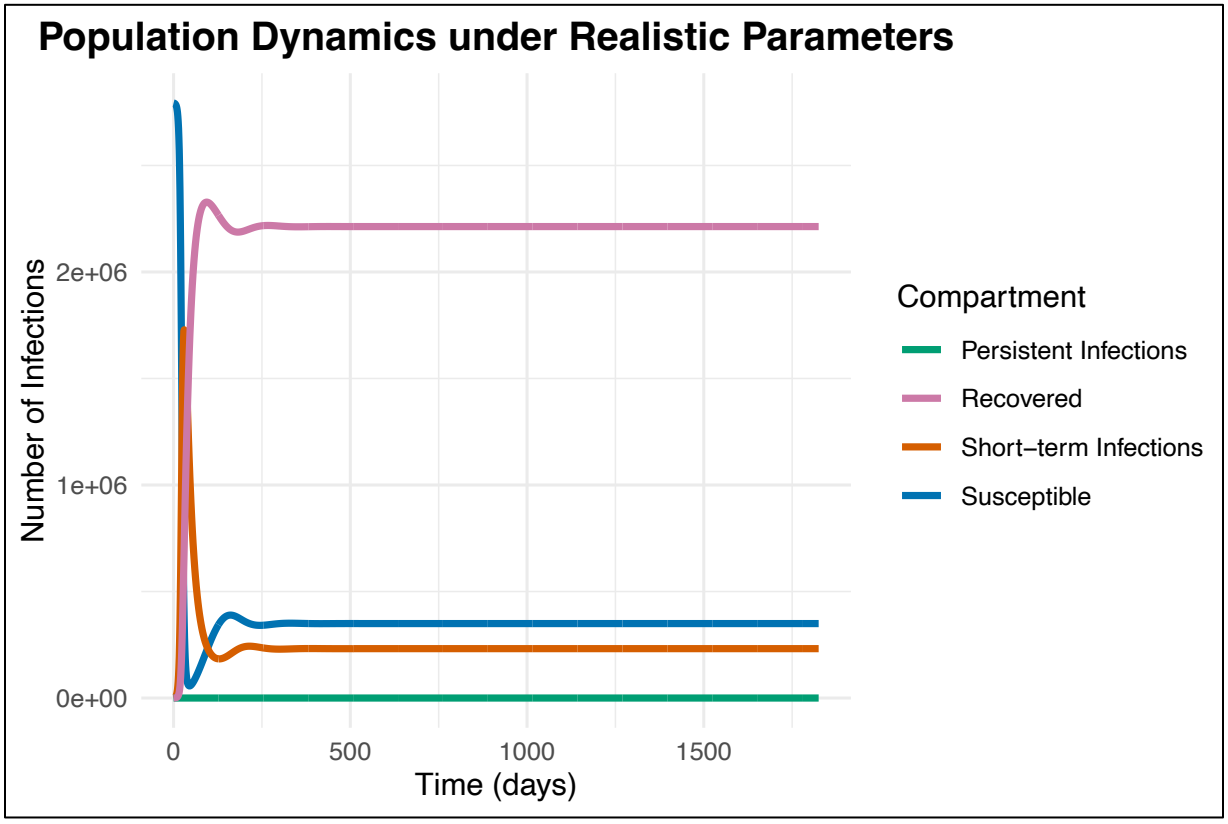

Figure 4: Population Dynamics Under Realistic Parameters. Sample plot of the population dynamics over a 5-year period under realistic $R_{0,p}$ values. The basic

reproduction numbers are $\boldsymbol{R_{0,s}}$ = 8 (short-term infections) and $\boldsymbol{R_{0,p}}$ = 2.5 (persistent infections). The waning immunity rate was constant at 0.005.

