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Research Article

Evolution of New Variants of SARS-CoV-2 During the Pandemic: Mutation-Limited or Selection-Limited?

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The recent SARS-CoV-2 pandemic has witnessed the emergence and succession of various virus variants. While the phenomenon of immunity-evading variants is known in other viruses like influenza, there is limited understanding of the ecological and evolutionary processes involved in this succession. Due to the availability of large-scale epidemiological data collected and shared publicly during the Covid-19 pandemic, it has become possible to explore evolutionary questions that also have implications for public health. We propose multiple alternative hypotheses regarding the origin and spread of these variants and evaluate them based on epidemiological data. Our analysis indicates that the invasion of novel variants is primarily limited by selection rather than mutation. Moreover, the repeated waves observed during the pandemic are not solely caused by the emergence of new variants. Instead, there is a significant overlap between conditions that lead to a wave and those that favor the selection of partially immune-evading variants. This association may contribute to the rise of a new wave alongside the invasion of a new variant. However, the association is not strong enough to support a causal role of the new variant. The dynamic interplay between epidemiological processes and selection on viral variants carries important implications for public health and can guide future policies aimed at effectively controlling infectious epidemics.

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The emergence of a new variant during an ongoing viral epidemic involves two key evolutionary processes: (i) the origin of the variant through mutations, and (ii) natural selection or drift acting on the frequency of the mutant. While both processes are fundamental to evolution, one of them can be rate-limiting in a given context. If a mutation provides a consistent selective advantage to the mutant but has a low probability of occurring in the population, the rate of evolution will be limited by mutation. On the other hand, if the population is large enough for a specific mutant to have a high probability of appearing, but the conditions necessary for the selection of that mutant are restrictive and context-dependent, then the evolution will be limited by the availability of the selective environment. Distinguishing between mutation-limited and selection-limited evolutionary dynamics[1] can significantly impact our understanding of a disease and subsequently influence public health policies.

In the field of infectious diseases and public health, there are two prevailing perceptions that make this question important. The first perception is that variants capable of evading host immunity, to some extent, are responsible for recurring outbreaks of infection. Such variants may undermine vaccination efforts and hinder epidemic control. The second common perception, reflected in policies and public information, is that the rise of new variants can be prevented by reducing viral transmission, thereby minimizing opportunities for the virus to mutate[2][3]. This perception assumes that evolution is primarily limited by mutation. Both perceptions need to be carefully evaluated to ensure clarity in understanding that influences public health policies.

Many epidemics occur in waves, and various potential causes for the re-emergence or recurrent wave patterns have been suggested. These include factors such as structured populations with heterogeneous exposure, changes in human behavior, and rapid waning immunity within the population[4][5][6][7][8]. Although there are multiple possible explanations for the repeated waves observed in the Covid-19 pandemic[9][10][11], the prevailing popular belief is that new waves are caused by new variants that can bypass the immunity provided by prior infection or vaccination[12][13][14]. While several studies have shown that some of the new variants are partially capable of

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evading immunity[15][16], their role as the "causal" factor for new waves has not been rigorously examined in comparison to alternative hypotheses. Due to the plausibility of multiple alternative cause-effect relationships, which are not mutually exclusive, it is necessary to investigate whether the emergence of partially immunity-evading variants during the pandemic was the sole or primary cause of the new waves.

Traditionally, the popular model used for epidemiological predictions is the compartmental or SIR model, along with its variations. In this model, the population is divided into compartments, including susceptible, infected, and immune or removed individuals. However, these models treat immunity as a binary variable, where individuals are classified as either susceptible or immune. Such models are inadequate for considering the gradual loss of immunity following natural infections or vaccination. In reality, immunity is a continuous variable, and only a few models account for this aspect[17][18]. Waves of infection are expected outcomes in models that incorporate the decline of immunity, independent of the emergence of new variants. Therefore, the loss of immunity and immunity-evading variants should be considered as competing, but not mutually exclusive, causes of recurrent waves. It is crucial to evaluate their respective contributions to the waves based on their differential testable predictions.

Below, we define different classes of alternative hypotheses regarding the evolution of new variants, the causal factors for their spread, the onset of new waves, and their interrelationships. We then present the specific testable predictions for each hypothesis, along with evidence that could potentially accept or reject them. Ultimately, these hypotheses will be evaluated using publicly available data on the Covid-19 pandemic.

Alternative hypotheses for the invasion of new variants and the occurrence of repeated waves

A. Invasion by new variants being mutation-limited

If the rise of new variants is primarily a mutation-limited process, we would expect most mutants to arise and spread during the peaks of prior variant waves since mutations are more likely to occur when the viral population is high. This can be tested by examining the time of invasion by different variants during the pandemic. Additionally, we can analyze the epidemiological patterns predicted by simulations of mutation-limited versus selection-limited models of variant evolution.

Within the mutation-limited paradigm, there are two distinct possible evolutionary paths for new variants.

Hypothesis 1: All-time selective advantage for new variants with immune evasion: When a prior variant has infected a portion of the population and individuals have developed immunity, any immune-evading mutant (with all other characteristics being identical) can be assumed to have a selective advantage. Consequently, the new variant will gradually replace the prior variant at a non-zero positive rate of invasion. It is also possible that a mutant with increased transmissibility has an all-time selective advantage and therefore invades the population whenever it arises.

