JULS

Perspectives

Perspective on Accuracy of Past SARS-CoV-2 Evolutionary Predictions

By: Juliette Blais-Savoie

Background

COVID-19 is a respiratory disease caused by the novel SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) virus. The COVID-19 outbreak began in 2019 and rapidly developed into pandemic status in the early months of 2020[1].

Over the course of the COVID-19 pandemic to date, the evolution of SARS-CoV-2 has been a key driver of the disease's epidemiology, with rises in infections and deaths often correlating with the emergence of new variants[2] as can be seen in Figure 1. These variants also have vital implications for the effectiveness of COVID-19 treatments and vaccinations[1]. Understanding and anticipating the evolutionary trends in SARS-CoV-2 is therefore a necessary component of planning future treatments and protocols aimed at diminishing the continued spread of COVID-19.

Existing infectious disease models have been adapted to the specific biology of the SARS-CoV-2 virus to make predictions about how it will evolve. This article is not a review of SARS-CoV-2 evolution, but instead a summarizes the predictions made about SARS-CoV-2 evolution during the early stages of the pandemic and evaluates them using the evolutionary trends seen to date while also proposing possible future directions for the evolution of the virus. The purpose of this perspective is to determine the accuracy of early predictions and inform as to which viral factors most influence SARS-CoV-2 evolution.

Method

This article compares predictions of SARS-CoV-2 evolution based on evolutionary models to empirical data collected throughout the COVID-19 pandemic. Five early prediction articles published between August 2020 and September 2021 which adapted pathogen evolutionary theory and infectious disease modeling to SARS-CoV-2 were selected. Empirical data on SARS-CoV-2 evolution was collected from Covariants.org with supplemental PubMed database searches.

Early Predictions

A virus's fitness is determined by its ability to generate new infections. Transmissibility, the ability of a virus to spread to new hosts, is a key part in this process, so increases in transmissibility will often improve fitness. However, transmissibility is thought to be limited due to the transmission-virulence trade-off hypothesis[3]. This hypothesis states that transmissibility and virulence are both functions of viral load, meaning that as transmissibility increases, so does virulence, which is detrimental to pathogen fitness for diseases spread directly between hosts like COVID-19. Therefore, these two traits typically act as opposing selective pressures on pathogen evolution.

Transmissibility

Day et al.[3] predicted strong selection on SARS-CoV-2 for increased transmissibility, especially in environments with dense populations of susceptible hosts, leading to mutations increasing transmission outcompeting others in such settings. These authors also predicted that as social distancing protocols decreased the transmission of all genotypes, these protocols would maintain a large susceptible population over a long period of time, strengthening selection towards increased transmission[2].

Virulence

Virulence is typically selected against over time[3]. However, the correlation between transmission and virulence provides a selective pressure opposing virulence costs. The experiments conducted by Berngruber et al.[4] support the notion that while the transmission-virulence tradeoff leads to an intermediate level of virulence over time, highly virulent strains of a pathogen are favored early in an epidemic. Based on this principle, there would be selection on SARS-CoV-2 for increased virulence prior to widespread immunity

