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REVIEW ARTICLE

Appraisal of SARS-CoV-2 mutations and their impact on vaccination efficacy: an overview

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Abstract

With the unexpected emergence of the novel 2019 Wuhan coronavirus, the world was faced with a sudden uproar that quickly shifted into a serious life-threatening pandemic. Affecting the lives of the global population and leaving drastic damage in various sections and systems, several measures have been constantly taken to tackle down this crisis. For instance, numerous vaccines have been developed in the past two years, some of which have been granted emergency use, thus providing sufficient immunity to the vaccinated individuals. However, the appearance of newly emerged SARS-CoV-2 variants with accelerated transmission and fatality has led the world towards another pandemic. Having undergone various mutations in genomic and/or amino acid profiles, some of the emerged variants of concern (VOCs) including Alpha, Beta, Gamma, and Delta have displayed immune evasion and pathogenicity even in the vaccinated population, hence raising concerns regarding the efficacy of current vaccines against new VOCs of COVID-19. Therefore, genomic investigations of SARS-CoV-2 mutations are expected to provide valuable insight into the evolution of SARS-CoV-2, while also determining the impact of different mutations on infection severity. This study was constructed with the aim of shining light on recent advances regarding mutations in major COVID-19 VOCs, as well as vaccination efficacy against those VOCs.

Keywords COVID-19 · Mutations · Vaccination. Viral evolution · Viral variants

Introduction

Ever since late 2019, the rapid emergence of a novel coronavirus named SARS-CoV-2 or COVID-19 has resulted in a life-threatening pandemic situation. Even though originally found in Wuhan province of China, COVID-19 has managed to spread globally at a fascinating rate thus resulting in a worldwide outbreak [1]. Owing to its incredibly fast spread and significant mortality rates, the new SARS-CoV-2 has continuously endangered the lives of many and has caused millions of deaths all around the globe [2, 3].

This non-segmented, positive-sense, enveloped virus possesses single-stranded RNA possesses an ever-evolving nature that has resulted in the emergence of numerous viral variants with alterations in genomic or amino acid profiles [4]. For instance, some of the mutations that take place in the Spike glycoprotein of SARS-CoV-2 enable the virus to escape the host's immune system or increase the binding affinity of Spike's receptor-binding domain (RBD) to its host Angiotensin-converting enzyme II (ACE2) receptors, hence alter some of the viral characteristics, such as increase viral pathogenicity and subsequent infection severity [5]. Moreover, mutations in the viral genome and amino acid profiles are also a subject of major research interest, due to their evident impact on vaccination efficacies [6–9].

While global vaccination is considered to be the golden approach for controlling the pandemic, it is crucial to note

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that formulation, development, and industrial production of vaccines is a task with great difficulty [10]. With the employment of various traditional and novel platforms for vaccine development, there is now a tremendous load of information regarding this highly complex process as well as its effectiveness against SARS-CoV-2. On the other hand, the emergence of new COVID-19 variants has recently raised a lot of concerns regarding the current vaccination efficacy against new variants [11, 12]. Even though data in this respective area is now growing at an ever-increasing speed, current literature is still faced with a lack of sufficient cohesion in available data. Therefore, this review was conducted with aim of providing well-organized information regarding SARS-CoV-2 genome analysis and current vaccine platforms with a special focus on the novel Delta (B.1.617.2) variant. It is in this work's best hopes to provide deep insight on current advances in this regard, as well as further elucidate the path to conducting new experiments and overcoming this ongoing battle of humans against coronaviruses.

Discussion

An overview on SARS-CoV-2: What we currently know

Clinical presentations and diagnostic tools

Individuals infected with COVID-19 might experience various symptoms. Fever, dry coughs, and shortness of breath are by far the most common symptoms observed in 83%, 82%, and 31% of patients, respectively [13]. Additionally, about 2–10% of patients were reported to have gastrointestinal symptoms including diarrhea, vomiting, and abdominal aches [13, 14]. Patients that experience severe symptoms are often admitted to ICU and are very likely to display symptoms of anorexia, diarrhea, dyspnea, dizziness, and muscular aches in the abdominal region [13]. In these cases, pneumonia, acute respiratory distress syndrome, multiple organ failure, and other serious conditions might occur, which are the most common causes of death due to coronavirus [15, 16].

Chest CT scans of patients with pneumonia and acute respiratory distress syndrome display ground-glass opacities that grow larger with time bizarre-paving patterns, lung consolidation, existence of nodular/cord-like shadows, and interlobular septal thickening, vascular thickening, and air broncho-gram signs inside the lesion in some cases [17]. Lesions are then absorbed after two weeks of opacity growth and left extensive opacities and subpleural parenchymal bands gradually as patients are starting to recover [18]. It is also important to mention that in the blood tests of patients with severe symptoms, leukopenia and high levels of ferritin have been observed as well as increased liver functions [19]. Of note, various investigations have aimed to explore potential factors that impact the severity of COVID-19 infection. Lymphopenia, described as reduced counts of lymphocytes in the blood, has been associated with contradictory results in the context of COVID-19 infection. However, a recent systematic review has suggested that COVID-19 infection is capable of decreasing the number of lymphocytes and impairing their normal functions, as individuals with severe COVID-19 infection had dramatically reduced lymphocyte counts in comparison with non-severe cases. Therefore, lymphocyte-targeting approaches may be of promising therapeutic value for increasing lymphocyte numbers thus improving the state of severely infected patients [20]. Furthermore, it is well-established that underlying co-morbidities such as cardiovascular diseases, diabetes, and metabolic disorders often play detrimental roles in the worsening of COVID-19 infection [21]. Metabolic dysfunctions affect many people worldwide and are considered to be a baseline of inflammation in suffering individuals [22]. Cytokine upregulations, insulin resistance, and impaired endocrine/paracrine signaling are some of the important downsides of such disorders, which may predispose patients with severe forms of COVID-19 infection [23]. On the other hand, insulin resistance has been linked with increased oxidative stress which can, in turn, expose β cells to consequent inflammation and functional impairment, hence leading to possible metabolic issues in long terms after COVID-19 infection [24, 25]. Oxidative stress, resulting from overproduction of reactive oxygen species, contributes to the progressions of a broad range of disorders such as gastrointestinal disorders [26], metabolic syndrome, and even deteriorates the severity of COVID-19 infection and is associated with cytokine storm amplification and cell hypoxia [27]. Strikingly, new studies suggest that COVID-19 may subsequently lead to the occurrence of new-onset diabetes [28] and pancreatitis [29].