Hypothesis 2: Random replacement by drift or selection unrelated to epidemic parameters: It is possible that new mutants/variants replace the previous ones purely by chance, such as through genetic drift. Additionally, there may be positive selection on the new variant for reasons unrelated to epidemiological parameters. Factors like intracellular competition or competition for entering a new host cell can involve trade-offs with net infectivity. Thus, a variant that is a stronger competitor within a host's body may not necessarily be more infectious at an epidemiological level. Infectivity at the epidemiological level is a complex phenomenon influenced by host population immunity, host behavior, and other social as well as climatic factors involved in transmission. Therefore, *in vitro* markers of infectivity may not be correlated with the rate of transmission in the host population.

B. Invasion by new variants being selection-limited

This school of thought assumes that, for most of the time during the epidemic, the viral population is sufficiently large to ensure a significant probability of an immune-evading mutant emerging. Whether the mutant can successfully replace the previous variant(s) depends on the specific selective conditions at a given time. Currently, there are limited efforts to comprehend the selection acting on new variants during the pandemic, and our understanding of the nature of this selection remains inadequate. We propose a descriptive model that outlines how selection is expected to operate on new variants with immune evasion under various conditions. Additionally, we present testable predictions derived from this hypothesis and compare them with available data.

Hypothesis 3: The Context-dependent selection model: The immune response to a pathogen is multifaceted, and our current understanding only encompasses some of the modes of immunity. The immune response targets various epitopes on the virus, and it is well-established that cross-immunity exists between viral variants[19]. Mutations do not simultaneously alter all epitopes, resulting in only partial immune evasion. While determining the exact level of immunity required for protection against infection is challenging, it is generally agreed that the levels of immunity achieved after natural infection or vaccination are significantly higher than the minimum threshold for immunity. Consequently, immunity following natural infection or vaccination is likely effective against partially immune-evading variants as well[20], albeit with lower "titers" compared to the original variant[21][16] (see Figure 1). Although the word titer is used and quantified in relation to antibody levels, we use it here conceptually to refer to any mechanism of immunity that is quantitative and shows a declining trend with time. When immune levels are high, partial immune evaders would be unable to establish widespread infection because titers against them would also be above the minimum needed for protection. This could explain why, even after the Omicron variant became predominant, Omicron-specific vaccines did not offer significantly greater protection compared to prior vaccine boosters[22]. Variants are unlikely to possess a selective advantage when hosts are at their maximum immunity level achieved after vaccination or natural infection. Acquired immunity is known to decline over time, albeit at varying rates. This decline appears to be considerable in the case of Covid-19[23][24]. Since the new variant initially has lower titers, it may fall below the minimum immune threshold sooner than the prior variant (see Figure 1). The period between the new variant's titer falling below the threshold and the prior variant's titer crossing it represents a window in which the new variant may have a selective advantage. Prior to this time window, the population is immune to both, and past the time window, it is susceptible to both. Only during this window does it allow infection by the new variant but not by the prior variant.

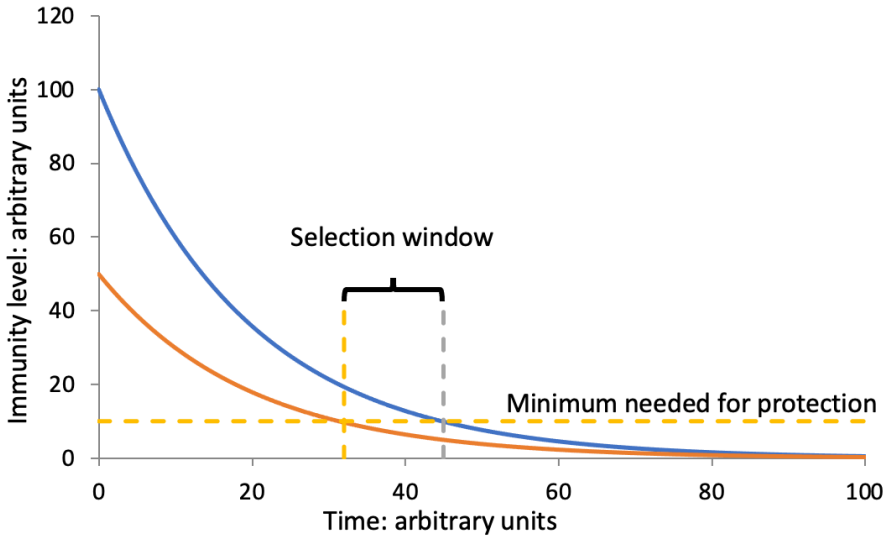

Figure 1. Dynamics of immunity and selection of the new variant: A host is expected to have a lower immunity titer against a new variant. Assuming the rate of immunity loss is the same, the new variant can cross the minimum immunity threshold before the old variant does, creating a window for selection. On either side of this window, there is no clear advantage for the new variant.

Models that incorporate declining immunity demonstrate that if population immunity falls below a certain threshold, a new wave is likely to occur even in the absence of a new variant[17]. The threshold for the onset of a new wave depends on various environmental factors, including host population density, temperature, humidity, and more. Thus, this threshold may or may not align precisely with the new variant crossing the minimum immunity threshold. As a result, the invasion of the new variant may precede, coincide with, or follow the occurrence of a new wave.

This conditional selection process for immune-evading mutants is still expected to lead to an association between the new variant and the new wave, although the association may be weaker and

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the cause-effect relationship may not be straightforward. Conditions that contribute to the emergence of a new wave also create favorable conditions for the introduction of a new variant. Consequently, while the new variant may not be the cause of the wave, it will coincide with it. The epidemiological predictions of this model differ from those in which a new variant "causes" the new wave.