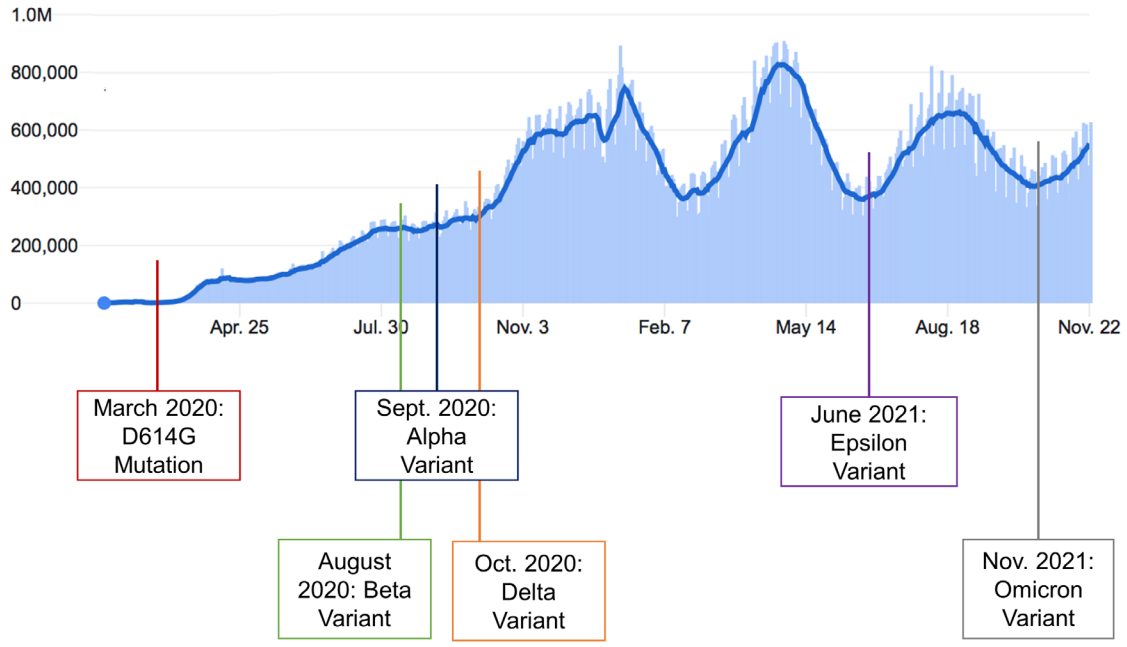

Figure 1: Global COVID-19 case count[20] with timeline of variant emergence[21,5]

and selection for decreased virulence once the virus became endemic[4].

Day et al.[2] predicted that the selection against virulence would not be strong in the case of SARS-CoV-2 since most transmission occurred during the pre-symptomatic phase (Figure 2) and so disease-induced mortality would rarely limit opportunities for onward transmission. If transmission and virulence were genetically or physiologically linked (as posited by the virulence-transmission tradeoff), then the lack of countervailing selection for reduced virulence could mean that selection for increased transmission would dominate, resulting in a correlated increase in virulence. This prediction was made based on the virus's unique disease progression. COVID-19 patients have the highest viral loads during their pre-symptomatic phase, and this load is largely depleted by the point of symptom onset, leading to negligible losses in transmission from host death. This trait causes increased virulence to be carried along as selection favors mutations which increase transmissibility[2]. This weakened limitations on increased virulence will likely lead to continued evolution towards higher virulence. The same prediction was made by Otto et al.[5] and Alizon & Sofonea[6], both of which provide the similar reasoning.

Immune Escape

Mutations that better allow SARS-CoV-2 to infect individuals who already have immunity against the virus will provide a greater number of possible hosts, increasing viral fitness. The articles reviewed here do not discuss possible immune escape evolution in great detail, likely because early in the COVID-19 outbreak there were not enough immune individuals for selection on immune escape to be significant. Otto et al.[5] predicted that as the population gained immunity, SARS-CoV-2 would evolve characteristics to evade host immune systems that could recognize the virus. However, such evolution was predicted to be limited due to SARS-CoV-2's proofreading mechanism which reduces detrimental mutations during replication and due to limited immune escape evolution in other human coronaviruses[6]. Despite this limitation, Alizon & Sofonea[6] did predict immune avoidance; wherein SARS-CoV-2 infections would increase in the upper respiratory tract (URT) which mounts a weak immune response as humans gained immunity in the lower respiratory tract (LRT) through prior infections which mount high immune responses in the LRT.

Observed Viral Evolution

A disproportionate number of mutations in the SARS-CoV-2 genome have been observed in the region that codes for the spike protein (S-protein), suggesting that there is increased selective pressure on this portion of the genome[5]. This is likely due to the fact that all of the viral traits mentioned previously can

be influenced by alterations in spike, which is a protein on the outside of the virus that binds to ACE-2 proteins for cell entry and is a target for host immune responses.

Transmission

The first mutation in SARS-CoV-2 to achieve near fixation is spike mutation D614G. Present in all major variants of the virus, this mutation improves spike cleavage, increasing the open configuration of the protein (as can be seen in Figure 3), a configuration required for interactions with human ACE-2 receptors, and subsequently host cell entry[7]. By doing this, D614G increases infection in the URT, a region rich in ACE-2 receptors, which increases viral load and transmission. However, D614G does not increase virulence[8] due to the fact that URT infections are less severe than LRT infections[9].

Subsequent VOCs have contained mutations linked to improved transmissibility, such as P681H present in Alpha, Delta, Mu, and Omicron[10,11], N501Y present in Alpha, Beta, Gamma, Mu and Omicron[7,11], and E484K/A in Beta, Gamma, Mu, and Omicron[11,12]. It is believed that the high number of spike mutations present in the Omicron genome is facilitating its high transmission rate.