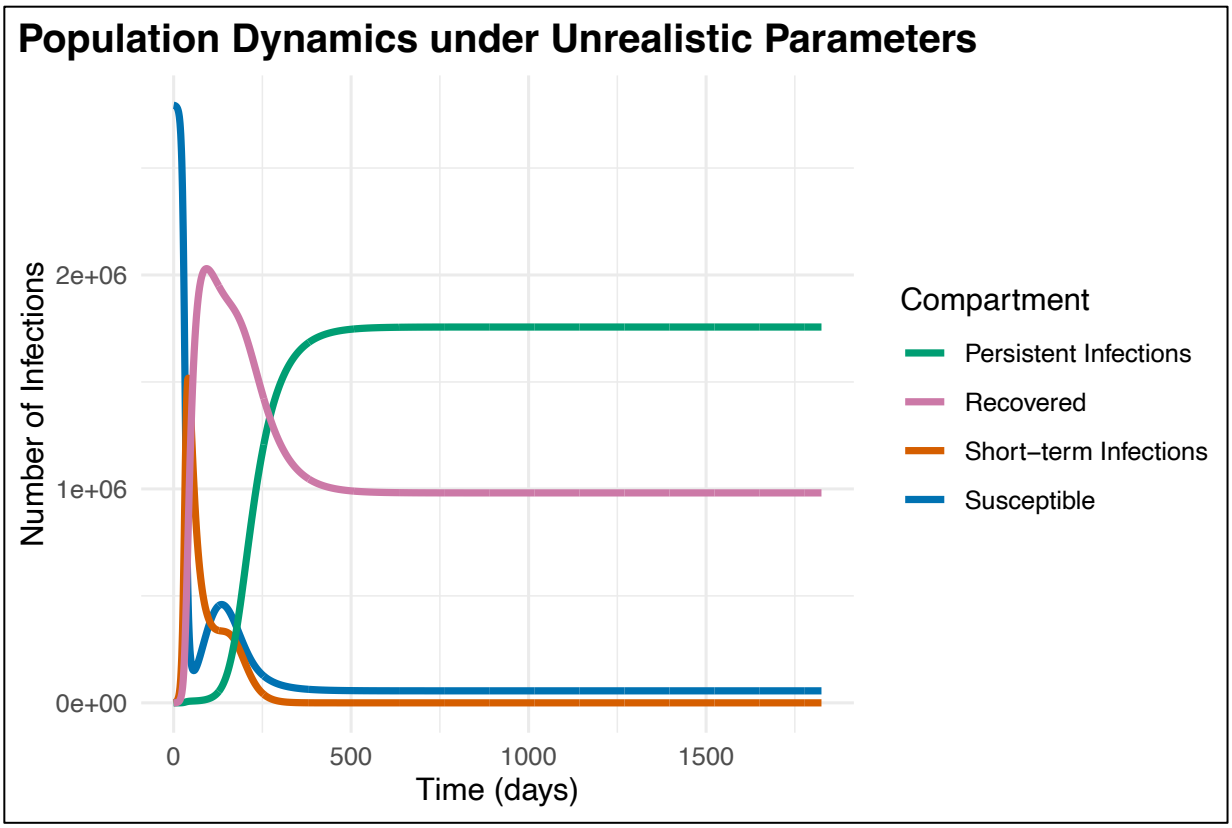

Figure 5: Population. Dynamics Under Unrealistic Parameters. Sample plot of the population dynamics over a 5-year period under an unrealistic $\boldsymbol{R_{0,p}}$ value. The basic reproduction numbers are $\boldsymbol{R_{0,s}}$ = 8 (short-term infections) and $\boldsymbol{R_{0,p}}$ = 20 (persistent infections). The waning immunity rate was constant at 0.005.

From the UI, snapshots of population dynamics capture how realistic and unrealistic $\boldsymbol{R_{0,p}}$ values affect each compartment.

Looking at Figure 3, under a $\boldsymbol{R_{0,p}}$ value of 2.5, the susceptible population initially decreases sharply and then stabilizes over time. The short-term Infections ($\boldsymbol{I_s}$) population shows a rapid increase at the beginning, reaching a peak, and then gradually declines to a steady state. The persistent Infections ($\boldsymbol{I_p}$) population remains very low and almost flat throughout the 5-year period. The recovered population increases sharply at the start, experiences some fluctuations, and then stabilizes at a higher level. Overall, these results indicate that the number of persistent infections ($\boldsymbol{I_p}$) remains negligible under realistic $\boldsymbol{R_{0,p}}$ conditions.

For figure 4, under an unrealistic $\boldsymbol{R_{0,p}}$ value of 20, the susceptible population initially decreases sharply and then stabilizes at a lower level over time. The short-term Infections ($\boldsymbol{I_s}$) population shows a rapid increase at the beginning, reaching a peak, and then declines to near zero. The Persistent Infections ($\boldsymbol{I_p}$) population increases significantly over the 5-year period and eventually stabilizes at a high level. The recovered population increases sharply at the start, experiences fluctuations, and then stabilizes at a higher level. These results indicate that the number of persistent infections ($\boldsymbol{I_p}$) increases substantially under unrealistic conditions, with the overall dynamics being primarily influenced by the high transmission rates and the resulting increase in persistent infections.