While we primarily used immunity decline as a variant-independent cause for repeated waves, other factors contributing to the wave pattern have also been suggested, such as cyclic changes in population behavior[10]. A variant with greater infectivity may arise due to mutation(s). However, whether increased infectivity is a sufficient cause for a new wave is an important question. Models treating immunity as a continuous variable show that only in certain phases of the epidemic is the transmission infectivity-limited. In phases where it is immunity-limited, increased infectivity alone is insufficient to cause a new wave[18]. A decline in population immunity is necessary for a new wave; a variant with increased infectivity is more likely to ride this new wave.

It is important to realize that the selection-limited view changes the focus of the question from the origins of a variant to the beginning of invasion by a variant. The origin might be local, by a mutation arising, or immigration from a different geographic origin. There are interesting hypotheses about the origin, such as chronic infections or alternative hosts, discussed by Markov et al[25]. What matters for the question here is not the origin but the beginning of population invasion by the variant.

Differentiating between the alternative hypotheses

According to Hypothesis 1, the majority of invasions should occur near the peak of the prior variant's incidence. If the new variant has a higher transmission rate, the invasion should be accompanied by an increase in the slope of the incidence curve. If the rise in slope is significant enough, it can lead to the formation of a detectable new wave. The new wave is expected to be characterized by a continuing or declining slope of the prior variant, with the rise in slope of the incidence curve entirely attributed to the new variant (Figure 2a).

Under Hypothesis 2, the probability of a new variant invading will either be directly proportional to the standing viral population or remain constant over time. The testable prediction of this hypothesis is that the probability of a new variant arising within a given time interval will be proportional to the area under the incidence curve or remain constant over time, depending on whether selection unrelated to epidemiological parameters or drift is the predominant factor.

Hypothesis 3 suggests that when a new wave begins, the incidence of the prior variant(s) is also likely to increase, at least in the initial phase of the wave (Figure 2b). Alternatively, the new variant may replace the prior variant(s) without immediately causing a wave (Figure 2c). Since wave patterns can occur independently of new variants in immunity decline models, new waves can arise without any detectable invasion by a new variant (Figure 2d). Therefore, the patterns depicted in Figures 2b, c, and d are consistent with Hypothesis 3. This hypothesis also predicts that new variants are unlikely to invade at or immediately after the peak of the prior wave, when population immunity is at its maximum. Invasion by new variants can only occur after a substantial time gap following the peak of the prior wave, when population immunity has sufficiently declined to allow for a new surge.

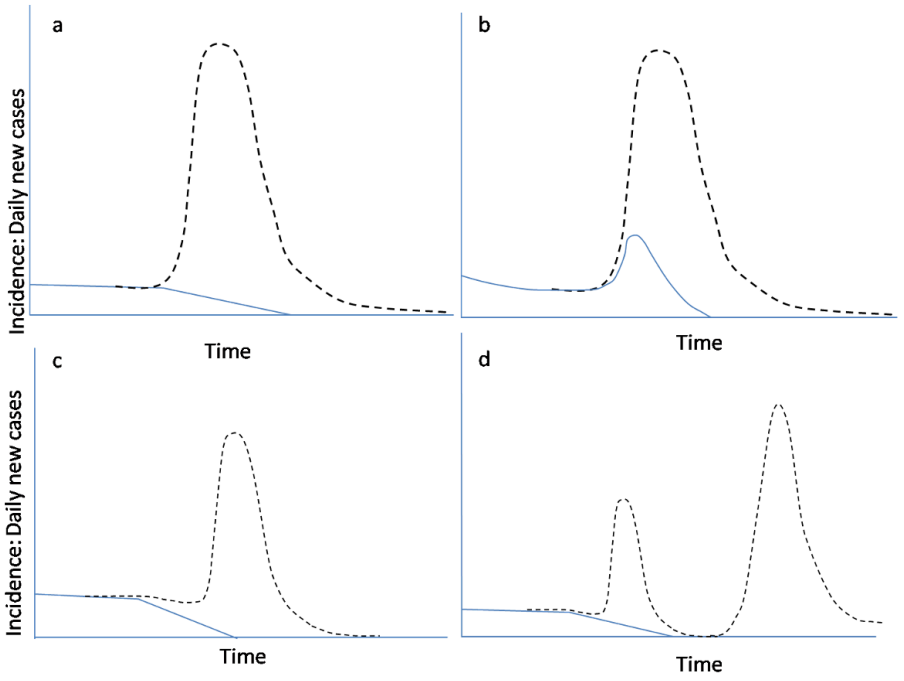

Figure 2. The solid line represents the incidence of the prior variant(s), while the dashed line represents the total incidence.(a) Hypothetical expected incidence curve if a new variant is the sole cause of the wave. We can visualize three different scenarios in which the relationship between the total incidence and the proportion of prior and new variants differs from the expectation of Hypothesis 1.(b) Prior variant wave: In this pattern, the incidence trend of the prior variant(s) also shows an upward shift during the early phase of the wave. Even if we remove the new variant, a detectable wave is still present. (c) Prior replacement: Partial or complete replacement of the old variant(s) by a new one occurs before the wave begins.(d) Complete wave course without a new variant: A wave arises and falls, completing its course without any new variant emerging during this period. This can happen if a new variant has completely replaced the prior one(s) before the beginning of a new wave. This pattern indicates that a new variant is neither necessary nor sufficient for a wave.