The evolution of SARS-CoV-2 towards increased transmission follows the predictions made by Day et al.[2] and Otto et al.[5]. Social distancing measures designed to limit transmission generated pressure for mutations improving transmissibility. These measures also intentionally kept the susceptible population high[5], which helped avoid overburdening healthcare systems, but provided more hosts over a longer period of time, maintaining selection for traits that increase transmission.

Virulence

As new COVID-19 variants have evolved increased transmission, they have also generally evolved increased virulence. This pattern matches the trends in Berngruber et al.[4] of high virulence being favored in early outbreaks of a pathogen. This trend in SARS-CoV-2 evolution is likely due in part to the carrying of virulence as a trait associated with increasing transmission as predicted by Day et al.[2], Otto et al.[5]. Lavine et al.[13]'s prediction that the virus will decrease in virulence by evolving to infect the URT more is supported by early data regarding Omicron[14]. This trait reduces the transmission-virulence tradeoff for Omicron and is especially helpful to the virus in areas where individuals who detect symptoms of SARS-CoV-2 self-isolate, but asymptomatic individuals interact with others and unknowingly spread the variant.

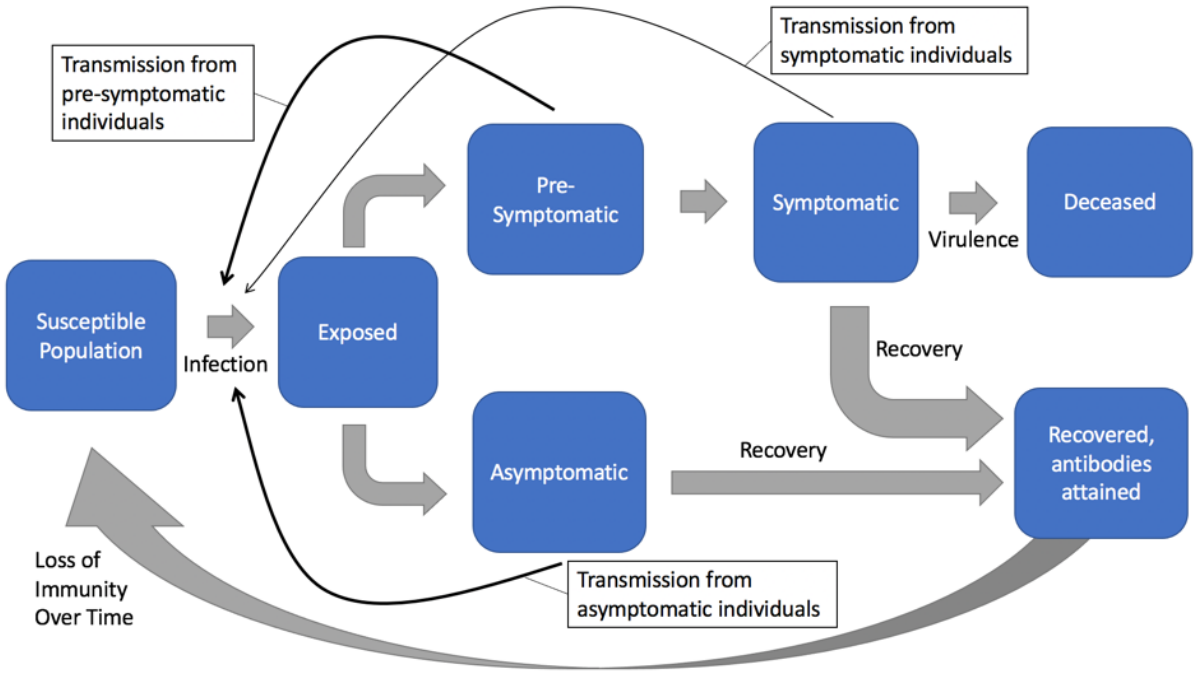

Figure 2. Diagram of COVID-19 disease progression. Gray arrows represent movement between host classes. Black lines represent interactions leading to transmission, where the weight of the line indicates the likelihood of transmission from a given class.

Immune Escape

While immune escape was not an evolutionary outcome that was predicted to have significant influence on SARS-CoV-2 evolution, a greater number of influential mutations have been attributed to this trait than to viral load and transmission combined. One possible explanation for this trend is that since antibody interactions with spike are not limited to the RBD or areas affecting open configuration, providing more potential sites for mutations to arise. Since antibodies interact mainly with the S-protein, mutations aiding immune escape are primarily found in spike. At least two independent mutations in the N-terminus of spike have been linked to immune escape[11,15,16]. Each new strain (including the most recent Omicron subvariatns BA.4 and BA.5) appears to have greater immune escape capabilities than the last[17,18,19], though this is likely now due to widespread immunity to older strains.