1.3: Multi-sensitivity Analysis

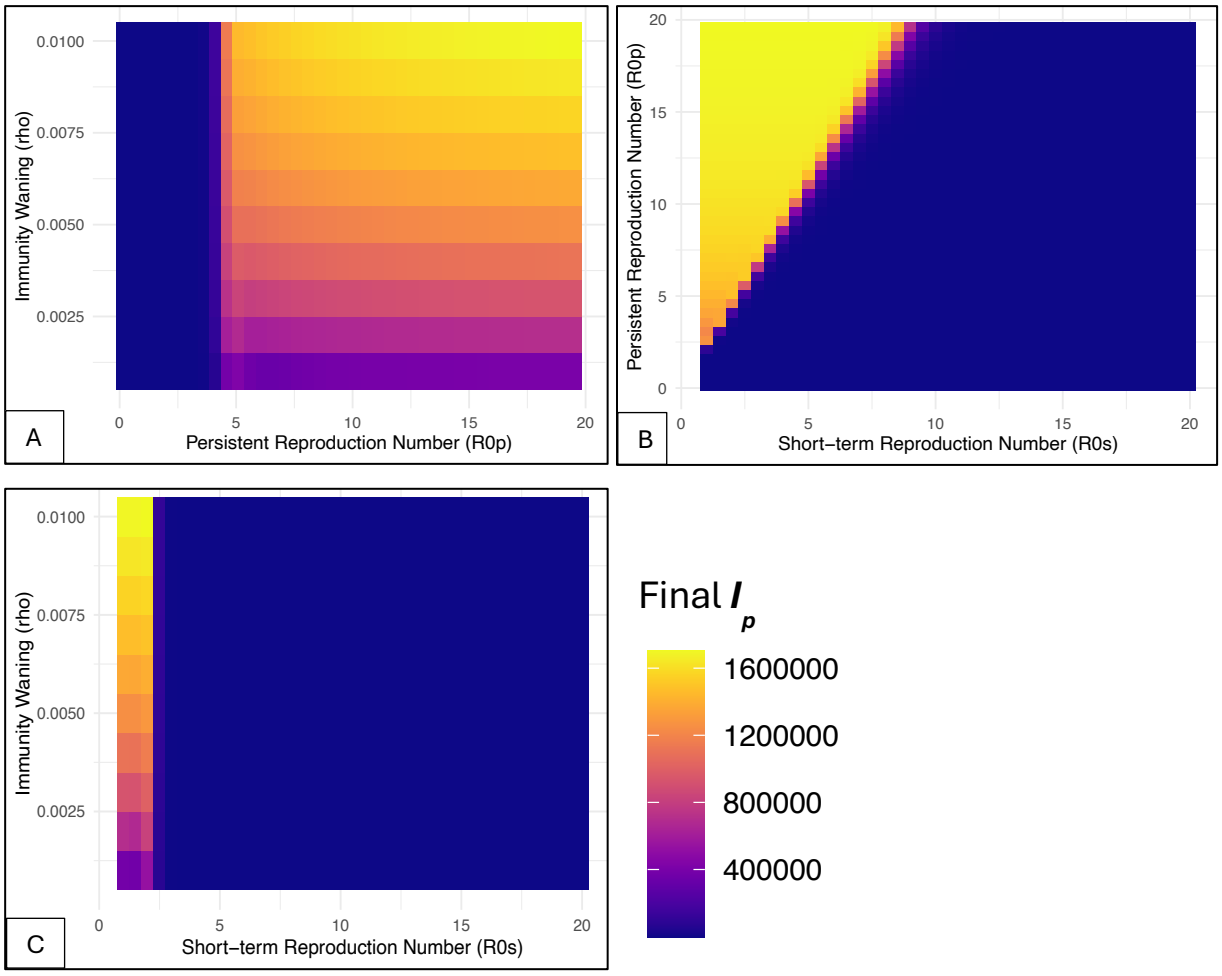

Figure 5: Sensitivity Analysis Heatmaps. The panels show the final number of persistent infections (I_p) across different parameter combinations. **(A)** Sensitivity analysis of ρ vs. $R_{0,p}$. **(B)** Sensitivity analysis of $R_{0,s}$ vs. $R_{0,p}$. **(C)** Sensitivity analysis of $R_{0,s}$ vs. ρ. Constants for each analysis are as follows: (A) $R_{0,s}$ = 8, (B) ρ = 0.005, and (C) $R_{0,p}$ = 2.5.