If the new variant is more infectious than the prior one(s) at any given phase of the epidemic, we would expect the slope of the total incidence curve to increase in relation to the standing proportion or the rise in proportion of the new variant. In the short term, it can be assumed that the host immunity status may not have changed sufficiently to affect this correlation. However, in the long run, as the host population acquires immunity to the new variant, the correlation may change. Therefore, such correlations should only be examined over a short time span before the new variant proportion saturates and/or the wave reaches its peak, whichever occurs earlier.

We also utilize simulations as a tool with limited implications. The purpose of these simulations is to qualitatively test the notion that if mutations are limited and an immune-evading mutant has a persistent advantage, most invasions will begin near the peak of the prior variant. Since we lack empirical information on many parameters, simulations cannot be used to make quantitative predictions that are meaningful.

Methods

Data Source: The data used to test the predictions were obtained from the public domain database https://ourworldindata.org/explorers/coronavirus-data-explorer. The database provides daily information on country-specific registered cases and deaths. In selected countries with sufficient sequencing efforts, there are bi-weekly updates on the proportion of recognized variants of concern among the sequenced samples. It is important to note that the accuracy of data recording may vary across countries, imposing limitations on the data. Since only a small fraction of samples undergo sequencing for variant identification, the detection of a variant may not necessarily indicate its origin but rather when and where it was first identified, which serves as a reasonable reflection of its

origin. The samples selected for sequencing are not randomized, and there may be some selection bias in favor of new variants, as suspected cases of new variants are more likely to undergo sequencing. Additionally, there can be variable delays in the sequencing process. Considering these data limitations, the following specifications and working definitions are used in the analysis. The sensitivity analysis section later discusses how these limitations and biases may affect the inferences.

Choice of Variants for Analysis: For the analysis, we utilize the variants being monitored (VBM) as listed by the CDC in https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html#anchor_1632158885160. Specifically, we focus on the variants with respective WHO labels: alpha, beta, gamma, delta, epsilon, eta, iota, kappa, zeta, mu, omicron, and their sub-variants. Data on all these variants are used to analyze predictions related to the origin of variants. However, since the delta and omicron variants have been largely associated with the second/third waves and subsequent waves, respectively, we specifically use these two variants for the analysis related to the association of variants with specific waves.

Data Segment: A data segment is defined as a period of two weeks since the available variants data represent proportions among sequenced samples over a two-week timeframe.

Origin of a Variant: The working definition for the origin of variants is determined based on the date and country where the variant was first detected.

Invasion by a Variant: In countries with variant data, the date from which the proportion of a variant among the sequenced genomes begins to monotonically increase for at least three consecutive data segments is considered as the working definition for the beginning of invasion by the variant.

Wave Definition: A wave is defined as a period in which there is a rise in daily registered new cases by at least a thousand from the baseline. A peak is recognized when there is a monotonic increase for at least two data segments followed by a monotonic decrease for at least two data segments.

Data Interval for Correlation Analysis: The data interval used to study the correlation between the proportion of a variant and the rate of transmission starts either when the invasion of the new variant begins or when a new wave begins (whichever occurs earlier). The interval ends when the proportion of the new variant saturates (often near 100%) or when the peak of the wave is reached, whichever occurs earlier. The association analysis is limited to this interval to avoid interference from host immunity to the new variant, which may change or even invert the correlation beyond that point.

Simulations

In order to study whether the mutation-limited model is compatible with the observed patterns in the pandemic, we use simulations to generate patterns expected by the hypothesis. Since this is the mainstream thinking, and most mainstream models are based on compartmental SIR models, we use the SIR model here. We initiate the simulations with a total population of one, where *S(0), I(0)*, and *R(0)* represent the initial fractions of susceptible, infected, and immune individuals, respectively. Using a starting variant V_0, the SIR model is executed with a rate of *S* to *I* conversion = $K_1.S.I$ and a rate of *I* to *R* conversion = $K_2.I$. The immune individuals can become susceptible again with a rate $K_3.R$. The probability of generating a new variant V_1 (and subsequently V_n) at a given time is directly proportional to *I*. A new variant is assumed to be generated when a randomly generated number is $<p.I$, and $V_n(t)$ is assigned a small value of 0.001. For the n^{th} new variant, $S_n(t) = 1- I(t)$, $R_n = 0$, and the simulation equations are applied similarly. These simulations assume that immunity to each variant is acquired independently of other variants, and there is no cross-immunity. Since conventional SIR models typically treat immunity as a binary variable, it is challenging to incorporate cross-immunity or gradual loss of individual immunity. The range of parameters used for the simulations were K_1 *=0.01 to 0.2;* K_1 *=.01 to 0.1;* K_3 *= 0.0001 to 0.1; p = 0.001 to 0.00001.*

The selection-limited models assume every individual's immunity as a continuous variable. Therefore, we used a model with a non-binary immunity state, described in detail in Watve et al. [18] along with its set of predictions. This model can predict repeated waves even in the absence of any immune-evading variant. By comparing and contrasting the predictions of the two models, we can derive some simple qualitative differential testable predictions for the hypotheses of interest. However, neither of the simulations was intended to make any quantitative predictions.

Results

Due to the absence of empirical estimates for many parameters, the simulations cannot provide quantitative predictions. However, they can offer limited insights into qualitative patterns. When considering mutation-limited evolution of variants and new variants as the necessary and sufficient cause of waves, we observe that most invasions tend to occur near the peaks of prior variant incidence, and the total incidence remains consistently high (see Figure 3a). Although there are stochastic fluctuations, a significant period with low incidence levels is not observed at any parameter values. In contrast, the Watve et al.[18] model, which treats immunity as a continuous variable, is capable of predicting a realistic life cycle of a wave, including a phase of low incidence resembling an endemic state between two waves.

