Malaysian Journal of Microbiology, Vol 19(1) 2023, pp. 92-100
DOI: http://dx.doi.org/10.21161/mjm.211389

Malaysian Journal of Microbiology
Published by Malaysian Society for Microbiology
(In SCOPUS since 2011)

The SARS-CoV-2 variants around us: A literature review

Duran Corebima Aloysius[1]* and Bea Hana Siswati[2]

[1]Faculty of Science and Technology, Kanjuruhan PGRI University, Malang, Indonesia.
[2]Faculty of Teacher Training and Education, University of Jember, Jember, Indonesia.
Email: durancorebima@gmail.com

Received 29 December 2021; Received in revised form 4 November 2022; Accepted 11 November 2022

ABSTRACT

The SARS-CoV-2 outbreak in Wuhan (China) has become a global pandemic. Various variants of SARS-CoV-2 have been detected and the variant number of the virus continues to grow. A particular SARS-CoV-2 variant can be detected in a country that was never infected before by the virus. Furthermore, a specific SARS-CoV-2 variant, which has been detected before in a country, can be detected too in another country. The emergence of SARS-CoV-2 variants is mainly caused by mutations and recombinations. The emergence of a SARS-CoV-2 variant in a country (which was never infected before by the virus), of course, can be explained easily as it is caused by the effect of the viral spread among countries, although there may be another explanation. On the other hand, the emergence of a SARS-CoV-2 variant (which has been previously detected in a country) in another country, always has been explained only as it is caused by the effect of the viral spread between countries. However, maybe it is caused by another factor. A literature review was performed to look for the explanation related to the emergence of a certain SARS-Cov-2 variant (which is already detected before in another country) in a country. Based on the literature review results related to the RNA virus genome and its mutation as well as its recombination, it is easy to explain the cause/agent of the emergence of a SARS-CoV-2 variant (which has been previously detected elsewhere) in another country. In this case, the emergence of a SARS-CoV-2 variant (which has been previously detected elsewhere) in a country may be caused by mutations and/or recombinations in addition to the probability that it may also occur due to the spread of the virus among countries; so the emergence of SARS-CoV-2 variant that has been previously detected elsewhere in other countries does not only occur due to the spread of the virus.

Keywords: RNA virus, RNA virus mutation, RNA virus recombination, SARS-CoV-2, SARS-CoV-2 mutation, variant emergence

INTRODUCTION

Many publications about the ongoing SARS-CoV-2 pandemic have reported various information about this group of viruses related to epidemiology, taxonomy, evolution, distribution, variant emergence and so on. Regarding the new variants of SARS-CoV-2 that have been reported, it has been reported too about the country where each new variant was first discovered or emerged. Several variants of those SARS-CoV-2 afterward were also found in other countries, which were directly interpreted (explicitly or implicitly) as a result of spreading from the former country where it was discovered/emerged before. However, does the origin of a SARS-CoV-2 variant in another country (outside the country where it was discovered before) always occur only through the spreading from its former country?

This article endeavors to reveal other explanations regarding the origin of a SARS-CoV-2 variant in another country outside the country where it was first discovered, other than those that were called the product of the spreading event. The choice of words used in this article is the variant origin and not the variant emergence, which is only concerned with molecular explanations.

This article was designed on the basis of a literature review. The reviewed literature were those articles that had been published in international journals related to viruses in general, RNA viruses, as well as SARS-CoV-2 especially. In relation to mutation and recombination, this article review did not explore too far the information about the cause agents as well as the molecular events. Operationally those aspects explored in this literature review about SARS-CoV-2 were epidemiology, riboviruses, genome, variants, mutation, recombination and variant origin in a country.

Epidemiology of SARS-CoV-2

The SARS-CoV-2 epidemic, which now can be said to have spread throughout the world. The epidemic started

*Corresponding author

ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(1) 2023, pp. 92-100
DOI: http://dx.doi.org/10.21161/mjm.211389

in Wuhan (China) and then spread to various other countries (Genaro *et al.*, 2020). In fact, WHO declared it a global pandemic on March 11, 2020 (Hsu *et al*., 2020); it is further stated that the second wave of the pandemic is already underway and perhaps the third wave would follow or might even be happening.

SARS-CoV-2 is an RNA virus (Ribovirus)

SARS-CoV-2 belongs to the subfamily Orthocoronavirinae, family Coronaviridae, order Nidovirales (Mavrodiev *et al.*, 2020; V'kovski *et al.*, 2021). This group of RNA viruses is classified as belonging to the genus *β-coronavirus* (Guo *et al.*, 2020). Coronaviruses have a genome of RNA.

