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FOCUS ON

(ARCHIVED) Conditions for the Emergence of New SARS-CoV-2 Variants

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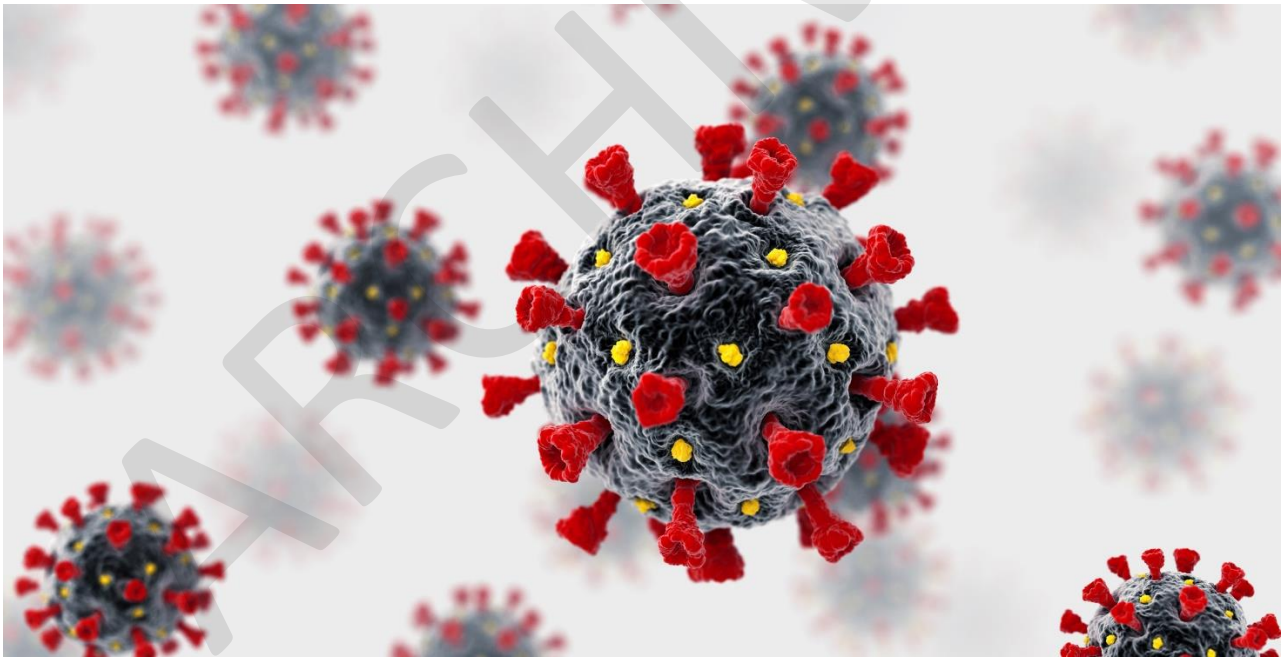


Key Findings

- Ongoing transmission is the main driver of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) evolution. High rates of transmission pose a risk for the emergence of new variants of concern (VOCs) due to natural selection.
- Interrelated factors such as emergence from zoonotic sources and interspecies transmission, as well as chronic infection in immunocompromised patients, can further contribute to the risk of new variants.

- Rapid and comprehensive vaccination in combination with public health measures and surveillance, is a prudent proactive approach to reduce the emergence and spread of new SARS-CoV-2 variants.

- Variant emergence in regions with low vaccination rates affects both low- and highly-vaccinated regions, reinforcing the importance of global vaccine equity as an approach to reducing the ongoing risk for the emergence of new variants of concern.

Introduction

- The emergence of SARS-CoV-2 variants generally occurs as a result of mutations during viral replication, and less frequently through genetic recombination (recombination when different viral strains infect the same host) and host-mediated ribonucleic acid (RNA) editing. Like other RNA viruses, coronaviruses including SARS-CoV-2 are prone to frequent mutations, although to a lesser extent than influenza, due to the presence of an exonuclease proofreading domain.[1] Over time, some genetic changes are naturally selected for and can lead to alterations in the transmissibility, virulence, immune evasion, and vaccine effectiveness.