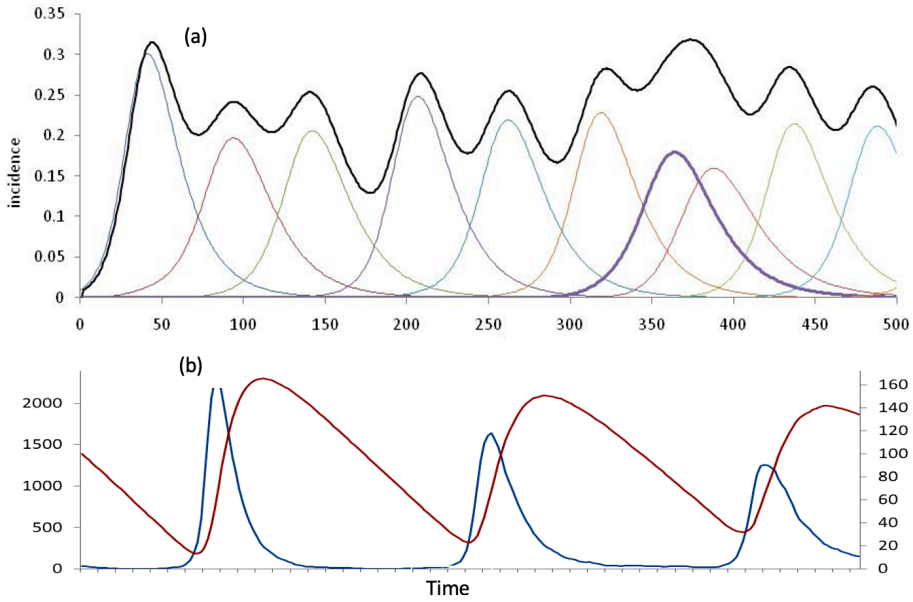

Figure 3. Example patterns observed in simulations using the two contrasting models.(a) SIR model incorporating the generation of novel immune-evading random mutations. The black line represents the total incidence, and the colored lines represent the incidence by successive variants. It is noteworthy that most new variants invade near the peaks of prior variants since the probability of a mutant arising is highest during that time. In this model, the net population is assumed to be unity, and incidence is in terms of the fraction of the population. (b) Result of the Watve et al.[18] model, demonstrating waves separated by a significant period of low incidence resembling an apparently endemic state. The blue line represents the incidence curve, and the red line represents the mean population immunity. In this model, waves can be observed even in the absence of a new variant. Since this was an agent-based model, the incidence is actual numbers, the total population in the simulation being 5000.

To test the predictions regarding the association between new variants and new waves, we had sufficient variant data for 125 waves from 64 countries. Notably, none of the 125 waves aligned with the expectation of Hypothesis 1 as depicted in Figure 2a. Instead, 72 waves exhibited a pattern consistent with a prior variant wave, as shown in Figure 2b. In 92 waves, there was evidence of prior invasion by a new variant well before the onset of the wave, as illustrated in Figure 2c. Additionally, 27 waves completed their course without the emergence of any new variant. Figure 4 displays representative patterns corresponding to Figures 2b to 2d, each from one country. These findings highlight that all 125 waves exhibit at least one of the three patterns contradicting Hypothesis 1.

Furthermore, there is a poor correlation between the standing proportion or increase in proportion of the new variant and the increase in the slope of the incidence curve. Correlations for both delta and omicron are weak, with less than 1% of the variance in the slope of the incidence curve being explained by the new variant (Figure 5a, b, c, d). These correlations do not support the idea that the initial rise in slope during a wave is solely due to the new variant being more infectious. This analysis challenges the popular belief that new variants are inherently more infectious than prior ones. There

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could be alternative factors contributing to the higher slopes and peaks observed in later waves, such as declined immunity resulting from lockdown measures that limit repeated exposures, or changes in people's behavior in later phases of the pandemic. In the Watve et al[18] model, which considers immunity as a continuous variable, the suppression of transmission in the first phase often leads to a higher peak in subsequent waves. Therefore, in the presence of alternative explanations, the steeper slopes and higher peaks observed in later phases of the pandemic cannot be taken as definitive evidence of higher transmission rates of later variants.

In summary, based on multiple tested predictions, it can be concluded that new variants are not necessary and sufficient causes of new waves as proposed by Hypothesis 1, although they may be associated with waves and may contribute to them. With multiple lines of evidence, we can confidently reject Hypothesis 1.

