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Coronavirus- The Emerging Strains and An Insight into Vaccine Development

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Abstract

Back in the 1960s viruses named zoonotic coronaviruses were discovered and from this time pestilential human coronaviruses were put in name to starting with the disclosure of SARS-CoV in 2002. From December 2019, spate comes as the conglomeration cases run into respiratory illness in Wuhan, China, proceeded by the global escalation. The SARS-CoV-2 genome codes for four structural proteins the nucleocapsid (N), the spike (S), the membrane (M), and the small envelope (E). To the present date more than 8000 single mutations are already observed in the SARS-CoV-2 genome have increase the serious concerns about alterations in the infectivity. Additionally, the geo-climate disposition of the mutations unravels the higher unique mutations plus disease severity in the European temperate countries. During the late 2020 the emergent of various mutants that possess furthermore elevation in public health risk which are designated as variants of concern and variants of interests. As of July 2021, the delta variant is considered as the most infectious form of the SARS-CoV-2 at present and is also leading to increase in transmission. Taking into sight the billions of people, 2020 has been arduous, but has positive stations also with as many as 58 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) be come out and in the trials. All embracing use of the safety and durability of efficacious vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), distinctively in concoction with multiple collateral prevention game plan, would retrench the coronavirus disease 2019 (COVID-19) pandemic.

Keywords: SARS-CoV-2, Genome, Covid variants, Vaccines.

Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, COVID-19: Coronavirus disease 2019, WHO: World Health Organization, RNA: Ribonucleic acid, ACE2: angiotensin converting enzyme-2, VOC: variant of concern, RBD: Receptor binding

domain, VUI: Variant under investigation, EUA: Emergency use authorization

Introduction

Back in the 1960s viruses named zoonotic coronaviruses were discovered and from this time pestilential human coronaviruses were put in name to starting with the disclosure of SARS-CoV in 2002. With the pre-eminent apprehension of SARS-CoV-2, to the present date the seven human coronaviruses are known as, the variant that cause the mild diseases are the 229E, OC43, NL63 and HKU1, and the pestilential emanated species are SARS-CoV, MERS-CoV and SARS-CoV-2. SARS-CoV and MERS-CoV having their origination in bats, and same condition thought to be associated to be with SARS-CoV-2 as well [1]. From December 2019, spate comes as the conglomeration cases run into respiratory illness in Wuhan, China, preceded by the global escalation. The samples (oral and anal swabs, blood and broncho-alveolar fluid lavage) from diseased individuals were derived to Wuhan Institute of Virology and these specimens were positive for CoV. This was then succeeded by genomic sequencing and metagenomics analysis study. The outcomes disseminate that this virus was identical (79.6%) to the genetic pattern of SARS-CoVBJ01 pre- emanating the WHO to entitle it as novel CoV-2019 [2]. The World Health Organization (WHO) has not long-ago divulged coronavirus disease 2019 (Covid-19) a public health predicament of intercontinental affair [3]. There are no medications for this infection and the steps fixed across innumerable nations such as social distancing, usage of mask to prevent entry of the virus into the respiratory tract, quarantine, and containment together have reduced the prevalence of this disease and mortality in highly susceptible individuals [4]. The symptoms suffered by these patients, including fever, dry cough, dyspnea and malaise, were confirmed as viral pneumonia. Keeping in mind the virus mutation and evolving properties during the pandemic, studies on viral virulence, management options and prophylactic vaccines should be considered as the the genetic properties of the virus [5].

Genome of coronavirus

Coronaviruses that result in respiratory and gastrointestinal tract illness are classified into four major genera: Alphacoronavirus, Beta coronavirus, Gamma coronavirus, and Delta coronavirus. All the strains that for the most part affecting mammals are listed in Table 1 [6]. The coronaviruses belong to the family of enclosed viruses that duplicate in the protoplasm of animal host cells. They are differentiated by the companionship of a single-stranded plus-sense Ribonucleic acid (RNA) genome wit approximate length of 30 kb that consists of 5′ cap structure and 3′ polyadenylation tract [7]. The coronavirus SARS-CoV-2 DNA contains the superior arrangement, ORF1ab that codes the proteins for the replication of the RNA, genes for non-structural proteins (nsp) and structural proteins. ORF1ab cipher the enzyme replicase which is required for the synthesis of polyproteins that are needed for viral RNA replication and transcription. The Papain-like proteinase (PL proteinase, nps3) is the first NSP encoded by ORF 1ab. Nsp3 is an essential and the largest component of the replication and transcription complex. 3CLPro protease (3-chymotrypsin-like proteinase, 3CLpro) and nsp6 are the other non-structural proteins are [8]. In the replication cycle of RNA viruses, the climacetric important process of RNA-templated RNA is overall performed by an RNA-synthesizing complex of the viral enzymes [9]. Additionally, the SARS-CoV-2 genome codes for four structural proteins the nucleocapsid (N), the spike (S), the

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membrane (M), and the small envelope (E) [10]. The spike S protein is a glycoprotein that contains two domains S1domain and S2 domain. Spike protein S1 attaches the virion to the membrane by communing with host receptor angiotensin converting enzyme-2 (ACE2), originating the contamination [11].