Like other coronaviruses, SARS-CoV-2 also has a natural origin and is a zoonotic one (Lu *et al.*, 2020). The natural reservoir of a wide variety of CoVs, including SARS-CoV-like and even MERS-CoV-like, was bats (Hampton, 2005). Zhou *et al.* (2020) stated that based on the results of genome sequencing, the similarity between the genome of SARS-CoV-2 and the genome of BatCoVRaTG 13 was 96.2%. Wu *et al.* (2020) also stated that the overall genome of SARS-CoV-2 was closer to that of the bat coronavirus when compared to other SARS-CoV viruses as well as to MERS-CoV viruses. It was also argued that most of the genomic proteins of SARS-CoV-2 were similar to those found in viruses of the SARS-CoV group, although there were specific differences. Similarly, it was said that there were some genomic and phylogenetic similarities between the Wuhan-Hu-1 Coronavirus and SARS-CoV viruses, especially those related to the S-glycoprotein gene and the receptor-binding domain or RBD, which proved the capability of direct human-to-human transmission. In this connection, Guo *et al.* (2020) also stated that bats were natural hosts of SARS-CoV-2; it was further stated that SARS-CoV-2 was transmitted from bats to an intermediate host before it infected humans. It was also argued that direct contact with intermediate host animals, or the act of consuming wild animals, was highly suspected as the main transmission route of SARS-CoV-2.

SARS-CoV-2 genome

It has been previously stated that as a coronavirus, the genome of SARS-CoV-2 is RNA. The coronavirus genome is a single-strand RNA, which is classified as positive sense (Song *et al.*, 2019). This RNA genome also acts as an mRNA in the translation process of replicase polyproteins (Maier *et al.*, 2015). Information referring to PAHO (2021) showed that to date (at least until January 2021), more than 414575 full genome sequencing results of SARS-CoV-2 have been reported; it is possible that the sequencing results number of SARS-CoV-2 whole genome in the last period has been much higher.

The size of the coronavirus genome ranges from 2732 kb (Sahin *et al*., 2020). Other sources state that the genome size is between 3032 kb (Genaro *et al.*, 2020). In this regard, the genome size of one of the reported SARS-CoV-2 (Wuhan-Hu-1 Coronavirus/WHCV) variants is 29.9 kb (Wu *et al.*, 2020); another reference also stated that the genome size of SARS-CoV-2 was about 30 kb (Andrews *et al*., 2021). The 5' end of the coronavirus genome is a 5' methylated cap and the 3' end of the genome is a 3' polyadenylated tail.

According to Song *et al.* (2019), the genome of SARS-CoV contains various numbers (611) of open reading frames (ORFs). Another reference reported that the genome of SARS-CoV-2 contains 6 ORFs (Tsai *et al*., 2020). It is further stated that two-thirds of the genome, especially those located on the first ORF (ORF 1 a/b), translates two polyproteins (pp1a and pp1b) and encodes 16 non-structural proteins (NSP). It is also said that the remaining ORFs encode accessory and structural proteins. The remaining genome parts encode four essential structural proteins, including the spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein and nucleocapsid (N) protein, as well as several accessory proteins that interfere with the innate response of the host (Cui *et al*., 2019).

According to Maier *et al*. (2015), the 5' end of the coronavirus genome contains a leader sequence and an untranslated region (UTR); UTR contains multiple stem-loop structures required for RNA replication as well as for transcription. It is further argued that the 3' end of the UTR also has the RNA structure necessary for replication.

SARS-CoV-2 variants

It can be quickly and concisely stated that the variants of coronavirus, including especially the SARS-CoV-2 variants, emerged as a result of mutation and recombination events. Many references explicitly and implicitly show that the SARS-CoV-2 variants are emerged by mutation and recombination (Pachetti *et al.*, 2020; Rambaut *et al.*, 2020; CDC, 2021; Garvin *et al.*, 2021; WHO, 2021).

Related to the mutations as the causal agent of the variant emergence of RNA viruses, including especially SARS-CoV-2, these variants can differ from each other, caused by either one or many mutations that have occurred (WHO, 2021); it is also said that a virus that has suffered from one or more new mutations is classified as a different variant of the early virus. The process of new variants emergence of SARS-CoV-2 is even claimed as a process taking place continuously because mutations constantly occur (CDC, 2021); it is stated further that new viral variants are randomly formed or disappear and sometimes after being formed, they will not disappear.

In addition to being explicitly stated as the results of mutation and recombination events, it is also argued that certain other factors or conditions can also cause the emergence of SARS-CoV-2 variants. It is argued that the SARS-CoV-2 variant could be formed as a result of selection pressure due to continuous vaccination programs (Rambaut *et al.*, 2021); however, there is no molecular explanation associated with this argumentation. There are also assumptions about other

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(1) 2023, pp. 92-100
DOI: http://dx.doi.org/10.21161/mjm.211389

Table 1: List of SARS-CoV-2 variant lineages up to July 21, 2021.