- Mutations can increase, decrease, or have no effect on viral infectivity. Variants that have evolved to be more transmissible, cause more severe disease, and/or are associated with a decrease in the effectiveness of public health measures are called "variants of concern (VOCs)". Whereas variants that have mutations with a lack of established increase in transmissibility or virulence are termed "variants of interest (VOIs)", which can potentially progress to VOCs if transmissibility/virulence data are obtained.[2] Several VOCs have emerged from the ancestral lineage of SARS-CoV-2, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2 and AY sub-lineages), and most recently Omicron (B.1.1.529 and BA sub-lineages) and its sub-variant BA.2.

- Currently, SARS-CoV-2 VOCs and VOIs share several mutations that have enabled later variants to spread in highly vaccinated populations while maintaining or increasing fitness, that is, the capacity of a virus to replicate in a given environment.[3] The concept of natural selection suggests that mutations that favour improved fitness including increased replication and/or transmissibility will be favoured.[4]

- The majority of SARS-CoV-2 mutations occur in the spike gene, which corresponds to the spike (S) protein that is located on the surface of the viral envelope.[5,6] The S protein plays a key role in host receptor (angiotensin-converting enzyme 2 [ACE2]) recognition and viral entry into the cell.[7] In addition, the S protein is a critical target for neutralizing antibodies and current vaccines that have been developed rely on the S protein as an immunogen, or a substance eliciting an immune response, either alone or together with other SARS-CoV-2 proteins.[7]

- High rates of ongoing transmission in the context of Omicron have led to concerns for the development of new or emerging variants which can impact vaccine effectiveness and further alter SARS-CoV-2 transmissibility and severity.

- The objective of this document is to summarize evidence on the conditions and risk factors for the emergence of new variants of SARS-CoV-2.

Methods

Searches were conducted in Ovid Medline, Google Scholar as well as a pre-print search on the National Institutes of Health (NIH) COVID-19 Portfolio. The following search concepts were included: SARS-CoV-2/COVID-19 and emerging variants.

Findings

At the population level, risk factors for emergence of new variants are not entirely known. Based on early findings evaluating SARS-CoV-2 and what is known about other RNA viruses, a number of factors may contribute to the emergence of SARS-CoV-2 variants. Generally, RNA viruses are prone to random mutations because of the lack of exonuclease proofreading activity of the virus encoded RNA polymerases. Mutations arise naturally as a by-product of viral replication. The mutation rate in the SARS-CoV-2 genome has been estimated at 1.87×10^{-6} nucleotide substitutions per site per day, roughly 5-fold lower than influenza A/H3N2 but higher than many other single stranded RNA viruses. Therefore, across the ~30,000 base-pair genome of SARS-CoV-2, approximately 20 genetic changes occur per year within a lineage.[1,8] With each additional mutation, there is an increased risk for emergence of a new variant. Rapid global spread and transmission of SARS-CoV-2, resulting in viral infection and replication, provide the virus with substantial opportunities for the natural selection of such rare but favourable mutations. Natural selection favours the emergence of VOCs that evade the immune response from infection and vaccination, particularly in the setting of incomplete population immunity.[9]

Factors Increasing the Occurrence of Favourable Mutations

Several factors may increase the occurrence of favourable mutations in the population[10,11] These factors are listed and described below.

NUMBER OF PERSONS INFECTED

The more the virus spreads, the more opportunities it has to mutate. Although the majority of mutations that occur in SARS-CoV-2 are deleterious to the virus and swiftly removed from the population or relatively neutral, a small proportion will affect functional properties that may alter infectivity, disease severity or interactions with host immunity.