RT-PCR assay is the most common method for diagnosis of COVID-19, but false-negative results are also possible in some samples [30], therefore in patients with suspicious clinical symptoms, repeated sampling is highly advised [31]. Sampling procedures are recommended to be carried out from the lower respiratory tract such as saliva and endotracheal aspirates, however, aerosols are often produced during this process and strict airborne precaution measures are highly required [32]. Moreover, bronchoalveolar lavage-based diagnosis has displayed a high yield for obtaining reliable results, but it is generally prohibited in order to minimize potential exposure risks for the healthcare team [33]. Chest CT scan is another reliable technique that was recently proved to be more efficient than RT-PCR assays [34] as it is shown to have 98% sensitivity which is significantly higher than the 71% sensitivity of the RT-PCR method [35].

Primary modeling results have displayed a log-normal distribution, which has also been observed in other acute respiratory diseases caused by viruses [36]. The average incubation period is 5.1 days, and 97.5% of patients have been reported to experience symptoms within 11.5 days post the initial infection. In an analysis based on 88 patients in Wuhan, the incubation period was indicated to be 6.4 days and changing in a range of 2.1 to 11.2 days [37, 38]. Another analysis of 158 people in Wuhan indicated a mean incubation period of 5.0 days ranging from 2 to 14 days [37]. It was also stated that 101 out of 10,000 infected patients develop symptoms after 14 days of quarantine [39], while a few cases displayed symptoms 24 days after initial infection, which is considered to be the longest incubation period yet observed. Moreover, a 14-day quarantine and monitoring are highly suggested for people who have had prior contact with potentially infected people in order to reduce the risk for further spread of this virus [37]. Interestingly, a recent study indicated that the mean duration of infection with mild or moderate COVID-19 is about 24.42 ± 1.67 days in the first episode, and reduced to 15.38 ± 5.57 days for the second episode (for mild or moderate reinfection). However, the severe form of infection lasted for an average of 21.80 ± 3.79 days and 19.20 ± 2.98 days for the first and second episode of infection, respectively [40].

Taxonomy of SARS-CoV-2 and variants of concern (VOCs)

SARS-CoV-2 is a member of the *Orthocoronaviridae* subfamily of the *Coronaviridae* family, belonging to the *Nidovirales* order. The large *Coronoviridae* family consists of four Alpha, Beta, Delta, and Gamma coronaviruses genera, among which COVID-19 falls into the Betacoronavirus genera [41]. The Betacoronivirus genus is comprised of four Embecovirus, Nobevirus, Merbecovirus, Sarbecovirus sub-genera, among which SARS-CoV-2, SARS, and Bat-SL-CoV reside in the latter sub-genera [42]. Due to the ever-evolving nature of coronaviruses and continuous emergence of new variants, the taxonomic classification of these viral species has undergone several re-examinations [41], and the final adjustment of this taxonomic classification is presented by the International Committee on Taxonomy of Viruses Executive [43].

The first variant of concern (VOC), known as the B.1.1.7 variant (Alpha VOC), was reported to possess 50–80% higher transmissibility due to the occurrence of several mutations in the RBD region of the spike glycoprotein [2, 44]. Being initially found in England, the B.1.1.7 variant managed to pave its way out to spread all around Europe in a short span of time [45]. Other VOCs were then detected in different regions, some of which were associated with increased transmissibility and mortality rates. As demonstrated in Table 1, B.1.351 VOC from South Africa [49], P.1 from Brazil [51], and B.1.617.2 variant from India (known as the novel Delta coronavirus) are some of the most fatal SARS-CoV-2 variants that have resulted in recurrent pandemic waves [51, 56] due to their accelerated contagion and drastic mortality [57].

With the constant evolution of this viral species, the emergence of novel VOCs is now a well-expected issue that has rapidly raised global concerns. As a result, genomic investigation of SARS-CoV-2 variants has recently attracted a lot of attention, as it may help to improve our understanding of SARS-CoV-2 viral origins and evolution pathways, help to detect highly mutable genomic regions, display valuable information regarding the correlation between different mutations and consequent pathogenicity and transmissibility, and also assist us in deepening our insight on the efficiency of current therapeutic approaches and vaccine development platforms against newly-emerging VOCs. For example, whole-genome analysis of SARS-CoV-2 strains has previously exhibited ~88%, ~87%, ~79%, and ~ 50% genomic similarity between the primary 2019 SARS-CoV-2 and bat-SL-CoVZC45, bat-SL-CoVZXC21, SARS-CoV, MERS-CoV, all in a respective order [58, 59]. However, the highest genomic similarity of the first Covid-19 sequence was detected in the bat-CoV (RaTG13) strain which further elucidates the possible origins of this virus [60]. Other investigations have also been conducted with the aim of studying genetic diversity between SARS-CoV-2 strains collected from multiple regions, some of which have published their obtained sequences in the GISAID database (https://www.gisaid.org/). Some of these studies specify the abundance and types of mutations (synonymous- nonsynonymous- deletion- insertion) in different genomic regions of the viral isolates [61], while some others mainly discuss high-frequency mutations across the sequenced COVID-19 strains [62] as these mutations can play a major role in viral transmissibility and pathogenicity [63].