Despite rarely being addressed in predictive papers, there has clearly been evolution towards immune escape in SARS-CoV-2 as evidenced by the numerous mutations associated with this trait. While Day et al.[2] postulated that there would be some evolution towards immune escape, the volume of mutations affecting this trait greatly outweighs the concern accorded to it. Selection has apparently overcome the evolutionary limitations predicted by Alizon & Sofonea[6] leading to variants with increasing immune escape abilities[14]. Because many of the mutations improving immune escape arose in 2020, well before vaccination was widespread, it is not likely that vaccine rollouts provided the selection pressure for this evolution early on. It is possible that variants with these mutations are generalists that transmit better in both naïve and immune hosts, or that some immune escape mutations are neutral within naïve hosts, but advantageous in immune hosts. Another possibility is that immunity from prior infection and recovery was providing enough selective pressure on SARS-CoV-2 to lead to the significant immune escape evolution observed.

Conclusions

Although it has not been the largest concern of the COVID-19 pandemic response to date, SARS-CoV-2 evolution has exerted great influence on the past trends and current state of the pandemic. The directions of SARS-CoV-2 evolution were correctly predicted for many viral traits, including transmissibility and virulence. However, the impact that selection for immune escape would play on the virus' evolution was grossly underestimated early in the pandemic. There is ample evidence that immune escape --typically observed as antigenic drift in the SARS-CoV-2 spike protein-- is a driving factor in the success of novel variants. Immune escape evolution therefore ought to be a primary factor of consideration for the design and implementation of novel COVID-19 vaccinations, therapies, and public health policies. As the COVID-19 pandemic continues, models implementing the relative importance of antigenic drift will more accurately predict the direction and magnitude of viral proliferation.

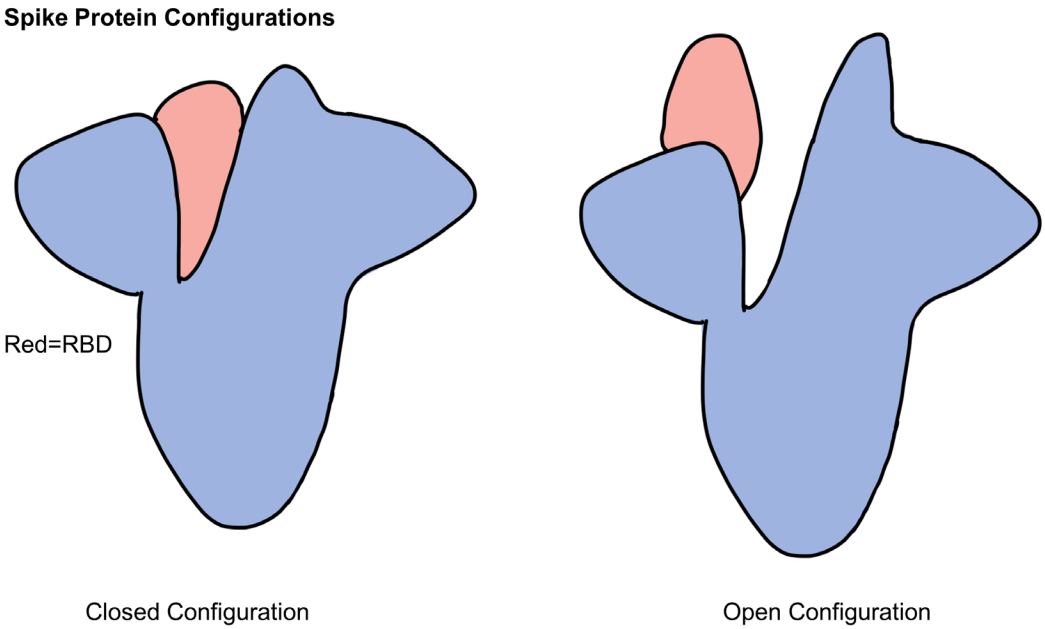

Figure 3. Open and closed configurations of SARS-CoV-2 spike protein. Spike must be in the open configuration to bind to human ACE-2 receptors and infect cells.

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Juliette Blais-Savoie is the corresponding author (juliette.blaissavoie@mail.utoronto.ca) and a student at the University of Toronto in Toronto, Ontario.

COMPETING INTERESTS

No competing interests declared.

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