SUPER-SPREADERS

Some individuals may transmit SARS-CoV-2 at a disproportionately high rate compared with others, termed super-spreaders. Super-spreading scenarios could play an important role in favouring certain SARS-CoV-2 variants, increasing their predominance in a population.[12]

IMMUNOCOMPROMISED HOSTS

Mutations arise as viruses replicate within an individual, and as a new variant arises during infection, favourable mutations will be naturally selected for. For SARS-CoV-2, these evolutionary processes have been best documented in immunocompromised patients.[13] These patients can maintain high viral loads over prolonged periods of time, allowing more opportunities for viral replication and selection, and leading to elevated mutation rates. Furthermore, prolonged infection can increase the duration of shedding novel variants.[14,15]

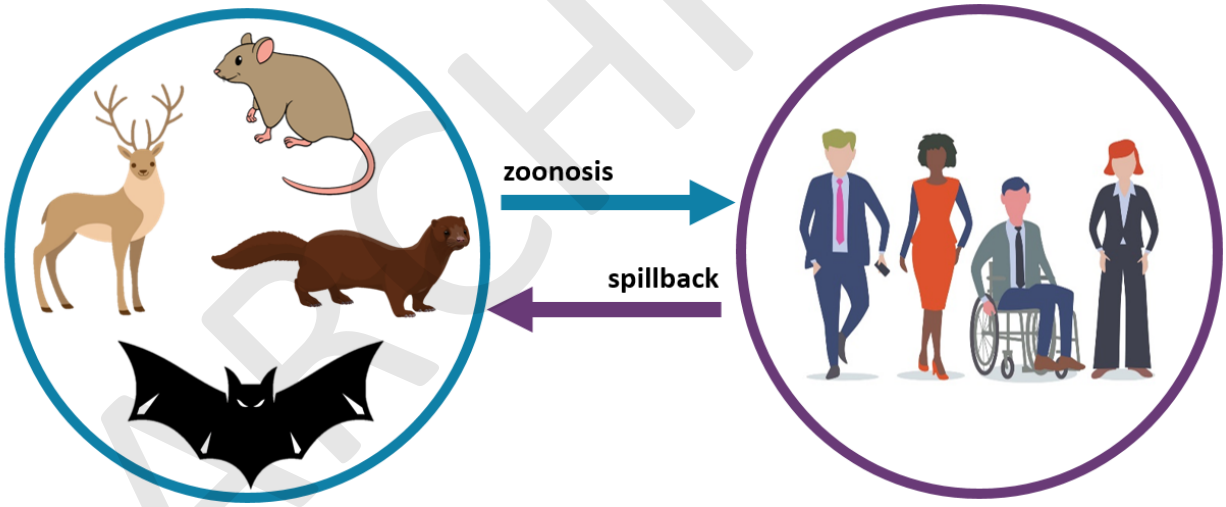
By sequencing SARS-CoV-2 at multiple time points, a number of studies have identified rapid changes to the composition of the viral population within a patient over the course of days.[16–18] These changes are faster than expected by drift in a large population, and suggest that natural selection for the virus is to

better replicate or evade a weakened immune system. As such, there are heightened public health implications for immunocompromised patients infected with SARS-CoV-2. Vaccination of immunocompromised patients and their close contacts, as well as strict adherence to self-isolation when infected should be a high priority.[13]

CROSS-SPECIES TRANSMISSION

SARS-CoV-2 may have originated from a zoonotic coronavirus, potentially from bats then transmitted to humans via an intermediate non-human mammal host.[19–21] The evolution of coronaviruses, including SARS-CoV-2, is complicated by the broad potential host range and known transmissibility to and from animals.[22–24] Coronaviruses can undergo both an enzootic cycle, where a virus is transmitted among non-human animals, and an epidemic cycle, where a virus is transmitted among humans. Since animals are reservoirs for SARS-CoV-2, selection for greater transmission within those species could lead to different disease attributes, which can accelerate evolution of the virus.[25] If a non-human animal population is infected by a human source of SARS-CoV-2 (known as spillback), followed by viral mutations within the non-human animal population and secondary transmission back to humans (known as spillover), the interspecies transmission cycle may contribute to new variants of SARS-CoV-2 (see Figure 1).[14] For example, there have been reports of animal-to-human transmission of novel variants of SARS-CoV-2 from farmed minks in the Netherlands and Denmark;[26] however, these variants were not associated with high transmissibility.[27]