Evolution of SARS-CoV-2: A genomic and amino acid perspective

Genomic organization of SARS-CoV-2

The genome of SARS-CoV-2 has been sequenced with metagenomic sequencing techniques and a total of 9860 amino acids were reported to be encoded by an entire genome size of 29,881 bp (NCBI genome databank, NC_045512.2) [64]. As presented in Table 2, genome compartments of SARS-CoV-2 fall into four main regions of 5′-UTR (untranslated region), 3′-UTR, non-structural regions, and structural regions [65]. To our knowledge, the initial 20 kb of the SARS-CoV-2 genome is composed of 5′-UTR and two open reading

Table 1 Major mutations of SARS-CoV-2 variants of concerns

SARS-CoV-2 VOC	Other nomenclature	Origin and date of initial detection	Transmissibility	Major mutations	References
Alpha (B.1.1.7)	British/Kent; 202,012/01; 20B/501Y.V1	UK, December 14, 2020	50% ↑	(ORF1ab): T1001I, A1708D, I2230T (Structural ORFs): Q27stop, R52I, andY73C at ORF8 (N): D3L and S235F (S): N501Y, A570D, P681H, T716I, S982A, and D1118H, Y144del (Nsp6): 3675-3677del 69-70del, D614G	[46–48]
Beta (B.1.351)	South African; 20H/501Y.V2	South Africa, December 18, 2020	25% ↑	(Spike's RBD): K417N, E484K, N501Y (Spike's NTD): L18F, D80A and D215G (Spike's loop 2): A701V (S): D614G (Neutralizing antibody epitope): K417N (Nsp6): 3675-3677del	[47, 49, 50]
Gamma, P.1 (B.1.1.28.1)	–	Brazil, January 12, 2020	1.4–2.2 fold ↑	(S): L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F (ORF1ab): S1188L, K1795Q, and E5665D (ORF8): E92K and SGF 3675-3677del (N): P80K	[11, 51]
Delta (B.1.617.2)	–	India, December, 2020	97% ↑	(S): L452R, T478K, D614G, P681R, P681H, T95I, G142D, L5F, A222V, D574YH, D950N, V1264L	[50, 52]
Omicron (B.1.1.529)	–	South Africa. November 2021	↑ (percentile yet unclear)	D614G, P323L C241U, A1892T del, T492I, P132H,	[53–55]

Table 2 Main genome compositions of SARS-CoV-2 isolate from Wuhan-Hu-1, 2019

Main genome compositions	Major genomic compartments	Encoded proteins		Nucleotide length and range	Amino acid length	Relative drugs and/or antibodies	Gene ID (NCBI)	Protein ID (NCBI)	Ref
5′ -cap-leader-UTR-replicase	–	Untranslated		265 (1–265)	–	–	43,740,578	–	[65–67]
Non-structural region	ORF1a	pp1a	NSP1 (N-terminal product of the viral replicase)	540 (266–805)	180 (1–180)	–	–	YP_009725297.1	
			NSP2 (N-terminal product)	1914 (806–2719)	638 (181–818)	Rapamycin, Zotatifin	–	YP_009725298.1	
			NSP3 (Papain-like proteinase)	5835 (2720–8554)	1945 (819–2763)	–	–	YP_009725299.1	
			NSP4 (Membrane-spanning protein-containing transmembrane domain 2)	1500 (8555–10,054)	500 (2764–3263)	Selinexor	–	YP_009725300.1	
			NSP5 ($3CL^{pro}$)	918 (10055–10,972)	306 (3264–3569)	Apicidin, Valproic acid	–	YP_009725301.1	
			NSP6 (Putative transmembrane domain)	870 (10973–11,842)	290 (3570–3859)	Bafilomycin A1, E-52862, PD-144418, RS-PPCC, PB28, Loratadine, Chloroquine	–	YP_009725302.1	
			NSP7 (RNA-dependent RNA polymerase)	249 (11843–12,091)	83 (3860–3942)	Entacapone, Indomethacin, Metformin	–	YP_009725303.1	
			NSP8 (Multimeric RNA polymerase; replicase)	594 (12092–12,685)	198 (3943–4140)	–	–	YP_009725304.1	
			NSP9 (single-stranded RNA-binding viral protein)	339 (12686–13,024)	198 (4141–4253)	Selinexor, Dabrafenaib	–	YP_009725305.1	
			NSP10 (Growth-factor-like protein possessing two zinc binding motifs)	417 (13025–13,441)	139 (4254–4392)	–	–	YP_009725306.1	
			NSP11 (Similar to the initial segment of NSP12)	47 (13422–13,468)	13 (4393–4405)	–	–	–	

Table 2 (continued)

Main genome compositions	Major genomic compartments	Encoded proteins		Nucleotide length and range	Amino acid length	Relative drugs and/or antibodies	Gene ID (NCBI)	Protein ID (NCBI)	Ref
	ORF1ab	pp1ab	NSP12 (RNA-dependent RNA polymerase (RdRp))	2769 (13468–16,236)	932 (4393–5324)	Ponatinib	–	YP_009725307.1	
			NSP13 (Helicase)	1803 (16237–18,039)	932 (5325–5925)	H-89, ZINC95559591, WDB002	–	YP_009725308.1	
			NSP14 (30–50 exonuclease (ExoN), 9))	1581 (18040–19,620)	527 (5926–6452)	Merimepodib, Migalastat, Mycophenolic acid, Ribavarin, Sanglifehrin	–	YP_009725309.1	
			NSP15 (poly(U)-specific endoribonuclease (XendoU)	1037 (19621–20,658)	346 (6453–6798)	–	–	YP_009725310.1	
			NSP16 (2'-O-ribose methyltransferase)	893 (20659–21,552)	298 (6799–7096)	–	–	YP_009725311.1	
Structural region	S region	S (Spike)		3821 (21563–25,384)	1273	Regdanvimab (CT-P59), Sotrovimab, Bamlanivimab, Etesevimab, TY027, DXP-593, Arbidol	43,740,568	YP_009724390.1	
	ORF3a	ORF3a		(25393–26,220)	275	–	43,740,569	YP_009724391.1	
	ORF3d	ORF3d		26 (26221–26,244)	11	–	–	–	
	E region	E (Envelope)		228 (26245–26,472)	75	JQ1, RVX-208, ABBV-744, dBET6, MZ1, CPI-0610	43,740,570	YP_009724392.1	
	M region	M (Membrane)		669 (26523–27,191)	222	Bafilomycin A1, UCPH-101	43,740,571	YP_009724393.1	
	ORF6	ORF6		186 (27202–27,387)	61	Selinexor	43,740,572	YP_009724394.1	
	ORF7a	ORF7a		366 (27394–27,759)	121	–	43,740,573	YP_009724395.1	
	ORF7b	ORF7b		130 (27756–27,887)	43	–	43,740,574	YP_009725318.1	

Table 2 (continued)

