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Mini-Review **Open Access**

Evolution of SARS-CoV-2 variants: a mini-review

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Abstract:

SARS-CoV-2 has evolved over time with several mutations, especially on the spike protein, which has led to emergence of various variants. With the evolution of SARS-CoV-2 come new challenges in surveillance, effectiveness of preventive and treatment strategies, and outcome of the disease. Despite the lockdowns, mask mandates and other preventive measures put in place, in addition to over 10 million vaccine doses that have been administered globally as of February 2022, COVID-19 cases have risen to over 435 million and resulted in over 5.9 million deaths, largely as a result of the evolution of SARS-CoV-2 variants. To review the evolution of these variants, we searched different online database sources using keywords such as "source of SARS-CoV-2", "SARS-CoV-2 origin", "evolution of SARS-CoV-2", "SARS-CoV-2 variants", "variants of concern", "variants of interest", and "variants of high consequence". This was to enable us give a good report about the various variants of SARS-CoV-2 that have emerged so far, and the public health challenges posed by them.

Keywords: SARS-CoV-2; COVID-19; variants of concern; variants of interest; variants of high consequence

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Évolution des variantes du SARS-CoV-2: une mini-revue

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Résumé:

Le SRAS-CoV-2 a évolué au fil du temps avec plusieurs mutations, notamment sur la protéine de pointe, ce qui a conduit à l'émergence de diverses variantes. Avec l'évolution du SARS-CoV-2 viennent de nouveaux défis dans la surveillance, l'efficacité des stratégies de prévention et de traitement, et les résultats de la maladie. Malgré les confinements, les masques obligatoires et les autres mesures préventives mises en place, en plus de plus de 10 million de doses de vaccins qui ont été administrées dans le monde en février 2022, les cas de COVID-19 sont passés à plus de 435 million et ont entraîné plus de 5,9 million de décès, en grande partie à la suite de l'évolution des variantes du SRAS-CoV-2. Pour examiner l'évolution de ces variantes, nous avons effectué des recherches dans différentes sources de bases de données en ligne à l'aide de mots clés tels que «source du SARS-CoV-2», «origine du SARS-CoV-2», «évolution du SARS-CoV-2», «SARS- variantes du CoV-2», «variantes préoccupantes», «variantes d'intérêt» et «variantes à conséquence élevée». C'était pour nous permettre de faire un bon rapport sur les différentes variantes du SRAS-CoV-2 qui ont émergé jusqu'à présent, et les défis de santé publique qu'elles posent.

Mots-clés: SARS-CoV-2; COVID-19; variantes préoccupantes; variantes d'intérêt; variantes de grande conséquence

Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the current coronavirus disease-2019 (COVID-19) pandemic originated from Wuhan, China (1). The virus is a positive sense RNA virus belonging to the Coronaviridae family, subgroup B Betacoronavirus, and is new to humans (1). It was first reported in December 2019 with many of the early cases (mainly market vendors and market workers) being associated with the Huanan seafoods wholesale market (1,2). SARS-CoV-2 is transmitted between humans by respiratory droplets and is reported to have much higher infectivity than SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV) (1,3,4).

The virus infects humans by binding with its spike protein to angiotensin converting enzyme 2 (ACE-2) receptors on the inside of the nose. It has a median incubation period of four to five days and symptoms are usually seen within 2 to 14 days of exposure to the virus. COVID-19 symptoms can range from mild, moderate, severe, to critical (death), with risk of severity increasing with age and severe disease usually occurring in persons of all ages with underlying conditions such as respiratory disease, cardiac disease, and diabetes (5). There could also be associated complications in severe cases leading to hospitalization and the need for intensive care which may ultimately lead to death. The symptoms include but are not limited to cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, new loss of smell or taste (5). Some other features unique to COVID-19 include its tendency to infect endothelial cell lining, hypercoagulability, multisystem inflammatory syndrome, and long-term sequelae (1).

