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Evolution of SARS-CoV-2 variants: A rapid literature scan

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Abstract

Emerging Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) variants continue to be a threat to tackling the pandemic and a challenge to scientists as they continue to find solutions to the evolving complexities of the pandemic. This rapid literature scan aims to synthesize evidence related to the existence of the new variants, their epidemiology, and data related to vaccine efficacy. Previous variants, such as Alpha, Beta, Gamma, Delta, and Omicron were identified as "Variants of Concern" (VOCs), whereas Lambda and Mu were classified as "Variants of Interest" (VOIs). The risk of hospitalization largely differs among all these variants and the research landscape is still evolving. According to the collective evidence, Gamma variant had the highest hospitalization risk (adjusted hazard ratio, aHR 3.20, 95% CI: 2.40 to 4.26) followed by Beta (aHR 2.85, 95% CI: 1.56 to 5.23), Delta (aHR 2.28, 95% CI: 1.56 to 3.34), Alpha (aHR 1.64, 95% CI: 1.29 to 2.07), and Omicron

(aHR 0.92, 95% CI: 0.56 to 1.52) as compared to the original Wuhan strain. It was also found that vaccination decreased the risk of hospitalization following infections with more virulent strains, such as Alpha, Beta, Gamma, and Delta. The risk of hospitalization was the lowest following Omicron infection among vaccinated individuals. Deltacron, a new hybrid strain (AY.4/BA.1) is believed to result from the previous co-circulation of SARS-CoV-2 Delta and Omicron during November 2021-February 2022. This hybrid virus may have been formed in the body of a person who was exposed to both viruses at the same time. Existing evidence suggested no change in epidemiology and severity of infections resulting from this hybrid strain. The COVID-19 pandemic continues to be insidious and treacherous in every form and variant. Vaccination offers a pragmatic solution to fight against the pandemic and in reducing the risk of hospitalizations. Further research and epidemiological surveillance will be needed to determine the evolving complexities of the variants and the pandemic, especially as the pandemic changes its course towards endemicity. The development of efficacious therapeutic interventions and increased vaccine uptake could reduce the morbidity and mortality associated with the SARS-CoV-2 variants.

Take-home message: The SARS-CoV-2 virus and its variants are going to appear as the part of typical evolution cycle. This review emphasizes the need for performing continuous genomic surveillance at all levels (local, national, and global) to monitor variant trajectories and outcomes.
Keywords: SARS-CoV-2; Omicron; Hybrid strain; COVID-19 pandemic; Variant of Interest; Variant of Concern; Delta; Alpha; Beta; Lambda; Mu; Genomic surveillance; Genomic Epidemiology.

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) has undergone several transformations through a series of mutations occurring in its causative agent Severe Acute Respiratory Syndrome (SARS-CoV-2) [1–3]. Over two years of the pandemic, SARS-CoV-2 has evolved into several lineages, which were the products of recombination, selective pressure, and point mutations [4]. These mutations can affect the transmission, efficacy of treatment and diagnostic procedures [4,5]. In addition, each newly emerging variant, which follows the original Wuhan strain, carries the risk of escaping immune surveillance and thus may lead to a significant or even complete reduction in the efficacy of vaccinations known to us so far. In May 2021, the World Health Organization (WHO), assigned simple labels to identify the variants based on the properties of genomic mutations, transmissibility, the severity of the disease produced, and evasion of the vaccine or treatment response: Variants of Interest (VOI), Variants of Concern (VOC), and Variants Under Monitoring (VUM) [6,7]. Previous variants, such as Alpha, Beta, Gamma, Delta, and Omicron were identified as VOCs, whereas Lambda and Mu were classified as VOIs [7]. The timeline of all SARS-CoV-2 VOCs and VOIs is summarized in Figure 1. We need to understand mutagenic profiles of the sub-variants of VOI as well as VOC groups because even small mutations after their accumulation can lead to the formation of new or hybrid variants, which may be highly transmissible.