Main genome compositions	Major genomic compartments	Encoded proteins	Nucleotide length and range	Amino acid length	Relative drugs and/or antibodies	Gene ID (NCBI)	Protein ID (NCBI)	Ref
	ORF8	ORF8	366 (27894–28,259)	121	Azacitidine, CCT 365623, Rapamycin, FK-506, Minoxidil	43,740,577	YP_009724396.1	
	N region	N (Nucleocaspid)	1260 (28274–29,533)	419	Silmitasertib, TMCB, Sapanisertib, Rapamycin	43,740,575	YP_009724397.2	
	ORF9b	ORF9b	294 (28269–28,562)	97	PB28, haloperidol, Metformin, Midostaurin, Ruxolitinib, ZINC1775962367, ZINC4326719, ZINC4511851, ZINC95559591, AC-55541, AZ8838, Daunorubicin, GB110, S-Verapamin, AZ3451	MN985325	–	
	ORF9c	ORF9c	222 (28719–28,940)	70		MN985325	–	
	ORF14	ORF14	NA	73	–	–	–	
	ORF10	ORF10	117 (29558–29,674)	38	CD5083, Pevonedistat, DBeQ, ML240	43,740,576	YP_009725255.1	
3'-UTR-poly (A) tail	–	Untranslated	229 (29675–29,903)	–	–	–	–	

frames (ORF1a and ORF1ab). ORF1a and ORF1ab are responsible for encoding 16 non-structural proteins (nsp1–16), the first eleven of which are also called polyproteins 1a (pp1a), and the rest are called pp1ab [68]. These NSPs are in charge of a wide range of viral functions. For instance, nsp1 is known to shut off the host's innate immunity and bind to the 40 S ribosomal complex of the host cell [69]. Nsp2 is considered to induce the production of type1 interferon (IFN-1) [70], while nsp3 and nsp5 are in charge of coding two vital proteases named papain-like protease (PL^{pro}) and 3–chymotrypsin-like main protease($3CL^{pro}$), in a respective order [71].

Moreover, the structural genome consists of 13–15 ORFs (ORF3a, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF14, and ORF10) as well as the S, E, M, and N regions [72, 73]. This region is mainly responsible for coding four crucial structural proteins of SARS-CoV-2, referred to as the Spike protein (S), Membrane (M), Envelope (E), and nucleocapsid (N) [74, 75]. Given the vital roles of ORFs and S, E, M, and N regions of SARS-CoV-2 and their consequent impact on viral pathogenicity, these genomic compartments are targets of significant value for vaccine development and drug design platforms [65].

The spike glycoprotein is a transmembrane protein that is capable of forming protruding homotrimers from the viral surface and is responsible for mediating virus invasion into host cells [76]. The S glycoprotein consists of S1 and S2 subunits that attribute to host cell receptor binding, and cellular and viral membrane fusion in a respective manner [77]. For the means of entering host cells, different coronaviruses use different domains of the S1 subunit named S_A and S_B domains. The S_B domain is employed by SARS-CoV-2 and other SARS-related coronaviruses to interact with angiotensin-converting enzyme and subsequently enter host cells [78]. Upon the binding of S protein and host cell receptor, virus entry into host cells is further facilitated through the activation of the S protein with the help of a host cell membrane enzyme called type 2 TM serine protease (TMPRSS2). Sequential to virus entry and the release of viral RNA into host cells, genome replication and transcription processes take place right before viral structural proteins are synthesized [4].

Due to the crucial importance of these proteins especially the S glycoprotein, various therapeutic strategies have been constructed upon targeting them. For this regard, 3CLpro inhibitor (3CLpro-1), ACE2-based peptides, and vinylsulfone protease inhibitor have been suggested and used efficiently for fighting the new coronavirus [79].

SARS-CoV-2 mutations

Main genetic mutations

The rate for mutation in viral species is a multifactorial issue in which several factors including genome type (RNA or DNA) and length play an important role [75]. Generally, DNA viruses are considered to experience fewer mutations due to their shorter genome, however, most DNA-containing viruses with larger genomic contents often benefit from the existence of a DNA repairing protein that increases their chance of possessing more favorable viral mutations. On the other hand, RNA viruses often have smaller genomic contents and thus are mostly associated with a more significant mutation rate. Another factor that is positively correlated with higher mutation rates in RNA-containing viruses is an enzyme called RNA-dependent RNA polymerase (RdRp). This enzyme, however, does not possess proofreading abilities due to the absence of a 3′ exonuclease domain and is, therefore, unable to repair non-favorable genomic mutations. In contrast, Coronaviruses possess significant proofreading activities that are not dependent on their RdRp enzymes. Moreover, RdRp of Coronaviruses consists of a 3′ exonuclease domain that results in the occurrence of fewer mutations as well as a larger genome size (about 26 kb) contrary to most other RNA-containing viruses [80].

Besides virus-dependent factors that contribute to the alterations in viral mutation rates, there are various host-dependent factors including host-encoded deaminases, apolipoprotein B mRNA editing catalytic polypeptide-like enzymes (APOBEC), and Urcacil DNA glycosylases (UNG) that play a critical role in viral mutation rates [81, 82].

COVID-19 virus has been predicted to undergo various mutations at a rate of $8.90e^{-04}$ subs/site/year which is close to the mutation rate predicted for other viruses, meaning that each genome sequence in the viral genome is subject to ~26 mutations each year [83]. The reference sequence of COVID-19 has been represented by the scrutiny of genetic diversity between different strains. Several studies have investigated various SARS-CoV-2 strains and classified them based on high-frequency mutations and informative nucleotide positions in different regions of the genome [84, 85]. In a study by Tang et al. [86], strains were categorized into S and L sections based on two nucleotides of 28,144 and 8782. Zhao et al. [85], used 17 nucleotides as a basis to separate strains into 19 groups with different geographical distributions. In contradiction to the geographical distribution of the MERS virus in which a special group exists in a specific region, the geographical distribution of SARS-CoV-2 different clades revealed that different clades exist in different regions but their abundancies differ from region to region which is due to the founder effects [87]. Synonymous mutations affect translation and transcription, and

nonsynonymous mutations affect the structure and functions of the related proteins. Therefore, more investigations are required to decode the exact influences of different mutations in different strains. The occurrence of mutations, especially nonsynonymous mutations with high frequency in coding regions such as the S protein, should be taken into consideration when developing new therapeutic strategies or vaccine designs [88, 89]. Several studies have investigated the functional effects of some types of mutations, for instance, mutation in the 28144th nucleotide of ORF8 results in the replacement of leucine amino acid with serine which effects the structural conformation of the protein [90]. Deletion of the 302nd nucleotide in ORF8 has resulted in an increase of N gene expression [91].