WHO nomenclature as of July 21th, 2021	Lineage	Status
Alpha	B.1.1.7	VOC
Beta	B.1.351	VOC
Gamma	P.1	VOC
Delta	B.1.617.2.AY.1 and AY.2	VOC
Zeta	P.2	VUI
Eta	B.1.525	VUI
	B.1.1.318	VUI
Theta	P.3	VUI
Kappa	B.1.617.1	VUI
	B.1.617.3	VUI
	AV.1	VUI
	C.36.3	VUI
Lambda	C.37	VUI
	B.1.621	VUI
	B.1.1.7 with E484K	Monitoring
Epsilon	B.1.427/B.1.429	Monitoring
	B.1.1.7 with S494P	Monitoring
	A.27	Monitoring
Iota	B.1.526	Monitoring
	B.1.1.7 with Q677H	Monitoring
	B.I.620	Monitoring
	B.1.214.2	Monitoring
	R.1	Monitoring
	B.1 with 214insQAS	Monitoring
	AT.1	Monitoring
	Lineage A with R346K,T478R and E484K	Monitoring
	Delta-like variant with E484A	Monitoring
	P.1 + N501T and E484Q	Monitoring
	B.1.629	Monitoring
	B.1.619	Monitoring
	C.1.2	Monitoring

Note: VOC: Variants of Concern; VUI: Variants under investigation.

factors or conditions that could lead to the emergence of SARS-CoV-2 variants; it is argued that prolonged infection in a patient may be the cause of the emergence of these new variants because there is a potential decrease in immunocompetence (Choi *et al.*, 2020; McCarthy *et al.*, 2020). The new alternative causes of the variant formation argued just now are also not supported by related molecular explanations.

The types of SARS-CoV-2 variants that have been revealed will be shown in Table 1. These variants are the ones that have been revealed until July 21st, 2021 (Public Health England, 2021). Information about the various variants is also not accompanied by information about the cause of the emergence of the variants (whether due to mutation or recombination) nor information about the location where these variants are found.

RNA virus mutation

Gene mutations are by chance as well as random events (Merlin, 2010). Furthermore, it is stated that in RNA viruses, the occurrence of mutations is a natural event and is expected in relation to its evolution (PAHO, 2021). Regarding mutations occurring within the scope of a nucleotide, every nucleotide of the genome (including the viral genome) has the opportunity to undergo mutations. In a wider scope than one nucleotide, each part of the genome (including the viral genome) has the opportunity to undergo mutations.

Although mutations are classified as by chance and random event, as well as every nucleotide or part of the genome (including the RNA virus genome) has the potential to mutate, there are certain positions or parts of the genome that are more frequently mutated. Related to RNA viruses, mutations are more common in certain parts of the genome. Until now, it has been revealed that there are hotspots of deletion mutations that occur in the NSP1 region, which have been reported in various countries (Lin *et al*., 2021). In relation to the existence of such hotspots, some reports state that some loci in the genomic region encoding the NSP6, NSP11, NSP13 and S proteins, have undergone similar mutations that are independent of each other (The Royal Society, 2020). On the basis of the information presented at The Royal Society (2020), it can be seen that the genetic diversity of SARS-CoV-2 is scattered throughout the genome of the virus; however, it is also said that the 3' region of the viral genome may be more diverse.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Referring to various related references, it is revealed that, in general, the types of mutations among RNA viruses are also classified as base pair substitution mutations (transition and transversion) and frameshift mutations (deletion and insertion). The base pair substitution mutation is also found in other groups of organisms, including those belonging to high eukaryotes.

Based on the report of Pachetti *et al.* (2020), it is clearly seen that right now, there are so many mutations that have occurred in the SARS-CoV-2 genome. However, it should be noted that regardless of the number of mutations that have been reported, the information should be interpreted as the number of mutations that have been detected and not as the number of mutations that have occurred; it is possible that the number of mutations that have occurred is actually far more than the number of the mutations that have been detected and reported.

Based on the results of the sequencing analysis, 45 cases of RT mutations, 39 transition mutations, 4 transversion mutations and two frameshift mutations were found (Garcia-Villada and Drake, 2012). This finding is in line with Sanjuan *et al.* (2010) reporting that among DNA and RNA viruses, on average, substitution mutations (transition and transversion) were four times more common than frameshift mutations (insertion and deletion).

SARS-CoV-2 mutations which are recorded in the first 2 phases of the pandemic between December 2019 and the summer of 2020 (Banoun, 2021), have occurred in 7 genome regions; the seven genome regions are Leader 5'UTR, orflab, spike, orf3a, orf8, nucleocapsid and orf10. Among these genome regions, orflab is the most frequently mutated region. In this connection, it is clear that the genome regions do not always have the same chance to undergo mutations. The mutation effects of these genome regions also vary, for example having an effect on viral replication, viral infectivity increase, etc., and some do not show any effect because the genome region experiencing the mutation is not transcribed.

The SARS-CoV-2 mutations detected in the first two phases of the pandemic (between December 2019 and summer 2020) proposed by Banoun (2021) are as already stated. However, it is also possible that other mutations that were not detected may have occurred too in the genome regions.

The information about the effects of mutations on the SARS-CoV-2 genome will be presented further, referring to various other references. The deletion mutation which occurred in the ORF8 region is thought to have an impact on viral fitness (Holland *et al.*, 2020). Furthermore, the deletion mutation in the ORF8 region involving 382 nucleotides (Young *et al.*, 2020) is thought to have an impact to attenuation of the SARS-CoV-2 phenotype and in fact, the mutation finally disappeared after March 2020. Moreover, the deletions that occur in the ORF7, ORF8 and ORF10 regions, as found in Bangladesh (Parvez *et al.*, 2021; Rahman *et al.*, 2021), have an impact on the attenuation of virulence. Other information suggests that the deletions occurring at or near the fluorine polybasic site of the spike protein are also associated with minor effects (Liu *et al.*, 2020).