Despite the lockdowns, mask mandates and other preventive measures put in place, in addition to over 10 million vaccine doses administered globally, there have been over 435 million SARS-CoV-2 cases and 5.9 million deaths from COVID-19, as of February 28, 2022 (6). This has been due largely to the evolution and emergence of different variants of the virus, which has impacted the overall disease outcome, in addition to the lack of adherence to preventive measures, vaccine hesitancy, and inequity in vaccine distribution. Although some studies have reported on the sources and variants of SARS-CoV-2, we seek to bring together in this mini-review what is known about the source of the virus, different variants, and the challenges that each of these variants pose to global health.

Methodology and Results:

In conducting this mini-review, different online databases including PubMed, Google Scholar and Web of Science were searched using keywords such as "source of SARS-CoV-2", "SARS-CoV-2 origins", "evolution of SARS-CoV-2", "SARS-CoV-2 variants", "variants of concern", "variants of interest", and "variants of high consequence". A total of 12,900 articles were identified following the initial search, and after deduplication, 3595 articles were identified. Abstracts of the articles were subsequently reviewed, which reduced the number of articles to 660. Full text review of the articles reduced the number of articles relevant to the study to a total of 35 articles (Fig. 1).

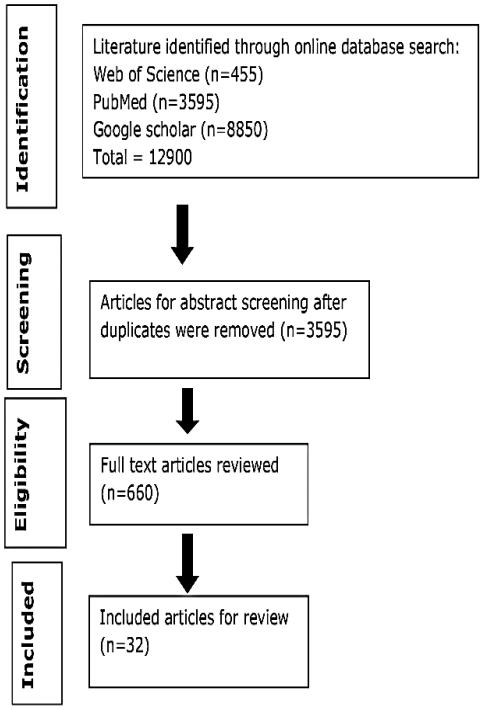

Fig 1: Process of selection of publications (PRISMA guide) used for the mini-review

Discussion:

Origin/source of SARS-CoV-2

Three years into the COVID-19 pandemic, the origin of the causative virus, SARS-CoV-2, remains elusive. SARS-CoV-2 is the seventh coronavirus to infect humans with, SARS-CoV, MERS-CoV and SARS-CoV-2 associated with severe disease while the other four coronaviruses are associated with mild diseases (3,7). SARS-CoV-2 was first reported in Wuhan, Hubei Province, China among individuals who presented with a novel pneumonia (1,2,3), al-

though findings from review of data from different countries suggest that SARS-CoV-2 could have been circulating a few weeks prior to the first reported case in Wuhan (1). Molecular sequence data also suggests that the outbreak occurred sometime in the months before mid-December 2019 (3). This suggests that the virus may have been introduced to humans through direct zoonotic spillover in which the reservoir population with high virus prevalence meets a novel host population, transmitting the virus to the host with or without transmission among the host (3).

The origin of SARS-CoV-2 can also be understood by looking back at the 2002 SARS-CoV outbreak in China which had zoonotic origins linked to live animals (civet cats), spillover events and laboratory accidents (2). A theme common to both SARS and COVID-19 is the trading of viral host animals with studies showing that the coronaviruses most highly related to SARS-CoV-2 are found in bats and pangolins making them possible reservoirs of the COVID-19 virus although neither are direct progenitors and there were no positive results with extensive animal and animal product sampling/testing in the 31 Provinces of China (1,2). Therefore, the intermediate host remains unknown.

The virus has also been found to be linked to the cold chain, persisting on packaging, frozen foods and cold-chain products supplied to China from other countries although initial tests done at the Wuhan market did not reveal any positive results from the cold chain packages (1). This could be a possible introductory route for the virus.