For this regard, major amino acid substitutions that have been previously detected in amino acid sequences of COVID-19's spike protein and confirmed by FUBAR (Fast Unconstrained Bayesian Approximation) are briefly discussed in the following section [92].

Main amino acid mutations and substitutions

Spike RBD mutations

Among the different regions of SARS-CoV-2 spike protein, RBD (receptor binding domain) and NTD (N-terminal domain) are two of the most important immunologically provoking regions [93–95]. Therefore, any mutations in these areas that enhance viral escaping from the immune system, are highly likely to reduce antibody-mediated neutralization. For instance, E484 residue of the RBD region is known to be a critical residue that can undergo amino acid substitutions with K, Q, or P and thus decrease immune system neutralization dramatically [96]. Another escape route in times of exposure with C121 and C144 mABs is the powerful E484K mutation that is capable of diminishing neutralization effects of two REGN10989 and REGN10934 mABs [88, 97, 98]. There is also other evidence that further emphasizes the importance of the E484 mutation, as all four E484A, E484D, E484G and E484 mutations of this residue exhibited great potential in reducing immune responses of all four sera in that study. However, a few mutations such as K444E, G446V, L452R, and F490S managed to escape three of the sera in that study. The same study also detected mutations at position 477 of the S glycoprotein (S477G, S477N, and S477R) that were capable of escaping mABs, and the S477G mutation was reported to be resistant to two of the four investigated sera.

A controversial mutation for which there is still not a clear result available is the N439K mutation. A recent study by Greaney et al., reported that this mutation is not associated with any remarkable reductions in polyclonal antibody-mediated neutralization in plasma [96]. However, another study indicated that this mutation is highly likely to result in the formation of a new salt bridge between RBM-ACE2 and thus promote viral binding to ACE2, and consequently disrupt neutralization by mABs and plasma, especially in a plasma with previously lower neutralization potential [99]. Such controversy in obtained results can be attributed to variations in experimental designs, detection techniques sensitivity, and different evasion routes than what was previously predicted to be only related to reducing the recognition capacities of antibodies. K444R, K444N, K444Q, V445E, and E484K are also several other immune system evasion mutations that have occurred in RBD [88, 97].

Spike NTD mutations

N3 loops (residues 140–156) and N5 loop (246–260 residues) are two of the most critical regions of Spike's NTD that are located at a conformational epitope and undergo mutations in order to increase viral immune escape rates [100]. There is strong evidence suggesting that deletion mutations play a continuous and remarkable role in altering NTD antigenic properties as well as contributing to the rapid transformation of COVID-19 [88, 94, 101]. RDR1 (Δ69–70), RDR2 (Δ141–144 and Δ146), RDR3 (Δ210), and RDR4 (Δ243–244) are four recurrently deleted regions (RDRs) of NTD, among which RDR1, RDR2, and RDR4 are situated in N2, N3, and N5 loops, while RDR3 is located in an area between N4 and N5 loops [101]. RDR2 deletions were shown to be associated with the emergence of Δ140 when incubated convalescent plasma, and causing a four-fold reduction in neutralization titer. Moreover, this Δ140 mutant variant resulted in the E484K mutation, which led to a further decrease in plasma neutralization titer [88]. This Δ140 + E484K mutant then caused a new insertion mutation throughout which 11 residues were added between Y248 and L249 compartments within the NTD N5 loop, followed by which, plasma neutralization was completely inhibited [88].

Furthermore, mutations at 15th and 136th cysteine residues of the signal peptide region within NTD, such as C136Y and S12P, are capable of altering the neutralization capacities of a few different mABs through the disruption of disulfide bond formation and removal of the antibody-targeted supersite [94]. ΔF140, N148S, K150R, K150E, K150T, K150Q, and S151P are also some of the other evasion mutations that have taken place in NTD [88, 97].

According to the GISAID database, mutations at 18th, 614th, and 222nd amino acid residues were reported to be the most common mutations compared to the original Wuhan-Hu-1 reference sequence (MN908947) [5]. Sequential to that, A222V is considered to be the second most common amino acid substitution in spike glycoprotein and has been found in the B.1.177 lineage which was originated from Spain [102]. Last but not least, the L18F amino acid

substitution that is capable of evading from various NTD-binding mABs [94], has been reported to have occurred about 21 times globally [103].

The ever-evolving nature of the new SARS-CoV-2 has been associated with the occurrence of new mutations and variants of COVID-19, of which the novel delta (B.1.617.2) variant is a recent example. The severity of pathogenicity and transmission rates of SARS-CoV-2 are in close correlation with the number and types of genomic and amino acid substitutions that occur in the virus. Such substitutions are also capable of determining the cross-protection of previous infections and/or vaccination efficacies against new viral variants [5, 8]. This issue has recently raised a lot of doubts regarding the efficacy and viral coverage of current vaccines. On the other hand, the lack of sufficient data on potential mutations that might alter viral pathogenicity and transmissibility is another issue of major concern. Recently, a new variant of concern named Omicron (B.1.1.529) was detected in South Africa which is now rapidly spreading throughout the globe. Having up to 59 mutations throughout its genome, this variant has shifted worldwide attention due to its enhanced immune system-escaping abilities, higher reinfection risks, and increased transmissibility. Omicron VOC contains 15 mutations located in the RBD including K417, E484, and N501 which are also present in Beta and Gamma VOCs and reduce vaccine-induced neutralization [104]. A recent study has revealed that Omicron possesses higher infectivity and successfully evades current vaccination regimens, however, booster doses of current mRNA vaccines have exhibited promising results thus suggesting their potential effectiveness in overcoming immune system evasion of Omicron VOC [105, 106].