Figure 1: Proposed SARS-CoV-2 enzootic and epidemic transmission cycles



SARS-CoV-2 likely emerged in bats, with transmission to a yet unknown intermediate host or directly to humans. The enzootic cycle includes transmission between and within populations of wildlife (e.g., white-tailed deer, rodents) and domestic or captive animals (e.g., mink). The epidemic cycle includes SARS-CoV-2 transmission between humans. While transmission from humans to animals (spillback) has been documented, transmission pathways from animals to humans (zoonosis or spillover) are unclear. **Key terms:** enzootic, transmission of a pathogen among non-human animals at expected levels with little die-off of infected animals; epidemic, transmission of a pathogen among humans above expected levels; zoonosis, transmission of a pathogen from non-human animals to humans (also called spillover or zoonotic spillover); spillback, transmission of a pathogen from humans to non-human animals (also called reverse zoonosis or zooanthroponosis).

More recently, molecular analyses indicate a possible mouse origin of SARS-CoV-2 Omicron variant, in which there could have been spillback from humans to mice as early as mid-2020 and transmission back to humans in late 2021, which may help to explain the relatively high number of mutations in the virus

and evolutionary differences from previous VOCs, such as Delta.[28] However, the lack of enhanced infectivity in rodent models does not support a mouse origin for Omicron at this time.[29] Several other animals have been reported to harbour and transmit SARS-CoV-2, including ferrets, cats, raccoon dogs, white-tailed deer and Syrian hamsters.[30–32]

DRUG, BIOLOGIC, AND CONVALESCENT PLASMA THERAPY

The use of certain drugs and biologic agents to treat COVID-19 in theory could apply selection pressure for new variants to arise.[33,34] For example, case series have suggested that therapy with bamlanivimab, a monoclonal antibody targeted against the spike protein of SARS-CoV-2, led to the emergence of a bamlanivimab-resistant mutation, E484K in several patients, which can lead to persistent infection, particularly in immunocompromised patients.[35,36] Similarly, cases of ongoing infection as a result of immune-escape variants emerging during convalescent plasma therapy have been reported.[33] In addition to antibody-based therapy, resistance to small molecule drugs like remdesivir has been reported.[37] However, there is a lack of clinical data on the prevalence of such mutants and if there are any differences in their risk for transmissibility and/or virulence. Given that drug therapy is not the main mechanism of control for SARS-CoV-2, it is unlikely to play a significant role in the emergence of new variants. Additionally, the short duration of infection and the reduced potential for viral replication in treated patients suggests a lower risk for emergence of resistance during therapy.[38] Notably, the emergence of new variants due to other mechanisms has rendered certain biologic agents ineffective which reduces the therapeutic options against COVID-19. For example, the antibody "cocktail" casirivimab/imdevimab lacks neutralizing activity against the Omicron variant.[39]

RECOMBINATION WITH OTHER CORONAVIRUSES

Instead of periodic point mutations over time, there is a possibility that large sections of the SARS-CoV-2 genome could recombine with another coronavirus (in a human or other mammal host) and lead to a new variant.[38] This potential for recombination may help facilitate interspecies transmission.[19] Other coronaviruses have been known to undergo recombination infrequently, and a recombination event has been hypothesized as a key factor in the origin of SARS-CoV-2.[40] Additionally, phylogenetic analyses reveal that the Alpha (B.1.1.7) VOC may have emerged from a recombination event with pre-existing strains of SARS-CoV-2.[41]