The final source proposed is through introduction into humans by a laboratory accident and this route has been reported as extremely unlikely because prior isolation of a progenitor virus with very high genetic similarity would be required for this to occur, which is not the case (1,3).

Distribution of SARS-CoV-2 variants

A characteristic of viruses which helps them adapt to their environment and evade detection by the immune system is their ability to mutate/change their genetic code leading to new variants of the viruses. This evolution of the virus can make them infective or virulent which may lead to persistence or elimination of the virus. As a result of this viral trait, variants will keep emerging and will require monitoring to enable appropriate actions to be taken. SARS-CoV-2 has shown this trait and evolved over time with several mutations, especially on the spike protein leading to various variants. The mutations have primarily been through purifying selection and to a lesser degree by positive pressure on specific protein coding genes (8,9). Some environmental factors such as temperature and humidity, physical irradiation and biocidal agents, climate change, and air pollution have been shown to affect infectivity, transmission, and spread of SARS-CoV-2 but the environmental impact on mutagenicity remains unclear (10). With the evolution of SARS-CoV-2, come new challenges in surveillance, effectiveness of preventive and treatment strategies, and outcome of the disease. The SARS-CoV-2 variants can be classified into several types as discussed below

Variants to be monitored

These are variants that show potential or confirmed impacts on the medical countermeasures approved for use to mitigate spread of the virus. Variants with low level circulation or that previously caused severe disease or enhanced transmission also fall into this category. Several variants of concern and variants of interest have been downgraded to this class due to sustained significant reduction in the circulating levels of these variants such that they no longer pose a threat to public health. Variants to be monitored include B 1.640 and XD. These variants are under monitoring but could be upgraded if the data, which are being constantly evaluated, suggests an increase in the circulating variant or shows increased risk to public health. This is a challenge with variants to be monitored.

Variants of interest (VOI)

This is a variant that shows specific genetic markers with changes to its ability to bind to receptors leading to certain consequences including; reduction in antibodies previously developed from natural infection or vaccines, reduced ability to neutralize the variants, reduced treatment efficacy, increase in transmission or severity of the disease or effects on diagnosis (11). Appropriate public health actions are required to mitigate the spread of VOI and these include assessment of the virus ease of spread, disease severity, increased surveillance and laboratory characterization, efficacy of prevention and treatment options.

At present, there are no variants in this category but previously considered VOIs include; (i) Epsilon B.1.427, and B.1.429, which were first detected in the USA and designated VOI in March 2021, but re-designated as previous VOI in July 2021; (ii) Zeta P.2 was first detected in

Brazil in April 2020, designated as VOI in March 2021 and redesignated as a previous VOI in July 2021; (iii) Eta B.1.525 was first detected in April 2020 in many different countries, was designated VOI in March 2021, and re-designated a previous VOI in September 2021; (iv) Theta P.3 was first detected in April 2020 in many different countries, was designated VOI in March 2021 and re-designated a previous VOI in July 2021; (v) Iota B.1.526 was first reported in the USA in November 2020, designated VOI in March 2021 and redesignated a previous VOI in September 2021; (vi) Kappa B.1.617.1 was first reported in India in October 2020, designated VOI in April 2021 and redesignated VOI in September 2021; (vii) Lambda was first reported from Peru in June 2021, assigned as VOI in June 2021, and redesignated a previous VOI in March 2022; and (viii) Mu B.1.621 was first reported in Colombia in January 2021, designated a VOI in August 2021 and redesignated a previous VOI in August 2021.

Variants of concern (VOC)

This is a variant with one or more mutations that allow the virus to infect people more easily or spread from person to person more easily, make the virus less responsive to treatments, or affect how well vaccines work against the virus (12).