Vaccination platforms: Where we stand and what to expect

COVID-19 has undoubtedly disrupted the lives of many people all around the world. Ever since the beginning of the pandemic, more than half of the earth's population has been going by extreme safety measures and limitations from social distancing in order to prevent further spread and infection of the virus. Under current circumstances, vaccines are of critical importance in order to provide safety and help global citizens to go back to their normal lives. To this day, various drug discovery and drug repurposing strategies [107, 108] and vaccine development approaches have been employed to enhance the public's immunity and reduce the global burden resulting from COVID-19 [109]. Moreover, experiences from previous efforts against other coronaviruses such as MERS and SARS have substantially helped in speeding up the process of COVID-19 vaccine development. There are currently a few FDA-approved vaccines that are being extensively used to immune people in a lot of countries. While obtaining significant results regarding the efficacies of these vaccines, there is a lot of doubt regarding their efficacy against new mutations of SARS-CoV-2, especially the Delta (B.617.2) and Omicron (B.1.1.529) variants that have recently raised the question of whether the world is moving toward another pandemic [110]. The answer to this question depends on a set of different factors and falls in close correlation with whether new genomic or amino acid mutations of SARS-CoV-2 will provide it with new escape routes from vaccine-induced immunity. Answering this question requires deeper investigations and more thorough analyses. However, a comprehensive classification of current literature in regard to vaccine development and efficacy against SARS-CoV-2 is considered to be of significant importance in order to provide scientists with an inclusive insight regarding where we now stand with current vaccines, and what we might expect in the near future.

Main vaccine development platforms

Inactivated viruses

Inactivated virus-based vaccines are quite easy to obtain and can be produced on a large scale with a rather fast speed. In regard to SARS and MERS viral species, inactivated virus-based platforms have previously shown remarkable immunization, and have also been capable of triggering both humoral and cellular immunity in animal models. However, it is not clear if this stimulation of the immune system response has the ability to induce complete immunity from the disease or not. This group of vaccines might also cause unwanted immune and inflammatory responses.

Development of Sinopharm's WBIP-CorV vaccine (Vero cells) as the first inactivated virus-based vaccine for COVID-19, was followed by the development of fifteen other vaccines based on this technology, including Qaz- COVID-in (NCT04691908), BBV152 (NCT04641481), BBIBP-CorV (NCT04560881, NCT04510207), COVIran-Barekat (IRCT20201202049567N1, IRCT20201202049567N2), and Sinovac Biotech Ltd's CoronaVac which is currently used in UAE and China [111].

Replicating and non-replicating viral vectors

Vaccines based on viral vectors have several benefits such as releasing antigens in a longer period of time, high antigenic protein expression and provoking stronger immune responses. Moreover, compared to recombinant proteins and inactivated viruses, this platform benefits from having the capability to stimulate more immunoglobulin A release, cause stronger mucosal immunity and consequently increase the strength of barriers' resistance to virus entry [11].

Despite its notable advantages, this platform is considered to be of less efficacy due to previously existing immunity against the utilized viral strain used as the vector [112], however, this limitation can often be partially compensated by priming this vaccine with a different vaccine or by adding a booster dose to the vaccination protocol [113, 114]. A vaccine based on recombinant and non-replicating adenoviral vectors, mostly known as Ad5-nCoV, has been designed by the CanSino Biological Inc. company and is undergoing phase III (NCT04526990) of its clinical trials [115–117]. In total, there are two replicating and seventeen non-replicating viral vector-based vaccines that are now being investigated in clinical stages [111].

DNA based vaccines

This category of SARS-CoV-2 vaccines mainly transfers the S gene of this virus into certain bacterial plasmids including CMVs [118]. Having the benefit of stimulating fast industrial production as well as being highly flexible toward antigenic domain manipulations and targeting both the humoral and cellular immune systems, DNA-based vaccines are considered to be promising platforms for vaccine development [119]. There are now eleven DNA-based vaccine candidates in for SARS-CoV-2, three of which are now passing phase III of their clinical examinations [111].

RNA based vaccines

Similar to DNA-based vaccines, this group of vaccines benefit from significant flexibility for antigenic domains changes [119, 120]. After less than three months from the publication of the SARS-CoV-2 sequence, Moderna Company succeeded in taking their vaccine into the clinical phases. This vaccine is an RNA-based (mRNA-1273) vaccination platform that stimulates the immune system against SARS-CoV-2 spike protein and is delivered into cells via lipid nanostructures [121]. BioNTech, Fosun Pharma, and Pfizer companies have also developed vaccines based on this technology that are currently being exploited worldwide. In total, 18 RNA-based vaccines have been designed so far that are now going through clinical trial studies.

Live attenuated viral vaccines

Being mainly produced by the use of live weakened viral strains or non-virulent species, this category of vaccines are capable of stimulating significant mucosal and cellular responses, similar to those caused by the natural invasion of the virus. Despite the employment of efficient methods in order to attenuate viruses (such as storage in low temperatures and genetic modification) [122, 123], SARS-CoV-2 vaccines built upon this technology suffer from several drawbacks, including high risks of unintentional viral transmission to the unvaccinated population through feces, existing possibility of viral species recombination in the host's body, as well as difficult formulation and quality control processes that decelerate the large-scale industrial production of vaccine [124].

This group of vaccines have the advantage of inducing significant immunization and also triggering both humoral and cellular immunity concurrently. Different viral antigens are capable of triggering the immune system thus resulting in the generation of a diverse range of antibodies and T memory cells. There are currently two vaccines with this platform (COVI-VAC (NCT04619628) and MV-014-212 (NCT04798001)) that have recently moved to clinical trial stages [111].

Protein subunit-based vaccines

Due to their desirably safe nature and efficient humoral immunity stimulation, protein subunit vaccines are the most abundant group of SARS-CoV-2 vaccines. The main mechanism of action of these vaccines mostly relies on the expression of the Spike glycoprotein or even just the Spike's RBD region [125]. The expression of the Spike protein is associated with moderate difficulty and has thus raised concerns regarding the production of vaccines with the use of this technology. However, several methods such as exclusive expression of RBD, have been proposed for minimizing this drawback [11]. There are now thirty-eight vaccine candidates that reside in this category, twelve of which are currently in Phase II/III and III of clinical trials. Novavax (NCT04611802), FINLAY-FR-2 (RPCEC00000354), EpiVacCorona (NCT04780035), and Vaxxinity (NCT04683224) are some of the examples of vaccines that have been developed with this technology Table 3 [111].