Role of Vaccination

- Due to a potential combination of immune evasion and inherent changes in viral transmission, Omicron has led to increased transmissibility and high rates of breakthrough infections in Ontario and globally. While vaccine effectiveness is significantly lower against Omicron, compared to previous lineages, three doses of a COVID-19 vaccine still provide significant protection against infection and severe disease caused by the Omicron VOC.[42,43]

- On the one hand, the evolution of SARS-CoV-2 in the context of a large, but incompletely, vaccinated population (and/or with waning immunity over time) may lead to selection of variants that escape the immune response from vaccination.[44] On the other hand, a quickly, and highly vaccinated population that is equitably and geographically dispersed is expected to reduce SARS-CoV-2 infection, transmission, and hence reduce selection pressure and slow the spread of new variants.[45]

- Although vaccination may be associated with the emergence of antibody-resistant SARS-CoV-2 mutants,[46] the rate and extent of vaccination coverage as well as public health measures such as masking, physical distancing and contact tracing can help to mitigate the spread of these mutants.[47] A modelling study from Rella et al. found that a fast rate of vaccination in the population reduces the likelihood of emergence of a vaccine-resistant strain of SARS-CoV-2. This can be further reduced in

combination with properly followed public health measures (e.g., strict adherence to masking and physical distancing) that reduce transmission particularly at the end of a vaccination campaign.[48] Variant emergence in regions with low vaccination rates will affect both low- and highly-vaccinated regions, reinforcing the importance of global vaccine equity as an approach to reducing the ongoing risk of new variants of concern.

- There was initial concern that dose-sparing strategies, such as extended vaccination intervals, could provide an environment for emergence of variants due to partial immunity. However, evidence from vaccination against SARS-CoV-2 and other viruses, such as influenza, suggest that these approaches will in fact decrease the risk for emergence of new variants due to the reduction of viral load and duration of infection provided by vaccination.[49]

- There is evidence that the diversity of SARS-CoV-2 lineages is inversely correlated with increasing rates of mass vaccination at the population level. This supports the concept that higher rates of vaccination may help to restrict SARS-CoV-2 evolution and hence stem the emergence of new variants.[50]

Role of Other Public Health Measures

- As discussed in the modelling study from Rella et al., even with high vaccination rates, non-pharmaceutical public health measures can help to reduce the emergence of vaccine-resistant strains by compensating for partial vaccine efficacy and leading to reduced SARS-CoV-2 transmissibility in the population.

- There is evidence that the level of stringency of public health interventions (e.g., lockdown measures) does not increase the risk of emergence of new SARS-CoV-2 variants, as these measures tend to decrease viral transmission regardless of the characteristics of the virus. In fact, Justo Arevalo et al. found that the introduction of public health control measures was associated with a similar reduction of both highly transmissible (specifically, the N501Y mutation) and less highly transmissible variants of SARS-CoV-2.[51]

Role of Surveillance

- Proactive screening and genomic sequencing (e.g., upon international travel) can identify emerging variants and prompt immediate public health interventions to reduce their introduction and spread in a new community.[52]

- Although humans are certainly the largest reservoir for SARS-CoV-2, there is a need for increased viral surveillance and sequencing in animals to improve early detection of new zoonotic variants at risk of spillover to humans.[28]

Conclusion

- While emergence of new variants of SARS-CoV-2 is an inevitable phenomenon, the conditions in which these variants arise and thrive are largely undetermined. However, a range of mechanisms is posited, which all relate to the concept of “natural selection”, that is, mutations that allow the virus to evade the immune response are more likely to become predominant over time. Ongoing transmission certainly increases the risk of mutation occurrence, which is further increased by chronic infections and the potential for zoonotic transmission.

- New variants continue to evolve to evade the immune response following vaccination or prior infection. However, widespread, rapid, and globally equitable vaccination in combination with other public health interventions are the best approach to mitigate the emergence and spread of new variants.

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