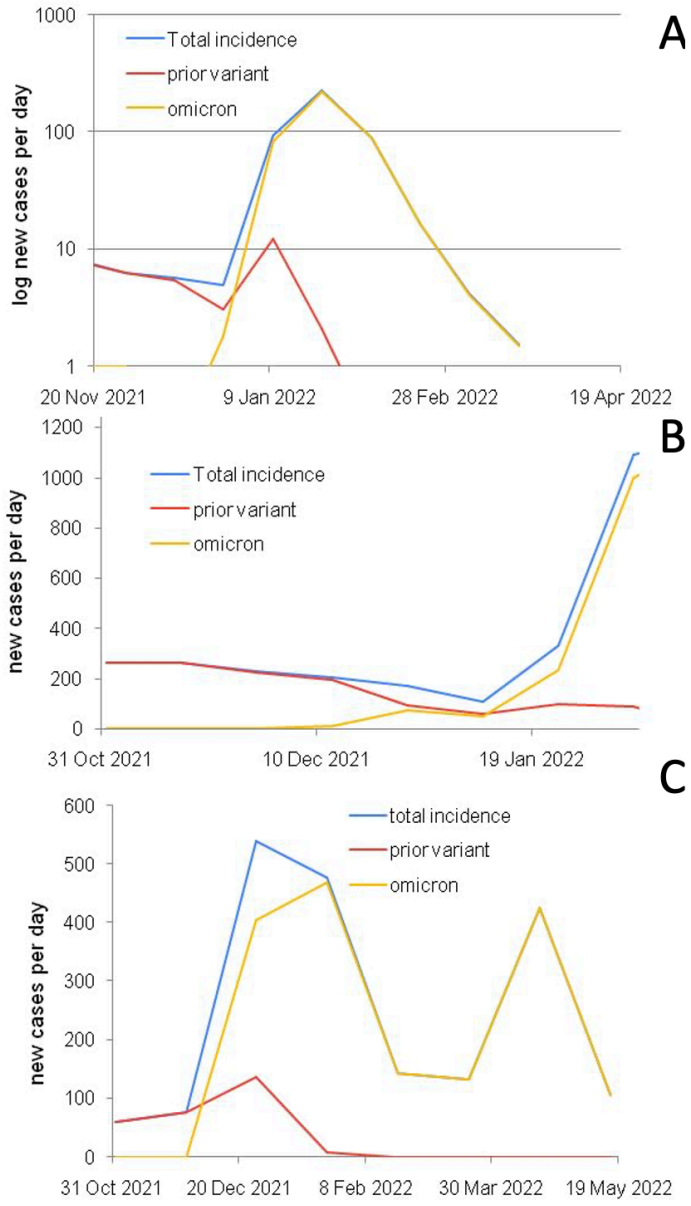

Figure 4. Sample incidence curves demonstrating deviations from the expected pattern proposed by Hypothesis 1.(a) Prior variant wave: The incidence of infection by prior variants also increases during the initial phase of the wave. Data shown is from the wave associated with omicron in India.(b) New variant prior invasion: Invasion by a new variant starts, and old variants are significantly replaced well before the onset of the new wave. Data from Russia at the beginning of the omicron-associated wave is presented. It is noteworthy that omicron replaced the prior variant delta by approximately 50% while the total incidence was decreasing.(c) Wave without any new variant: The second wave depicted in this figure, observed in Canada, seemingly occurred without the presence of a new variant.

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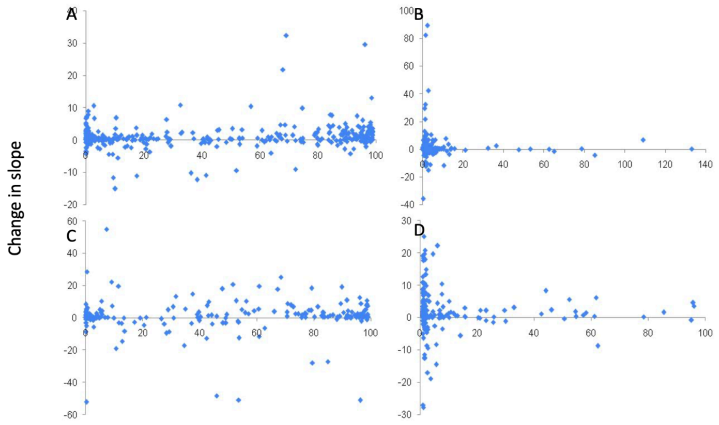

Figure 5. Correlations between the standing proportion of the new variant (percentage) and the change in slope of the incidence curve (left panel) and between the proportionate increase in the new variant and the change in slope of the incidence curve (right panel). Panels A and B represent data for waves associated with the delta variant, while panels C and D represent data for waves associated with the omicron variant. The coefficient of determination (r^2) for all four correlations was less than 10^{-4}.

When plotting the beginning of invasion by a variant alongside the incidence curves, it becomes evident that, contrary to the general prediction of mutation-limited hypotheses, most variants start invading at low levels of incidence (Figure 6), contrary to the expectation of the mutation-limited hypothesis and simulation results (Figure 3a). Since there are only 16 distinct identifiable origins of variants or subvariants, we did not conduct a quantitative analysis to determine whether the probability of a new variant arising is constant over time or proportionate to the area under the curve. However, considering that 14 out of the 16 origins occurred at lower levels of incidence, the data does not align with the predictions of the mutation limitation paradigm.