Similarly, the D614G mutation that occurs outside the receptor binding domain (RBD) results in the replacement of one asparagine by one glycine at the C end of the surface spike protein (Tomaszewski *et al.*, 2020). Regarding the D614G mutation, it is said that it is not clear whether or not this mutation results in an infectivity increase; however, it is currently accepted that this mutation does not increase viral virulence (Korber *et al.*, 2020). There are still many impacts or effects of mutations in the SARS-CoV-2 genome reported by Banoun (2021), as a result of article reviews, especially those that occurred in 2020; these impacts have an effect on both the virus as well as on the human host.

Related to nucleic acid spontaneous damage, physical and chemical mutagens are the mutation cause of the virus, including the RNA viruses, especially the SARS-CoV-2 (Pachetti *et al.*, 2020). It is further stated that the mutations in the virus genome also depend on the viral enzymes themselves that catalyze nucleic acid replication (which, in this case, is also associated with little or no proofreading capability and/or nucleic acid repair capability after replication); moreover, it is also stated that the enzymes of the host cells (infected cells) also have the potential to induce mutations. Similarly, Sanjuan and Domingo-Calap (2016) also stated that mutations that occurred in viruses were not only limited to the replication occurrence of nucleic acid; these mutations could occur in relation to the editing process of nucleic acids and the spontaneous destruction of nucleic acids. Regarding the mutation causes of the SARS-CoV-2 genome associated with the nucleic acid replication events, Grubaugh *et al.* (2020) stated that mutation was a natural by-product of viral replication.

In general, it is known that the mutation rate occurring in RNA viruses (riboviruses) is higher than the mutation rate occurring in microbes having DNA genetic material (Drake *et al.*, 1998). On the other hand, there is also an opinion stating that there are not yet many studies underlying this conclusion (Domingo and Holland, 1997). In line with the view of Drake *et al.* (1998), Peck *et al.* (2018) and Lauring and Hodcroft (2018) also stated that the mutation rate of the virus was even higher than the mutation rate of most organisms having DNA genetic material.

The mutation rate of the RNA viruses (ribovirus) is said to have a correlation with genome size. This is a negative correlation (except for retroviruses), according to Bradwell *et al.* (2013). In this case, it can be interpreted that the smaller the genome sizes of the RNA viruses are, the higher the mutation rate will be. Regarding the mutation rate, there is an opinion stating that the mutation rate of RNA viruses is the highest one in nature (Domingo, 2006; Holmes, 2009). On the other hand, Sanjuan *et al.* (2010) also reported that the rate of substitution mutations of RNA viruses varied from 10^{-6} to 10^{-14} per nucleotide per cell infection (s/n/c).

Regarding the mutation rate of the RNA virus, it has been stated that the mutation rate is even up to one

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(1) 2023, pp. 92-100
DOI: http://dx.doi.org/10.21161/mjm.211389

million times higher than the mutation rate of the host (Duffy, 2018); it is also said that this high mutation rate is related to virulence as well as the benefit for adaptation. In relation to the SARS-CoV-2 mutation rate, another reference also reported that the mutation rate of the virus was lower than that of SARS-CoV (Jia *et al*., 2020).

Whatever information or reports are obtained about mutations in RNA viruses, including coronaviruses, cover the SARS-CoV-2; the occurrence of these mutations is a major cause agent of genomic diversity, including the variety of related phenotypic characters. In this connection, Sanjuan *et al.* (2010) stated that the mutation rate was the primary source of genetic variation, even though genetic variation depended on many factors.

RNA virus recombination

To date, there have been many kinds of literature reporting on the occurrence of recombination in RNA viruses (Lai, 1992; Simon and Bujarski, 1994; Ball, 1997; Straus and Straus, 1997). Regarding recombination in viruses, it is said that this event can only occur if at least two viral genomes are in the same host cell as a result of coinfection, which is followed by an exchange of genome segments (Peres-Losada *et al.*, 2015; Ignatieva *et al.*, 2022). Ignatieva *et al.* (2022) stated further that the recombination event occurs before the formation of new viral particles in the infected cells, which will then be released as new viral descendants.

RNA virus recombination is also a random event and this phenomenon has been revealed through experimental studies (Bobay *et al.*, 2020). It is further stated that, in reality, most of the recombination events among coronaviruses take place in the genomic region that functions to control the interaction between the virus and the host cell.

Recombination is increasingly believed to be a major driving factor of evolution among viruses (Stedman, 2018). In this connection, it is stated that in addition to mutation, recombination is also the main cause agent of genetic diversity (Peres-Losada *et al.*, 2015). Generally, it is known among viruses that recombination events can indeed give rise to new genotypes, which will have an impact on the emergence of viral phenotypic characters (VanInsberghe *et al.*, 2020).