Panel A of Figure 5 illustrates the sensitivity analysis of the final number of persistent infections with respect to the immunity waning rate (ρ) and the basic reproduction number for persistent infections ($R_{0,p}$). The heatmap reveals a critical threshold for $R_{0,p}$ around 3, beyond which the number of persistent infections increases

significantly. At lower values of $R_{0,p}$, the number of persistent infections remains minimal, even with varying ρ. However, as $R_{0,p}$ exceeds 3, an increase in ρ further amplifies the number of persistent infections, indicating that both high $R_{0,p}$ and high ρ contribute to persistent outbreaks.

Panel B presents the sensitivity analysis of the final number of persistent infections in relation to $R_{0,s}$ and $R_{0,p}$. From the heatmap, it appears that R0p and R0s have opposite effects on I_p . Higher $R_{0,p}$ values lead to an increase in the final number of persistent infections, while lower $R_{0,s}$ values similarly contribute to a rise in persistent infections. This inverse relationship creates a distinct diagonal gradient in the heatmap, as the combined effects of increasing $R_{0,p}$ and decreasing $R_{0,s}$ work together to amplify the persistence of the virus within the population.

Panel C displays the sensitivity analysis of the final number of persistent infections with respect to $R_{0,s}$ and ρ. The heatmap shows that the number of persistent infections is relatively low across most combinations of $R_{0,s}$ and ρ, except for low values of $R_{0,s}$ and high values of ρ. These parameters have an inverse relationship with each other to increase I_p. The overall pattern suggests that while both parameters influence the number of persistent infections, their impact is less dramatic compared to the influence of $R_{0,p}$ observed in Panels A and B.

Discussion:

Model Interpretation:

The extended epidemiological model demonstrates that while it performs adequately for outlier values of variable parameters, its use for more real-time scenarios remains limited. This observation emphasizes the need for further refinement and enhancement of the foundational model to accurately capture the full range of persistence dynamics. To truly understand the conditions under which SARS-CoV-2 evolves increased persistence, the model must be improved upon by incorporating additional complexities and addressing its current limitations.

Figure 3 illustrates the relationship between the persistent reproduction number ($\boldsymbol{R_{0,p}}$) and the number of final persistent infections ($\boldsymbol{I_p}$). From $\boldsymbol{R_{0,p}}$ values of 0 to 3, the number of persistent infections remains relatively low, indicating that the virus struggles to establish a significant foothold in the population below this threshold, preventing widespread and long-term persistence. As $\boldsymbol{R_{0,p}}$ increases to between 3 and 5, there is a rapid escalation in persistent infections, suggesting that surpassing this threshold allows the virus to sustain and amplify its presence in the population. However, the model's behavior at $\boldsymbol{R_{0,p}}$ values above 5 raises questions about its realism. In reality, $\boldsymbol{R_{0,p}}$ for persistent SARS-CoV-2 infections is generally expected to range from 0 to 4, as persistent infections typically establish viral reservoirs in organs with low transmission rates (Chen et al., 2023 & Davis et al., 2023). Higher $\boldsymbol{R_{0,p}}$ values would imply an unrealistically high transmission rate for persistent infections, which contradicts the known behavior of

chronic viral persistence. Moreover, in real-time, the selection for persistence gradually increases in the long-term, not exponentially (Chen et al., 2023). Therefore, these results likely reflect a limitation of the model rather than a realistic scenario.

The population dynamics graphs (Figure 4 and 5) under both realistic and unrealistic parameter settings reveal key areas for model improvement. Under realistic parameters where $\boldsymbol{R_{0,p}}$ **=** 2.5 (original Wuhan strain), the number of persistent infections remain very low consistently throughout the 5 years (Rahman et al., 2020). The time frame may need to be extended to capture the gradual increase in persistent infections, as the population dynamics graph showed Ip numbers remaining close to zero during the observed period. The $\boldsymbol{I_s}$ line showed an exponential increase followed by a decrease with $\boldsymbol{R_{0,s}}$ **= 8** (Omicron) (Albright et al., 2023). This rapid spread is characteristic of short-term infections, which are typically associated with acute outbreaks and higher transmission rates. Under unrealistic conditions where $\boldsymbol{R_{0,p}}$ **=** 20, the $\boldsymbol{I_p}$ line increases exponentially and then plateaus at a high value. Interpretating this would mean that persistence is being selected for as a fitness advantage in a short-time frame. This contradicts the evidence that shows it gradually being selected for in the long run (Chen et al., 2023). The dynamics of short-term infections, where $\boldsymbol{R_{0,s}}$ **= 8,** reflect typical fluctuations in the number of short-term infections. It appears that due to the high $\boldsymbol{R_{0,p}}$ value**,** the persistent strain outcompeted the short-term strain. However, persistent infections in real-time are increasing based on reinfection through latency and reactivation (Proal & VanElzakker., 2021). A variable for recurrence must be incorporated into the model to account for reactivation.