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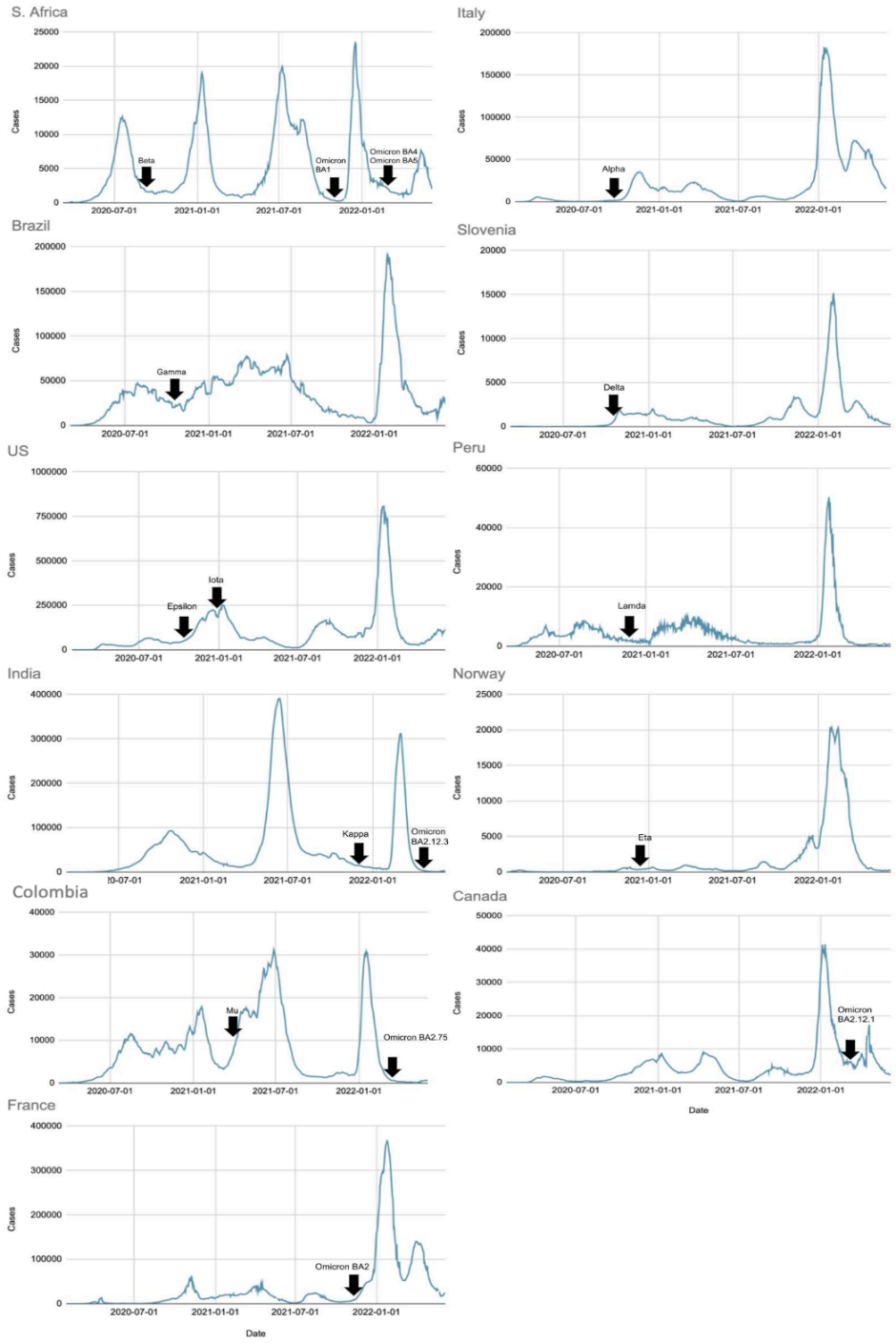

Figure 6. The countries and time of origin for the 16 variants and sub-variants being monitored. The origin of a new variant is indicated by an arrow along the incidence curve. It is noteworthy that the majority of variants were first detected when the incidence was low.

Furthermore, when examining the onset of new variant invasions across all countries with variant data, it is evident that these invasions predominantly occur during periods of low incidence. This distribution is not random or proportional to the area under the curve, thereby contradicting hypotheses related to drift or independent selection. On the contrary, the beginning of an invasion is typically observed after a certain time gap following a prior peak (Figure 7), aligning with the expectations of Hypothesis 3.

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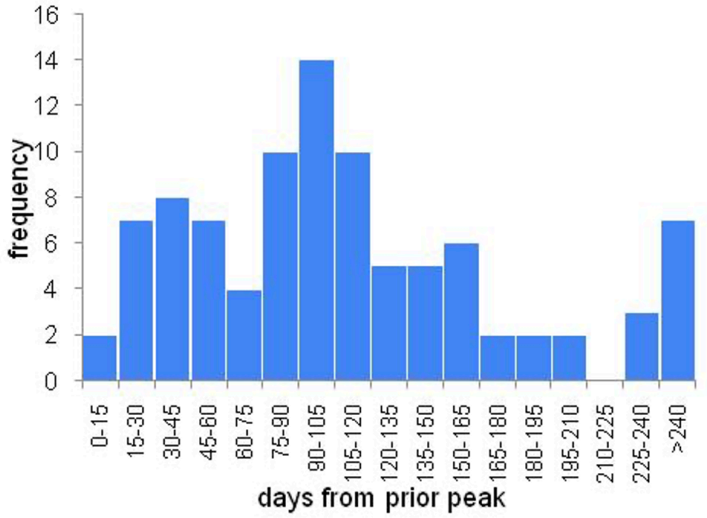

Figure 7. The frequency distribution of the time gap between a prior peak and the onset of a new variant invasion. The mode of this distribution occurs at approximately 100 days. It is worth noting that very few invasions take place during or immediately after the peak, which is inconsistent with the predictions of the mutation-limited paradigm.