Animal models for the evaluation of SARS-CoV-2 vaccination efficacy

The utilization of animal models for testing the efficacy of vaccines is a common yet critically important subject. In the case of SARS, high specificity of this virus's S protein to human ACE2 receptors had previously made it difficult to find a proper animal model for testing vaccination efficacy in the past, but with creating transgenic mice that express human ACE2 receptor proteins this issue was mainly solved. Due to the similarity of ACE2 receptors in both SARS and COVID-19 infections, those transgenic mice are likely to be suitable for use for COVID-19 as well. Rhesus macaques have also been successfully used for testing COVID-19 vaccines by Sinovac companies in China [147, 148]. For SARS and MERS, other

Table 3 List of currently approved vaccines for use in different regions and their efficacy against major VOCs

Vaccine	Developers	Technology	Number of countries with approval	Major phase3 trials	Efficacy against main VOCs				
					2019 reference virus (Wuhan)	Alpha, B.1.1.7 (Britain/Kent)	Beta, B.1.351 (South Africa)	Gamma, P.1, B.1.1.28.1 (Japan/Brazil)	Delta, B.1.617.2 (India)
BNT162b2	Pfizer, BioNTech; Fosun Pharma	mRNA-based vaccine	98	NCT04368728 NCT005125 NCT04800133 NCT04951323	95% [126]	90% [127]	75% [127]	No reduction reported	95% [128]
mRNA-1273	Moderna, BARDA, NIAID	mRNA-based vaccine	69	NCT04805125 NCT04649151 NCT04796896 NCT04470427	94.1% [129]	2.3–6.4 fold reduced efficacy [121]	Reduced efficacy [121]	Reduced efficacy [121]	6.8 fold reduced efficacy [121]
AZD1222 (Vaxzevria, Covishield or ChAdOx1 nCoV-19)	Oxford, AstraZeneca	Non-replicating vector (Viral vector)	121	NCT04973449 NCT05007951 NCT04864561 CTRI/2020/08/027170 NCT04885764 NCT04800133	55–81% [126]	66% - 75% [9]	10% [130]	NA	60–71% (single dose) and 92% efficacy against hospitalization [128, 131]
Sputnik V	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Recombinant adenovirus vaccine (rAd26 and rAd5)	71	NCT04640233 NCT04564716 NCT04530396 NCT04642339 NCT04656613 NCT04954092	91.6% [132]	No significant changes were observed	3.1 fold reduction in antibody neutralization [133]	2.8 fold reduction in antibody neutralization [133]	83.1% reduction in hospitalization, 2.5 fold reduction in antibody neutralization [134]
Sputnik Light	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Recombinant adenovirus vaccine (rAd26)	13	NCT04741061	79.4% [Mounting evidence suggests Sputnik COVID vaccine is safe and effective]	NA	NA	NA	NA
Ad26.COV2.S	Janssen Vaccines (Johnson & Johnson)	Non-replicating viral vector	59	NCT04505722 NCT04614948, ISRCTN14722499 NCT04838795	72% [135, 136]	66%–70% [136, 137]	57% (USA), 66% (Latin America), and 57% (South Africa) [137]	66% [137]	NA
CoronaVac	Sinovac	Inactivated virus	39	NCT04942405 NCT04992260 NCT04800133 NCT04456595	50–90% [138]	NA	NA	50.38% [139, 140]	NA
NVX-CoV2373	Novovax	Protein subunit	–	CTRI/2021/02/031554 NCT04583995 NCT04611802	89.3% [141, 142]	85.6% [142]	49.4% [142, 143]	NA	NA

Table 3 (continued)

Vaccine	Developers	Technology	Number of countries with approval	Major phase3 trials	Efficacy against main VOCs				
					2019 reference virus (Wuhan)	Alpha, B.1.1.7 (Britain/Kent)	Beta, B.1.351 (South Africa)	Gamma, P.1, B.1.1.28.1 (Japan/Brazil)	Delta, B.1.617.2 (India)
BBIBP-CorV	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Inactivated virus	60	NCT04560881, BIBP2020003AR NCT04917523 NCT04984408	79% [144]	NA	NA	NA	NA
EpiVacCorona	ederal Budgetary Research Institution State Research Center of Virology and Biotechnology	Peptide vaccine	3	NCT04780035	NA	NA	NA	NA	NA
Convidicea (PakVac, Ad5-nCoV)	CanSino Biologics	Recombinant vaccine (adenovirus type 5 vector)	9	NCT04526990 NCT04540419	NA	NA	NA	NA	NA
Covaxin (BBV152)	Bharat Biotech, ICMR; Ocugen; ViroVax	Inactivated virus	9	CTRI/2020/11/028976, NCT04641481 NCT04918797	77.8% effective against symptomatic COVID-19, 93.4% effective against severe symptomatic COVID-19, and 63.6% protection against asymptomatic COVID-19 [145]	NA	NA	NA	65.2% [145]

Table 3 (continued)

Vaccine	Developers	Technology	Number of countries with approval	Major phase3 trials	Efficacy against main VOCs				
					2019 reference virus (Wuhan)	Alpha, B.1.1.7 (Britain/Kent)	Beta, B.1.351 (South Africa)	Gamma, P.1, B.1.1.28.1 (Japan/Brazil)	Delta, B.1.617.2 (India)
WIBP-CorV	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Inactivated virus	1	NCT04885764 ChiCTR2000034780 NCT04612972 NCT04510207	72.8% [146]	NA	NA	NA	NA
CoviVac	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Inactivated virus	1	–	NA	NA	NA	NA	NA
ZF2001 (ZIFIVAX)	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Recombinant vaccine	2	ChiCTR2000040153, NCT04646590	NA	NA	NA	NA	NA
QazVac (QazCovid-in)	Research Institute for Biological Safety Problems	Inactivated virus	1	NCT04691908	NA	NA	NA	NA	NA
Unnamed	Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.	Inactivated virus	1	NCT04852705	NA	NA	NA	NA	NA
COVIran Barekat	Shifa Pharmed Industrial Group	Inactivated virus	1	IRCT20201202049567N3	NA	NA	NA	NA	NA

Table 3 (continued)