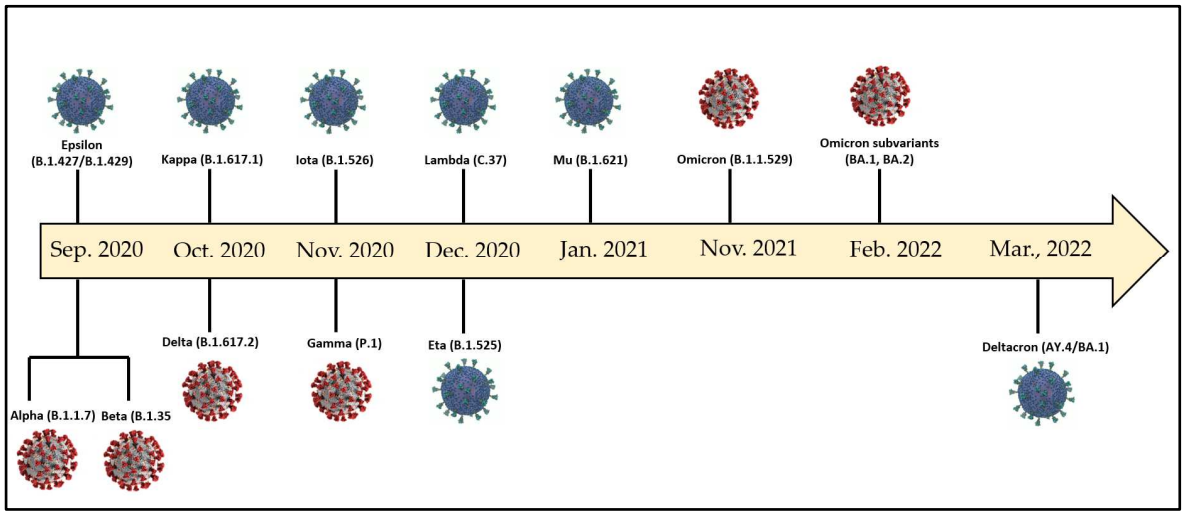

Figure 1. The timeline of emerging SARS-CoV-2 variants.
Legend: Strains with the red spikes are "variants of concern," whereas those with the blue spikes are "variants of interest"

SARS-CoV-2 variants and their mutagenic profiles

The Alpha variant (lineage B.1.1.7) was first identified among the cases occurring in the United Kingdom (UK) and had nine mutations compared with the parent virus isolated in China (Wuhan strain) [5–8]. These nine mutations were responsible for the virus's increased transmissibility, as well as heightened risk of hospitalizations and mortality. In addition to the mutations occurring in the Q493N, Q498Y, H69del, V70del, P681H, and D614G a new mutation--E484K-- was reported in December 2020 [7,9]. This mutation was detected among vulnerable patients following infection with the Alpha variant during the monotherapy treatment [9,10]. The most dominant mutation detected among the majority of the cases worldwide was D614G [9]. The Beta variant (lineage B.1.351) was first identified in South Africa and also had nine mutations in the spike protein as opposed to the original virus [8,9,11]. This variant had 19 times more affinity towards the Angiotensin Converting Enzyme (ACE2) cellular receptors due to three mutations, namely K417N, E484K, and N501Y [11,12]. This strain largely affected younger and healthier individuals, who developed the severe disease and were more likely to be hospitalized and die [13]. The Gamma variant (lineage P.1) which also arose from lineage B.1.1.28 was detected among cases in Japan and Brazil and had 12 mutations in its spike proteins [6,8]. The rate of reinfections was more with this strain largely due to the mutations (L18F, K417N/T, E484K, N501Y, and D614G), which were common with the Beta strain [14,15]. The Kappa variant (sub-lineage B.1.617.1) was reported in India, which was a predecessor of the Delta variant (sub-lineage B.1.617.2) [6]. The Delta strain was also first identified in India and had a total of 11 mutations [6]. By June 2021, the delta strain became globally dominant with its high transmissibility and was detected among fully vaccinated as well as unvaccinated individuals [16]. Further, the evolution of the virus occurred through several strains, such as Epsilon, Eta, Iota, Lambda, and Mu [6,8]. The geographical areas where these strains were first identified in given in Table 1 shown below.

Table 1. List of geographical areas where SARS-CoV-2 were identified.

Variant (lineage)	***Country where it was first identified or reported***
Alpha variant (lineage B.1.1.7)	United Kingdom
Beta variant (lineage B.1.351)	South Africa
Gamma variant (lineage P.1)	Japan and Brazil
Delta variant (sub-lineage B.1.617.2)	United States of America (USA)
Epsilon variant (B.1.427 & B.1.429)	USA

Eta variant (B.1.525)	This variant was detected worldwide but African countries have the high prevalence
Iota variant (B.1.526)	United States of America
Kappa variant (B.1.617.1)	India
Lambda variant (C.37 lineage)	Peru
Mu variant (B.1.621 lineage)	Columbia and Ecuador
Omicron variant (B.1.1.529)	Botswana, Africa
Deltacron (AY.4/BA.1)	France, The Netherlands, Denmark

Next, the Omicron variant (lineage B.1.1.529) was first identified in Botswana, Africa, and had over 30 mutations in the spike protein [6,8,17,18]. The Omicron parent virus has several closely related variations (aka sub-lineages) and diverged into BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 [17-20]. BA.1 is the most pervasive sub-lineage and was identified among 99% of the cases in the US [19,20]. On the contrary, BA.2 ("Stealth Omicron") was the most commonly found strain in other countries, including Denmark, Nepal, and the Philippines [19,20], and recently gained attention. Due to the genetic mutations, this strain is hard to detect during testing, which is why it was named "stealth" [21–23]. A higher proportion of BA.2 was found in wastewater samples in California [24]. According to the Centers for Disease Control and Prevention (CDC), the prevalence of BA.2 is tripling every two weeks and is expected to be the dominant strain in the near future [21–24,25].