Sensitivity analysis

We now examine whether the observed patterns could be influenced by inherent biases and limitations in the data. The variants are defined as lineages, and data are only available for the variants of concern as defined by the World Health Organization (WHO). However, mutations continue to accumulate within these variants and sub-variants, and not all of them have been identified and named, leading to a lack of data on their frequencies. Therefore, the presence of waves without new variants (Figure 2d and 4c) cannot be considered strong evidence against Hypothesis 1. It is possible that these waves are associated with certain mutations for which we do not have available data. Hence, we exercise caution in over-interpreting the patterns observed in Figure 2d and 4c, which depict waves without new variants. The apparent time lag between the rise or immigration of a new variant and its first detection can introduce bias in determining the time of origin or the onset of invasion. The actual origin or beginning of invasion would be earlier than what is observed in the data. Any correction for this bias would actually strengthen the prior invasion pattern (Figure 2c and 4b) more than it appears. Assuming the actual onset of invasion to be 2 to 3 weeks prior to its first detection, the majority of invasion points still align with regions of low incidence on the curve. Therefore, this provides a compelling reason to reject Hypothesis 1. The bias in the samples chosen for sequencing is likely to result in an overrepresentation of new variants, as acknowledged by Ritchie[26]. Despite this bias, we observe prior variant waves (Figure 2b and 4a) in 72 instances. Any adjustment made to account for this bias would actually strengthen the pattern of prior variant waves. Thus, this also serves as strong evidence against the mutation-limited perspective. The data intervals selected for the correlation analysis were chosen to avoid ranges where biases could arise. For example, we exclude the slopes in the declining phase of the wave, which can be attributed to the population acquiring significant immunity to the new variant. We also refrain from using data after a variant completely replaces the prior variant or reaches saturation since the subsequent flattening of the curve would weaken any correlation. Therefore, the overall correlation between the increase in the proportion of the new variant and the apparent rate of transmission can be deemed inherently weak with confidence. Although data bias may weaken some of the evidence, there are still substantial grounds to reject Hypothesis 1. The selection limitation paradigm, which assumes a common cause of immunity decline for both new waves and the selection of partially immune-evading variants, garners support throughout the analysis.

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Discussion

The epidemiological patterns observed in the origin and invasion of new variants, as well as the emergence and increase of new waves in the incidence curves, contradict the mutation-limited paradigm and provide support for the selection-limited paradigm. It is important to realize that both mutation and selection are central to viral evolution, but mutations being necessary is different from mutations being limiting. The hypothesis of immunity decline as a common cause for the rise of new waves and the selection of new variants appears more promising. This concept may have broader implications that extend to other viral infections such as influenza and the common cold, where new variants frequently arise. With improved data collection in the public domain, it was possible to test multiple differential predictions during the COVID-19 pandemic, and this opens up the possibility of revisiting influenza and gaining new insights. The question of why variants arise frequently in influenza and coronaviruses but not in pox viruses or poliovirus, for example, remains unanswered, and the answer may lie in the dynamics of immunity. All viruses mutate, and it is impossible that mutations altering antigenicity do not arise in any virus. According to our hypothesis, if the rate of immunity decline is rapid, it creates the window of selection for new variants (figure 1). For long-lasting immunity, such a window may not appear within the lifetime of host individuals. Therefore, if immunity declines faster, we would expect a higher frequency of new variant appearances. Immunity to poxvirus or poliovirus is known to be long-lasting, which may inhibit the evolution of new variants.

The question of why immunity to certain groups of viruses is longer-lasting than to others remains completely open. An adaptive hypothesis can be proposed, although it is purely speculative at this stage. Immunity carries a high cost, as does long-term immune memory. The immune response needs to be optimized considering the cost of infection. The cost of the immune response should not exceed the cost of the infection itself. As a result, the immune system has evolved to invest more in immunity against groups of viruses that are potentially more virulent, while allocating marginal resources for viral groups that generally cause mild symptoms. This hypothesis can be tested through a careful comparative study of immune responses against all groups of pathogens. These novel possibilities require serious exploration, both theoretically and epidemiologically, especially when evidence fails to support the hypothesis of new variants driving waves.

The concept of selection-limited evolution also requires a significant revision of mainstream thinking regarding the epidemic and mitigation measures. Attempts to limit transmission through lockdown measures, as advocated by organizations like the World Health Organization (WHO) and other health authorities, are unlikely to be effective for several reasons. Firstly, lockdown measures have not been proven to be highly effective in curbing transmission, except during the initial stages of the epidemic. Secondly, since the rise of new variants is not limited by mutations alone, restricting the viral population to realistic limits may not prevent the emergence of new variants. Viral populations, even within individual hosts, are quite large, and RNA viruses have high mutation rates. Therefore, the frequent occurrence of mutants is expected. The more relevant question for understanding viral evolution is whether the conditions favor the selection of these mutants. The role of declining immunity-driven selection has the potential to provide valuable insights into viral evolution and warrants further investigation at both theoretical and empirical levels.

On this background, important questions arise: Can we influence the selective conditions for new variants through appropriate public health strategies? How would alternative non-pharmaceutical preventive measures affect the selective landscape? How would vaccines and booster shots shape the selective landscape? These questions remain open and require both theoretical and empirical research. Gaining an insightful understanding of the selection pressures acting on virus variants is likely to refine and appropriately design preventive strategies with long-term effects for future epidemics.

Statements and Declarations

Data Availability

Publicly available datasets were analyzed in this study. This data can be found here: Our World In Data COVID-19 Data Explorer (https://ourworldindata.org/explorers/coronavirus-data-explorer) and CDC COVID Data Tracker Variant Proportions (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

Author Contributions

Conceptualization, M.W.; Methodology, S.B. and M.W.; Software, S.B.; Validation, S.B. and M.W.; Formal Analysis, S.B.; Investigation, S.B.; Resources, M.W.; Data Curation, S.B.; Writing – Original Draft Preparation, S.B. and M.W.; Writing – Review & Editing, M.W.; Visualization, S.B.; Supervision, M.W.; Project Administration, M.W.

Ethics

This study utilized publicly available, aggregated, and anonymized data provided by Our World In Data and the Centers for Disease Control and Prevention (CDC). No individual patient data was accessed or analyzed. Therefore, institutional ethical approval was not required for this study.

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Declarations

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