The multisensitivity analysis in Figure 5 reveals the impact between the short-term reproduction number ($\boldsymbol{R_{0,s}}$), the persistent reproduction number ($\boldsymbol{R_{0,p}}$), and the immunity waning rate ($\boldsymbol{\rho}$) in determining the final number of persistent infections ($\boldsymbol{I_p}$). The heatmap in panel B shows that $\boldsymbol{R_{0,s}}$ and $\boldsymbol{R_{0,p}}$ behave antagonistically to each other. $\boldsymbol{R_{0,s}}$ must decrease and $\boldsymbol{R_{0,p}}$ must increase to maximize the number of persistent infections. If $\boldsymbol{R_{0,s}}$ decreases, then the persistent strain would have a greater chance of outcompeting the short-term strain. It's also important to refer to table 2 for acceptable parameter ranges. Under combinations of realistic values for $\boldsymbol{R_{0,s}}$ and $\boldsymbol{R_{0,s}}$ **,** no persistent infections are present in the population according to panel B. This further emphasizes the need for a recurrence variable within the transmission rate equations **(**$\boldsymbol{B_s}$ and $\boldsymbol{B_p}$) to show the considerable difference between persistent and short-term infections. The analysis also highlights the critical role of immunity waning; as $\boldsymbol{\rho}$ increases, so does $\boldsymbol{I_p}$, especially in scenarios with high $\boldsymbol{R_{0,p}}$ values and lower $\boldsymbol{R_{0,s}}$. This indicates that reduced immunity duration enables the virus to reinfect individuals more easily, leading to more persistent infections (Menegale et al., 2023).

Model Improvements and Future Work:

This is a foundational model that must account for additional complexities. First, the model should be adjusted to ensure that the reproduction number for persistent infections ($\boldsymbol{R_{0,p}}$) remains within a biologically realistic range, reflecting the typical behavior of viruses that establish chronic infections rather than acute outbreaks. This could involve

implementing stricter thresholds for $\boldsymbol{R_{0,p}}$ and incorporating mechanisms that account for the lower transmission rates associated with persistent infections. As previously mentioned, a variable for recurrence must be incorporated to ensure both strains aren't at level playing field.

The model also assumes that if the number of persistent infections gradually increases, then persistence is being selected for as a fitness advantage. However, stochastic elements must be added to capture the divergence/mutation rate as well. This is vital to accurately predict new persistent variants that can circulate within the population long-term.

Lastly, the model excludes the possibility of co-infection and cross-immunity. By adding compartments that pertain to co-infection and cross-immunity, the model would become more complex. This would allow for an analysis of viral competition and its potential contribution to the evolution of persistence. Cross immunity refers to when the immunity of one virus provides some level of protection against another related virus (Bhattacharyya et al., 2021). This would allow for an evaluation of how previous exposure to one strain can affect the infection dynamics of another.

After building upon the metapopulation model, future research must involve connecting this to a within-host model to capture the overall nuances of SARS-CoV-2 persistence. Some within-host models for SARS-Cov-2 have been curated by other researchers, yet persistence wasn't the main purpose of their studies (Wang et al., 2022). Extending upon these existing models can account for viral replication and immune

evasion mechanisms (Wang et al., 2020). Connecting these models together can provide an overall picture for the conditions that increase persistence at the cellular level and at the population level. Furthermore, it is still speculated if SARS-CoV-2 can move between transmissible and non-transmissible organs. If this were true, then individuals with persistent infections through time would be overall more infectious compared to those with short-term infections. If viral reservoirs with heightened replication rates are present and facilitate movement of the virus to the lungs, this could trigger a ratcheting effect, where persistence is gradually selected for over time. Thus, this would lead to an increase in the number of persistent infections.

With the discussed model improvements and future areas of research, the trajectory of chronic infections like long COVID can eventually be tracked. This is all to ensure that public health interventions are informed by the most accurate predictions for persistence evolution.

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