On the other hand, recombination event in SARS-CoV-2 occurring between strains is found to be quite limited (VanInsberghe *et al.*, 2020); in fact, some references state that there has not been any evidence indicating recombination events along the SARS-CoV-2 genome (Bobay *et al.*, 2020). Furthermore, some reports show that in some SARS-CoV-2, 0.22.5 percent of the virus is found to be recombinant (VanInsberghe *et al.*, 2020). Regarding the number of recombination events in the SARS-Cov-2 genome, Ignatieva *et al.* (2022) also reported that although many previous reports tend to state that the number of recombination in the genome is small, very little or none, with the support of robust methods, multiple recombination events have been found (even though the sample used was relatively small). Therefore, it is easy to understand the opinion stating that recombination is very likely to be the source or explanation of the ability of the SARS-CoV-2 variants to spread rapidly (Garvin *et al.*, 2021), which is basically in line with the opinion of Stedman (2018) and Peres-Losada *et al.* (2015) which have been previously described. In relation to the number of recombination events in the SARS-CoV-2 genome, it is essential to realize that any reported events should be understood as the number of events detected, not as the number of events that have actually occurred.

The origin of the SARS-CoV-2 variant in a country

In the previous explanation, it has been said that the causal agent of the emergence of SARS-CoV-2 variants is the mutation events as well as the recombination events that occurred along the RNA genome, although it is possible too that other cause agents are still needed to be confirmed. In this connection, based on various supporting references, it is very clear that the mutation rate among SARS-CoV-2 is very high and recombination also occurs commonly. Regarding mutations, other references also state that 4000 mutations of SARS-CoV-2 have been found in the genomic region that translates spike proteins (Hossain *et al.*, 2021); although it is also stated that most of these mutations do not have any effect on the virus itself either, in terms of, its ability to spread, or its ability to cause disease. Furthermore, it is also said in the previous explanation that mutations and recombination among SARS-CoV-2 are by chance as well as random events along the RNA genome.

Based on the facts related to the occurrence of mutation and recombination that have been stated, it is very reasonable to conclude that mutation and recombination occurred in a part of the SARS-CoV-2 genome can be different among different people in a region, in the different areas and even in different countries. In this connection, related to mutations, the analysis results concerning the SARS-CoV-2 genotypes found in patients in several Chinese provinces have been reported; the reports said that SARS-CoV-2 had mutated in different patients (Zhang *et al.*, 2020). Such a phenomenon as reported by Zhang *et al.* (2020), of course, can also occur in other countries (outside China); the problem is just whether or not this fact has been revealed. Consequently, if this is the case, then new SARS-CoV-2 variants can also emerge in those countries.

Based on the explanation presented before, it is very reasonable to conclude that different mutations and recombinations can occur in the same person, in one infected cell, or even in the same viral genome region because the number of the SARS-CoV-2 infecting a person (even infecting a cell), can be more than one particle. In this case, if the number of SARS-CoV-2 particles infecting one person or one cell is more than one or even many, so the RNA genomes of that virus have the same chance to undergo mutations, even recombinations;

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 19(1) 2023, pp. 92-100
DOI: http://dx.doi.org/10.21161/mjm.211389

and the problem is only related to whether or not this fact has been revealed. Therefore, if it is the case, a diversity of SARS-CoV-2 would be found in one person or even in one cell; thus, new variants of the virus would also emerge. Moreover, some reports revealing the coinfection phenomena among different virus strains have been found in Europe and North America (Haddad *et al.*, 2021). In this connection, it has also been known that the genome of RNA viruses (including SARS-CoV-2) is sensitive to undergo mutations during each replication cycle (Grubaugh *et al.*, 2020); it is further stated that the replication cycles can even go on for hours so that various generations of viral descendants will emerge in only one infected host.

Since mutation and recombination are by chance and random events, so related to SARS-CoV-2, the same mutation or recombination may occur in different people (in one country or in various countries); similarly, the same mutation or recombination can also occur in the same person, or even in one infected cell. From a more operational point of view, the same mutation and recombination can occur in the same part of the SARS-CoV-2 genome (of different people, of one person, even of the same infected cell). As it is previously stated, the issue is only related to whether or not it has been revealed. Therefore, the same mutation and recombination can occur in these people (in one country or in various countries); and if such an event occurs, the same virus variant will emerge in one person or in one infected cell.

Thus, a SARS-CoV-2 variant can be detected in various countries where it emerged due to mutation or recombination; if so, the emergence of the same SARS-CoV-2 variant in those different countries is the result of mutation or recombination and not always the result of some other events. Therefore, the emergence of a SARS-CoV-2 variant (which has already occurred before in a country) in a country (which has been infected by the virus) can be caused by mutation or recombination and can be caused by another event. It is easy to understand that when a SARS-CoV-2 variant (which has already emerged in a country) infects a country that has not been infected before by the virus, it can be easily interpreted as the result of spreading between countries, although there may be other explanations. In this connection, when a new SARS-CoV-2 variant (which has not already emerged before in any country) appears in a country (which has been infected by the virus), it can be easily interpreted as the result of mutation or recombination, although there may be other explanations. Furthermore, when a new SARS-CoV-2 variant (which has not already emerged before in a country) occurs in a country (which has not been infected before by the virus), it can be caused by spreading between countries, although there may be other explanations.