(i) Omicron - B.1.1.529 and BA lineages

This lineage was first identified in South Africa in November 2021 and shown to be more infective or spreads easily (13,14), but less virulent than other variants thereby causing less severe disease in general (15-19). Omicron has at least 30 mutations in its spike protein, a marked increase from Beta which had 10 and Delta with 9 (20). Omicron is currently the dominant variant globally and the challenge with this variant is that, although it is associated with less severe disease, more people can be infected in a shorter time leading to increased hospitalization, overwhelming the health system and ultimately causing increased mortality (11,20).

Breakthrough infections have also been reported because of this variant among vaccinated individuals, but boosters are effective for preventing severe disease, hospitalization, and deaths (21,22). Infection with this variant can also be treated with monoclonal antibodies. Currently, the subvariant BA.2 is circulating rapidly in Asia and Europe, although the incidence is rising in the United States as well. It is more transmissible than the subvariant BA.1 while BA.1.1 and B.1.1.529 subvariants have higher incidence in the United States.

(ii) Delta - B.1.617.2 and AY lineages 99

This lineage was first identified in India in December 2020 and found to spread more easily than previous variants (11,23), and also causes more severe disease than other variants (11,24,25). Although the authorized vaccines are effective against this variant, breakthrough infections and transmission were seen among fully vaccinated individuals (11,24,26-28).

Previously circulating variants of concern or de-escalated variants

These variants have now been de-escalated either because they have been circulating without serious epidemiological impacts, or because the variants have ceased circulating or scientific evidence does not show any concerning properties.

(i) Alpha (B.1.1.7 and Q lineages)

This lineage was first identified in the United Kingdom with approximately 50% increase in transmissibility than the original SARS-CoV-2 (12). Following the emergence of the Delta variant however, circulation of this strain has mostly ceased.

(ii) Beta (B.1.351 and descendent lineages)

This lineage was initially identified in South Africa in September 2020 with greater transmissibility and more disease severity (29-31) than alpha variant and the original SARS-CoV-2. Beta variant is also less responsive to monoclonal antibodies and vaccines (12,32,33). From the 9th of March 2022, Beta (B.1.351) variant was removed from being a VOC and de-escalated to a variant of previous concern because of limited circulation.

(iii) Gamma (P.1 and descendent lineages)

This was first seen in Brazil in December 2020. This variant had increased transmissibility and disease severity than the original SARS-CoV-2 but less than alpha variant (31,34). It also showed reduced responses to monoclonal antibodies and vaccines as the beta variant (12, 35). The Gamma (P.1) variant was also de-escalated on the 9th of March 2022 to become a variant of previous concern.

Variants of high consequence (VOHC)

Variants with proven evidence of significant reduction in effectiveness of preventive measures or medical countermeasures when compared with previous variants in circulation are variants of high consequence (VOHC) (11, 12). The presence of these variants will require notification of international health regulatory

bodies for preventive and control measures to be updated to contain the variants and maintain the health of the global population.

The challenge with VOHC is that they have the characteristics of VOCs and additional attributes including; demonstrated failure of the diagnostic test targets, evidence to suggest a significant reduction in vaccine effectiveness, a disproportionately high number of infections in vaccinated persons, or very low vaccine-induced protection against severe disease, significantly reduced susceptibility to multiple emergency use authorized (EUA) or approved therapeutics, and more severe clinical disease and increased hospitalizations. There are no variants currently in this category.

Conclusion:

SARS-CoV-2 which caused the COVID-19 pandemic has evolved over time and keeps evolving, thereby creating new variants with varying impact on transmissibility, disease severity and immune response because of mutations usually in the spike protein, that enable the virus to adapt and escape the immune system. The rapidity with which the virus has evolved over time is an indication that more variants will emerge.

Anticipating this evolution should therefore influence genetic sequencing, epidemiological surveillance, environmental factors evaluation, vaccine improvement and uptake, as well as other preventive measures and treatment modalities required to minimize the spread of the virus and optimize the global disease outcome.

Authors contributions:

TOM conducted the literature review, wrote and edited the manuscript. BA designed the review outline, proofread and edited the manuscript. NM edited the review. All authors contributed to the article and approved the submitted version.

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Conflict of interest:

The authors declare that they have no known conflict of interests that could have influenced the work reported in this review.

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