A report by the World Health Organization (WHO) indicates that 86% of cases reported worldwide between February 16, 2022, and March 17, 2022, were caused by the BA.2 subvariant [26]. A report by the UK Health security Agency (April 2022) indicated that the BA.2 subvariant was growing 80% faster than the earlier form of omicron in England and accounted for 44% of all positive cases in London [27]. The CDC reported BA.2 as the most dominant strain of COVID-19 in the US, making up 74% of new infections as of April 16 [28–31]. The variant has been found to be more transmissible than the BA.1 but produces less severe disease. Common symptoms resemble the "common cold" and other seasonal viral infections. Signs include fever chills, fatigue, cough and body aches, shortness of breath, and sore throat [32]. These symptoms may be mild with the new variants; however, the transmissibility of these mutants is higher. For instance, the reproductive number (R0) of the original Wuhan strain was 3.3 as opposed to Omicron (subvariant BA.1) having the R0 of 9.5 [33]. A South Africa-based study indicated that the growth potential of BA.2 sub-lineage is more than BA.1 and similar patterns were found between BA.4 & BA.5 with BA.5 having more growth potential [33].

On March 11, 2022, with an unofficial name of "Deltacron," a new hybrid strain (AY.4/BA.1) was detected among recent cases across several countries in Europe, such as France, the Netherlands, and Denmark [31]. It was believed to be a combination of different pieces of parent viruses: Delta and Omicron [2,6,8]. Experts believe the hybrid virus was formed in the body of a person who was exposed to both viruses at the same time. According to a contemporaneous report, this strain may have resulted from the previous co-circulation of SARS-CoV-2 Delta and Omicron during November 2021-February 2022 [34], which might indicate recombination of the virus. Recombination is a process through which viruses undergo evolution following a series of mutations--something especially prevalent among RNA viruses [35]. Varabyou and colleagues analyzed about 88,000 SARS-CoV-2 genomes and reported 225 sequences related to the recombinant origins [36]; however, it is still elusive if these are real recombination or merely an artifact resulting from contamination or technical aspects [36].

Evidence of Co-circulation

According to results from gene sequencing performed a few days earlier, the first Omicron case in the US was reported on December 1, 2021. During the same period, the Delta variant was the predominant strain, which might point to the possible co-circulation of both Delta as well as Omicron in the US [37,38]. Bolze et al reported in their study that the emergence of this new strain

may have resulted from cases with co-infections of Delta and Omicron [34]. They also found that only two cases may have been attributed to the virus recombination [34]. Experts have emphasized that recombinant viruses are somewhat common and are more likely to happen at the time of "switch-over" from one dominant strain to another [39].

Epidemiology of so-called "Deltacron"

Early reports suggested no change in epidemiology and severity of infections resulting from this new strain [39]. Currently, this new strain is not worrisome; however, the literary landscape is still too dynamic to derive any conclusions. On further analyses of the virus morphologic characteristics, most of the "Deltacron" spike proteins come from the less severe forms of Omicron, with the rest being from the Delta variant [40]. Research is still underway to investigate the reproductive potential of this new strain, which will provide more insight into the trajectory of the pandemic in near future. Although there haven't been any reported changes in the severity of the Deltacron, studies have revealed that the virus has almost the same transmission level as the contagious virus of measles [41].

Variants vs. vaccine efficacy

Vaccine efficacy is defined as the ratio of disease risk among vaccinated individuals to the disease risk among unvaccinated individuals [42–44]. Globally, over 150 lead vaccine candidates were developed and came to the market within nine months [42–44]. Several research groups [45–53] published data related to vaccine efficacy; however, immunologic properties may differ depending upon the type of vaccine, and mutagenic, structural, and virologic properties of the infectious agents [42,43]. Table 2 describes the details of some approved vaccines and associated efficacy rates. Data indicated that additional doses of Pfizer, Moderna, or Janssen vaccines improved the activity of antibodies neutralization against Omicron variant [42–44]. The correlation between vaccination coverage rate and point mutation frequency of the full genome is inverse as demonstrated by the case of the Delta SARS-CoV-2 variants in 16 countries [54]. This suggests that full SARS-CoV-2 vaccination will be critical to prevent subsequent mutations [54]. Given the vast majority of people worldwide are still unvaccinated, the emergence of new mutations is likely. Therefore, it is necessary for developed nations to support developing countries in achieving equitable access to vaccines. Additionally, concerted efforts to promote booster vaccination rates and the introduction of social campaigns to combat anti-vaccination movements will be instrumental. Increasing vaccine literacy and vaccine confidence among hesitant individuals would be vital to curb the COVID-19 pandemic. [55–61].