So far, the emergence of a previously known variant of SARS-CoV-2 (which has previously emerged in a country) in another country (which has been infected before by the virus), has always been interpreted directly or indirectly as the result of the virus spreading between countries; there has never been any mention of information in the mass media, as well as especially in scientific journals reporting that the emergence of a variant was caused by mutation or recombination, which occurred directly in viruses that infect people in the country. These facts were always interpreted directly or indirectly only as the result of spreading between countries; moreover, if the information in the mass media and scientific journals explicitly states that it is the result of spreading. Whereas viral variant emergence can also be caused by mutation or recombination.

CONCLUSION

The conclusion related to the origin of a SARS-CoV-2 variant (which has been ever or never reported before) around us can be proposed further based on the explanation that has been presented. In this connection, the origin of a SARS-CoV-2 variant in a country maybe the product of spreading or as the product of mutation as well as recombination; and not only as the product of spreading. The conclusion details related to several probabilities will be presented further.

1. The origin of a SARS-CoV-2 variant (which has emerged or reported previously in a country) in another country (which has been infected before by the virus) may occur due to the product of mutation as well as recombination or as a product of spreading.
2. The origin of a SARS-CoV-2 variant (which has emerged or reported previously in a country) in another country (which has never been infected before by the virus) may be due to spreading, although there may be other explanations, such as the product of mutation or recombination.
3. The origin of a new SARS-CoV-2 variant (which has not already emerged or been reported before in a country) in another country (which has been infected by the virus) may be due to the product of mutation as well as recombination, although there may be other explanations.
4. The origin of a new SARS-CoV-2 variant (which has not already emerged or been reported before in a country) in another country (which has not been infected by the virus) may be due to spreading, although there may be other explanations, such as the product of mutation or recombination.

Which one is true (or actually happened) about the possible origin of a SARS-CoV-2 variant around us related to each point of the conclusion details will only be confirmed/ensured through scientific research; it should not only be confirmed through a logical explanation. As a concrete example, related to the first point of conclusion, in addition to the results of spreading, the origin of the Delta variant (which was previously known as the SARS-CoV-2 variant emerged in India) in other countries (which have been infected before by the virus) can also occur due to mutation or recombination in the genome of SARS-CoV-2 infecting people in those other countries, and not only due to the viral spreading.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

REFERENCES

Andrews, R. J., O'Leary, C. A., Tompkins, V. S., Peterson, J. M., Haniff, H. S., Williams, C. *et al.* (2021). A map of the SARS-CoV-2 RNA structurome. *NAR Genomics and Bioinformatics* **3(2), lqab043.**

Ball, L. A. (1997). Nodavirus RNA recombination. *Seminars in Virology* **8(2), 95-100.**

Banoun, H. (2021). Evolution of SARS-CoV-2: Review of mutations, role of the host immune system. *Nephron* **145, 392-403.**

Bobay, L. M., O'Donnell, A. C. and Ochman, H. (2020). Recombination events are concentrated in the spike protein region of *Betacoronaviruses*. *PLoS Genetics* **16(12), e1009272.**

Bradwell, K., Combe, M., Domingo-Calap, P. and Sanjuán, R. (2013). Correlation between mutation rate and genome size in riboviruses: Mutation rate of bacteriophage Qβ. *Genetics* **195(1), 243-251.**

CDC, Centers for Disease Control and Prevention. (2021). About variants of the virus that causes COVID 19. CDC: https://www.cdc.gov/coronavirus/ncov/transmission/variant.html

Choi, B., Choudhary, M. C., Regan, J., Sparks, J. A., Padera, R. F., Qiu, X. *et al.* (2020). Persistence and evolution of SARS-CoV-2 in an immunocompromised host. *New England Journal of Medicine* **383(23), 2291-2293.**

Cui, J., Li, F. and Shi, Z. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology* **17(3), 181-192.**

Domingo, E. (2006). Quasispecies: Concept and Implications for Virology. Springer-Verlag, Berlin Heidelberg.

Domingo, E. and Holland, J. J. (1997). RNA virus mutations and fitness for survival. *Annual Review of Microbiology* **51, 151-178.**

Drake, J. W., Charlesworth, B., Charlesworth, D. and Crow, J. F. (1998). Rates of spontaneous mutation. *Genetics* **148, 1667-1686.**

Duffy, S. (2018). Why are RNA virus mutation rates so damn high? *PLoS Biology* **16(8), e3000003.**

Garcia, L. and Drake, J. W. (2012). The three faces of riboviral spontaneous mutation spectrum, mode of genome replication and mutation. *PLoS Genetics* **8(7), e1002832.**

Garvin, M. R., Prates, E. T., Romero, J., Cliff, A., Gazolla, M., Pickholz, M. *et al.* (2021). The emergence of highly fit SARS-CoV-2 variants accelerated by epistasis and caused by recombination. *bioRxiv*, **doi: https://doi.org/10.1101/2021.08.03.454981**