Vaccine	Developers	Technology	Number of countries with approval	Major phase3 trials	Efficacy against main VOCs				
					2019 reference virus (Wuhan)	Alpha, B.1.1.7 (Britain/Kent)	Beta, B.1.351 (South Africa)	Gamma, P.1, B.1.1.28.1 (Japan/Brazil)	Delta, B.1.617.2 (India)
Unnamed	Chinese Academy of Medical Sciences, Institute of Medical Biology	Inactivated virus	1	NCT04659239	NA	NA	NA	NA	NA
Abdala (CIGB 66)	Center for Genetic Engineering and Biotechnology	Protein subunit vaccine	1	IG/CIGB-66I/ CVD19/2103	NA	NA	NA	NA	NA
Soberana 02	Finlay Institute of Vaccines; Pasteur Institute	Conjugate vaccine	2	–	NA	NA	NA	NA	NA
MVC-COV1901	Medigen Vaccine Biologics Corp.; Dynavax	Protein subunit vaccine	1	–	NA	NA	NA	NA	NA

animals such as rabbits, hamsters, ferrets, pigs, marmosets, cats, and cows have been used as animal models [149, 150].

Vaccination efficacy against the Delta variant

Recent literature has displayed that vaccine-induced immunity followed by one dose of BNT162b2 or ChAdOx1 nCoV-19 vaccines was about 48.7% and 30.7% against the Alpha and Delta variants respectively. Vaccine-induced immunity with two doses of BNT162b2 was also reported to be about 93.7% and 88.0% against the Alpha and Delta viral variants while being 74.5% and 67% for the ChAdOx1 nCoV-19 vaccine, all in a respective order [9]. Similarly, another investigation has recently reported that this new Delta variant possesses 6.8 times higher resistance to sera-induced neutralization in individuals who were vaccinated with either Moderna or Pfizer vaccines. Accordingly, neutralizing antibody titer in infected and vaccinated people followed by exposure with the Delta variant was shown to have declined dramatically, nevertheless, 79% of all samples of sera obtained from mRNA vaccinated individuals were able to neutralize the Delta viral variant [110]. While information regarding other vaccines is limited, a study constructed in Scotland investigated the vaccination efficacies of ChAdOx1 nCoV-19 (AstraZeneca) and BNT162b2 (Pfizer–BioNTech vaccine) against the B.1.617.2 SARS-CoV-2 variant. Both of these vaccines were reported to reduce infection risks and hospitalization post infection with Delta variant, however, they were less efficient compared to their immunity against the Alpha variant, which is consistent with previous results [151].

Of note, obtained viral loads in nasal swabs of vaccinated and unvaccinated individuals were reported to be similarly followed by exposure with the Delta variant. Moreover, 68% of the infected individuals who had been vaccinated beforehand were tested PCR-positive for COVID-19 infection, even though 8 of them did not suffer from symptoms of infection at the time of PCR. These findings were indicative of the importance of wearing masks despite the state of vaccination, as it appears that vaccinated individuals might also be capable of spreading the virus [152]. Lastly, due to the limited data addressing the efficacy of vaccines against the Delta variant of COVID-19, there is still a lot of doubt revolving around this matter. However, currently available data confirms the crucial necessity for vaccination, as it can still provide the public with lower yet excellent immunity against severe SARS-CoV-2 infection.

Challenges in vaccine development regulatory systems

Vaccine development with passing phases I, II, and III of clinical trials and getting approval licensures is a rather long process that normally requires 6 to 11 years [153]. Before clinical trials, regulatory agencies should check production processes and information obtained from preclinical tests for vaccine safety assurance [154].

Even though a lot of attention is directed towards global candidate vaccine efficacy, it should be noted that even if a vaccine is capable of reducing disease severity but not preventing it completely, it's still a potential candidate for decreasing mortality rates significantly [155]. Therefore, while some vaccines might lack the desired and ideal efficiency, they can still contribute greatly to viral shedding and preventing the rapid spread of the virus [11, 156]. Due to the relevantly high risk for vaccine failure with the emergence of new variants, vaccine investors often define multiple steps for the manufacturing and the process is paused after each step in order to make sure of chances of success for that part, and then further investments take place for the next steps [157]. It is clear that this method for vaccine development takes a lot of time and is likely to be inefficient for a fast pandemic or epidemic situation, as a large population will probably be infected by the time that vaccine is fully developed. It has been suggested that for speeding up this process, industrial production of vaccines with higher chances of success and efficacy (according to information from phases I and II of clinical trials) should be initiated so they will be available for the public to use soon after receiving efficacy approval [153, 158]. Even though obtaining and mass production of a vaccine isn't a limiting step, but multi-step production and obtainment of approvals from regulatory agencies turn this into a rather long and time-consuming process. The occurrence of several epidemics in the past two decades has challenged the efficiency of this time-consuming process in protecting public health. It seems that a change of routine, methods, and regulatory agencies' rules for faster scrutiny of safety measures, effectiveness and possible side effects of vaccines and subsequently developing faster approaches and methods for vaccine evaluation is necessary [159, 160].

Conclusion

With the continuous evolution of SARS-CoV-2, the emergence of novel and potentially more fatal variants is now a well-established phenomenon. Mutations within the genome and amino acid profiles of SARS-CoV-2 are affected by several factors, and while some of the observed mutations cease to exist in the next generations of SARS-CoV-2, there are several mutations that are passed on to the next mutated strains and further enhance their pathogenicity and transmissibility through different pathways and mechanisms. Aside from the increased infection severity

and faster spread, the impact of mutations on vaccination efficacy is now one of the most serious concerns regarding this matter. Being mainly constructed against certain previous VOCs, it is now unclear whether the developed vaccines are capable of providing sufficient immunity toward the newly emerging strains of SARS-CoV-2. With such doubts in mind, recent studies of vaccines have been mainly indicative of reduced but yet still desirable immunity against new VOCs, and further confirming the fact that global vaccination is still a reliable platform for overcoming this battle of humans against coronaviruses. With that in mind, this study was constructed with the aim of exploring recent advances regarding SARS-CoV-2 mutations as well as providing readers with comprehensive information about some of the latest COVID-19 vaccines and aid them in gaining insight regarding where we now stand in this crisis, and what to expect.

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Declarations

Conflict of interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

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