SARS-CoV-2 variants and risk of hospitalization

Several studies investigated the risk of hospitalization associated with the Wuhan strain (aka the ancestral or wild-type strain) and other emergent strains [62–66]. According to the collective evidence, the Gamma variant had the highest hospitalization risk (adjusted hazard ratio, aHR 3.20, 95% CI: 2.40 to 4.26) followed by Beta (aHR 2.85, 95% CI: 1.56 to 5.23), Delta (aHR 2.28, 95% CI: 1.56 to 3.34), Alpha (aHR 1.64, 95% CI: 1.29 to 2.07), and Omicron (aHR 0.92, 95% CI: 0.56 to 1.52) [62]. It was also found that vaccination decreased the risk of hospitalization following infections with more virulent strains, such as Alpha, Beta, Gamma, and Delta [62]. The risk of hospitalization was lower in Omicron infection among vaccinated individuals [62].

Table 2. Data related to vaccine efficacy against SARS-CoV-2 strains.

Vaccine name/ Manufacturer	*Type*	*Country of origin*	*Efficacy of original virus*	*Efficacy against variants*	*Reference#*
BNT162b2, Pfizer BioNTech	mRNA	USA, Germany	96%	89.5 against Alpha strain 75% against Beta variant	45, 46

Mrna-1273, Moderna	mRNA	USA	94.5%	61% against gamma variant 88% against Iota variant 45.8% protection with single dose and 90.4% with two doses in Mu variant infections	47,48
Ad26.COV2. S, Janssen	Viral vector	USA, Netherlands	66.3%	NA*	49
AZD1222, Oxford AstraZeneca (Covishield or Vaxzevria)	Viral Vector	United Kingdom, Sweden	81.3%	10% against Beta variant 50% against Gamma variant	50
Ad5-nCov, Cansino	Viral Vector	China	65.3%	NA	51
Sputnik V, Gamaleya	Viral Vector	Russia	91.6%	NA	52
Covaxin (BBV152)	Whole-virion inactivated vaccine	India	77.8%-93.4%	NA	53

Note: NA: Data not available

SARS-CoV-2 variants and re-infection

Previous studies found that naturally acquired immunity from a previous SARS-CoV-2 infection can lower the risk of re-infection and hospitalization by 95% and 87%, respectively [64,65]. According to a CDC report, unvaccinated individuals were 2.34 times more likely to be re-infected as opposed to their fully-vaccinated counterparts [66]. Another study found that vaccinated individuals with a history of prior SARS-CoV-2 infection had sufficient antibodies to neutralize the viral strains, especially those having spike mutations [67], suggesting natural infection and vaccine-induced response have an additive effect [67] to prevent re-infections. One phylogenetic analysis indicated that antibody reserves decline with time and the probability of the re-infection increases with a median timeframe of reinfection being 16 months. As the pandemic enters the endemic phase, re-infections will be more common, which would need persistent efforts, such as booster vaccination, to combat the health impact (morbidity and mortality) of the pandemic [68].

CONCLUSIONS

COVID-19 continues to be insidious and treacherous in every form and variant. Not much information is currently available to determine how deadly the new SARS-CoV-2 variants are [69–72]. Vaccination is a pragmatic and effective solution to defeat the virus. It is our collective responsibility to ensure that our communities are protected from this virus. Given the inverse correlation between vaccine coverage and mutation frequency of the genomes, it is important to target areas with poor vaccination rates. Aiding under-developed nations that lack the necessary resources to combat pandemics and infection is crucial. Further research is needed to determine the evolving complexities of the variants and the pandemic. Such a solution can be helpful in understanding the properties of variants, particularly their ability to evade the immune response and therapeutic interventions. This underscores the need of continuous genomic surveillance at all levels (local, national, and global) to monitor variant trajectories and outcomes. Efforts to improve

public health, such as expanding public health infrastructure, and using genomic epidemiology to understand SARS-CoV-2 variants will be critical. More investments in clinical trials to test therapeutic interventions will be warranted to combat the challenge posed by the COVID-19 pandemic.

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