Genaro, F. D., Pizzol, D., Marotta, C., Antunes, M., Racalbuto, V., Veronese, N. *et al.* (2020). Coronavirus diseases (COVID 19) current status and future perspectives: A narrative review. *International Journal of Environmental Research and Public Health* **17(8), 2690.**

Grubaugh, N. D., Petrone, M. E. and Holmes, E, C. (2020). We shouldn't worry when a virus mutates during disease outbreaks. *Nature Microbiology* **5(4), 529-530.**

Guo, Y., Cao, Q., Hong, Z., Tan, Y., Chen, S., Jin, H. *et al.* (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID 19) outbreak - An update on the status. *Military Medical Research* **7, 11.**

Haddad, D., John, S. E., Mohammad, A., Hammad, M. M., Hebbar, P., Channath, A. *et al.* (2021). SARS-CoV-2: Possible recombination and emergence of potentially more virulent strains. *PLoS ONE* **16(5), e0251368.**

Hampton, T. (2005). Bats may be SARS reservoir. *JAMA* **294(18), 2291.**

Holland, L. A., Kaelin, E. A., Maqsood, R., Estifanos, B., Wu, L. I., Varsani, A. *et al.* (2020). An 81-nucleotide deletion in SARS-CoV-2 ORF7a Identified from sentinel surveillance in Arizona (January to March 2020). *Journal of Virology* **94(14), e00711-20.**

Holmes, E. C. (2009). The Evolution and Emergence of RNA Viruses. Oxford University Press, London.

Holmes, E. C. (2009). The evolutionary genetics of emerging viruses. *Annual Review of Ecology Evolution and Systematics* **40, 353-372.**

Hossain, M. K., Hassanzadeganroudsari, M. and Apostolopoulos, V. (2021). The emergence of new strains of SARS-CoV-2. What does it mean for COVID-19 vaccines? *Expert Review of Vaccines* **20(6), 635-638.**

Hsu, L. Y., Chia, P. Y. and Lim, J. F. (2020). The novel coronavirus (SARS-CoV-2) epidemic. *Annals of the Academy of Medicine, Singapore* **49, 105-107.**

Ignatieva, A., Hein, J. and Jenkins, P. A. (2022). Ongoing recombination in SARS-CoV-2 revealed through genealogical reconstruction. *Molecular Biology and Evolution* **39(2), msac028.**

Jia, Y., Shen, G., Zhang, Y., Huang, K. S., Ho, H. Y., Hor, W. S. *et al.* (2020). Analysis of the mutation dynamics of SARS-CoV-2 reveals the spread history and emergence of RBD mutant with lower ACE2 binding affinity. *bioRxiv*, **doi: https://doi.org/10.1101/2020.04.09.034942**

Korber, B., Fisher, W. M., Gnanakaran, S., Yoon, H., Theiler, J., Abfalterer, W. *et al.* (2020). Tracking changes in SARS-CoV-2 spike: Evidence that D614G increases infectivity of the COVID-19 virus. *Cell* **182(4), 812-827.**

Lai, M. M. (1992). RNA recombination in animal and plant viruses. *Microbiology Reviews* **56, 61-79.**

Lauring, A. S. and Hodcroft, E. B. (2021). Genetic variants of SARS-CoV-2 – What do they mean? *JAMA* **325(6), 529-531.**

Lin, J., Tang, C., Wei, H., Du, B., Chen, C., Wang, M. *et al.* (2021). Genomic monitoring of SARS-CoV-2 uncovers on Nsp1 deletion variant that modulates type 1 interferon response. *Cell Host and Microbe* **29, 489-502.**

Liu, Z., Zheng, H., Lin, H., Li, M., Yuan, R., Peng, J. *et al.* (2020). Identification of common deletions in the spike protein of severe acute respiratory syndrome coronavirus 2. *Journal of Virology* **94(17), e00790-20.**

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H. *et al.* (2020). Genomic characterization and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *The Lancet* **395, 565-574.**

Maier, H. J., Bickerton, E. and Britton, P. (2015). Coronaviruses: Methods and Protocols. Methods in Molecular Biology. Springer Science+Business Media New York.

Mavrodiev, E. V., Tursky, M. L., Mavrodiev, N. E., Ebach, M. C. and Williams, D. M. (2020). On classification and taxonomy of coronaviruses (Riboviria, Nidovirales, Coronaviridae) with special focus on severe acute respiratory syndrome-related coronavirus 2 (SARS-Cov-2). *bioRxiv*, **doi: https://doi.org/10.1101/2020.10.17.343749**

McCarthy, K. R., Rennick, L. J., Nambulli, S., Robinson-McCarthy, L. R., Bain, W. G., Haidar, G. and Duprex, W. P. (2020). Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. *bioRxiv*, **doi: https://doi.org/10.1101/2020.11.19.389916**

Merlin, F. (2010). Evolutionary chance mutation: A defense of the modern synthesis' consensus view. *Philosophy, Theory, and Practice in Biology* **2, e103.**

Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., Masciovecchio, C., Angeletti, S., Ciccozzi, M., Gallo, R. C., Zella, D. and Ippodrino, R. (2020). Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. *Journal of Translational Medicine* **18, 179.**

PAHO, Pan American Health Organization. (2021). Epidemiological update: Occurrence of variants of SARS-CoV-2 in the Americas. 26 January 2021. PAHO/WHO, Washington, D.C.

Parves, M. S. A., Rahman, M. M., Morshed, M. N., Rahman, D., Anwar, S. and Hosen, M. J. (2021). Genetic analysis of SARS-CoV-2 isolates collected from Bangladesh: Insight into the origin, mutational spectrum and possible pathomechanism. *Computational Biology and Chemistry* **90, 107413.**

Peck, K. M. and Lauring, A. S. (2018). Complexities of viral mutation rates. *Journal of Virology* **92(14), e01031-17.**

Peres-Losada, M., Arenas, M., Galan, J. C., Palero, F. and Gonzales-Candelas, F. (2015). Recombination in viruses: Mechanisms, method of study, and evolutionary consequences. *Infection, Genetics and Evolution* **30, 296-307.**

Public Health England. (2021). SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 6. Public Health England, London.

Rahman, M. M., Kader, S. B. and Rizvi, S. M. S. (2021). Molecular characterization of SARS-CoV-2 from Bangladesh: Implication in genetic diversity, possible origin of the virus, and functional significance of the mutations. *Heliyon* **7(8), e07866.**

Rambaut, A., Loman, N., Pybus, O., Berclay, W., Barret, J., Carabelli, A. *et al.* (2020). Preliminary genome characterization of an emergent SARS-CoV-2 lineage in the UK defined by an novel set of spike mutations. COVID-19 Genomics Consortium UK. https://virological.org/t/preliminary-genomic-characterization-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

Sahin, A. R., Erdogan, A., Agaoglu, P. M., Dineri, Y., Cakirci, A. Y., Senel, M. E. *et al.* (2020). 2019 Novel coronavirus (COVID-19) outbreak: A review of the current Literature. *Eurasian Journal of Medicine and Oncology* **4(1), 1-7.**

Sanjuan, R. and Domingo-Calap, P. (2016). Mechanisms of viral mutation. *Cellular and Molecular Life Sciences* **73(23), 4433-4448.**

Sanjuan, R., Nebot, M. R., Chirico, N., Mansky, L. M. and Belshaw, R. (2010). Viral mutation rates. *Journal of Virology* **84, 9733-9748.**

Simon, A. E. and Bujerski, J. J. (1994). RNA-RNA recombination and evolution in virus-infected plants. *Annual Review of Phytopathology* **32, 337-362.**

Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y. *et al.* (2019). From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses* **11(1), 59.**

Stedman, K. M. (2018). Viral recombination: Ecology, evolution, and pathogenesis. *Viruses* **10, 358.**

Strauss, J. H. and Strauss, E. G. (1997). Recombination in Alphaviruses. *Seminars in Virology* **8(2), 85-94.**

The Royal Society. (2020). The SARS-CoV-2 Genome: Variation, Implication and Application. The Royal Society, UK.

Tomaszewski, T., DeVries, R. S., Dong, M., Bhatia, G., Norsworthy, M. D., Zheng, X. *et al.* (2020). New pathways of mutational change in SARS-CoV-2 proteomes involve regions of intrinsic disorder important for virus replication and release. *Evolutionary Bioinformatics* **16, 1-18.**

Tsai, P., Wang, M., Yang, D., Liang, K., Chou, S., Chiou, S. *et al.* (2020). Genomic variance of open reading frame (ORFs) and spike protein in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Journal of Chinese Medical Association* **83(8), 725-732.**

V'kovski, P., Kratzel, A., Steiner, S., Stalder, H. and Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology* **19, 155-170.**

VanInsberghe, D., Neish, A. S., Lowen, A. C. and Koelle, K. (2020). Recombinant SARS-CoV-2 genomes are currently circulating at low levels. *bioRxiv*, **doi: https://doi.org/10.1101/2020.08.05.238386**

WHO, World Health Organization. (2021). An update on SARS-CoV-2 virus mutations and variants. WHO: https://www.who.int/publications/m/item/update-47-sars-cov-2-virus-mutations-variants

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Wu, F., Zhao, S., Yu, B., Chen, Y., Wang, W., Song, Z. *et al.* (2020). A new coronavirus associated with human respiratory disease in China. *Nature* **579, 265-269.**

Young, B. E., Fong, S., Chan, Y., Mak, T., Ang, L. W., Anderson, D. E. *et al.* (2020). Effect of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: An observational cohort study. *Lancet* **396(10251), 603-611.**

Zhang, L., Shen, F., Chen, F. and Lin, Z. (2020). Origin and evolution of the 2019 novel coronavirus. *Clinical Infectious Diseases* **71(15), 882-883.**

Zhou, P., Yang, X., Wang, X., Hu, B., Zhang, L., Zhang, W. *et al.* (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **579, 270-273.**

 ISSN (print): 1823-8262, ISSN (online): 2231-7538