Genus	Type of coronavirus
Alphacoronavirus	HCoV-NL63 HCoV-229E
Beta coronavirus	Severe acute respiratory syndrome coronavirus (SARS-CoV) Middle East respiratory syndrome coronavirus (MERS-CoV) HCoV-OC43 HCoV-HKU1

Table 1: Type of coronavirus

The spike glycoprotein of SARS-CoV-2 carry a furin-like bifurcation area [12]. The furin remembrance site is dominant for being concede by pyrolysis and therefore, pitch into the zoonotic contamination of the virus. The envelope (E) protein of the virion interacts with protein present in the membrane M in the budding pocket of the host cell. The M protein holds presiding immunogenicity of the cell [13].

To the present date more than 8000 single mutations are already observed in the SARS-CoV-2 genome have increase the serious concerns about alterations in the infectivity. Observationally, such infectious rate is directly proportional to the binding rapport in the middle of SARS-CoV-2 spike glycoprotein and host ACE2 receptor [14]. Compared with SARS-CoV, SARS-CoV-2 S protein has 725 mutations, among 725 mutations on SARS-CoV-2 S protein, 89 were on the RBD, which has a total of 194 residues, suggesting that the RBD is subject to more mutations [15]. A number of unreported mutations, which cover both mismatches and deletions in translated and untranslated regions of the SARS-CoV-2 genomes. Additionally, the geo-climate disposition of the mutations unravels the higher unique mutations plus disease severity in the European temperate countries [16]. The D614G point-mutation in the Spike protein of SARS-CoV-2, which rapidly became the most widespread variant of SARS-CoV-2 had also observed that this mutation clustered with a series of other point mutations, including one in the polymerase gene [17]. Some common covid-19 variants are:

- 20I/501Y.V1, VOC 202012/01, or B.1.1.7: The covid strains has been designed in many different ways as they are based on different nomenclature systems: (1) “VOC 202012/01,” as a variant of concern (VOC) followed by year, month, and number (2) the “B.1.1.7 lineage,” based on the dynamic lineage nomenclature system of SARS-CoV-2.“20I/501Y.V1,” applying “20I” from the Next strain clade naming strategy combining the year and letter in a system and “501Y.V1” which denotes the replacement of asparagine (N) by tyrosine (Y) in the receptor binding domain (RBD) of the spike protein at position 501. “V1” stands for the first variant examined of N501Y [18]. The variant was first identified in the United Kingdom (UK), is becoming a high concern area for the management of the corona virus disease (COVID-19) pandemic. This SARS-CoV-2 variant 20I/501Y.V1 (501Y.V1) includes the expunction at site 69–70 of the spike (S) protein in the intent region of the Thermo Fisher Taq Path PCR probe which targets the S gene that leads to amplification loss [19]. The first and the foremost case of infection with 501Y.V1 was identified on 13 December 2020. By the end of December, 38%

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(n = 87) of the SGTF viruses detected by the TaqPath RT-PCR had been confirmed as 501Y.V1 by sequencing [20]. The B.1.1.7 variant is appraised to have come in light in September 2020 and has very fastly become the authoritative disseminate SARS-CoV-2 strains in England B.1.1.7 has been recognized in more than 30 countries, together with the United States. U.K. provinces with a higher proportion of B.1.1.7 sequences had seen the faster epidemic growth than did the other areas [21].

- 20H/501Y.V2 or B.1.351: The SARS-CoV-2 variant of concern (VOC) named as 202012/02 (also known as B.1.351 in PANGOLIN phylogeny or 20H/501Y.V2 in NextStrain phylogeny) was emerged in South Africa and caused a major havoc of COVID-19 [22]. This variant of lineage B.1.351 displays several mutations in the S gene (including N501Y and E484K [3-5]) associated with higher transmissibility and immune escape [23].B.1.351 contains 9 spike mutations in addition to D614G, including a cluster of mutations (e.g., 242–244del & R246I) in NTD, three alterations (K417N, E484K, & N501Y) in RBD, and one mutation (A701V) near the furin cleavage site [24].
- P.1: P.1 was first reported in December 2020 from Manaus in Amazonas province of Northern Brazil. A large first wave of infection was seen ~75% of individuals from the region were estimated to have been infected, representing a very high attack rate P.1 has three changes in the RBD (K417T, E484K, and N501Y), which are a particular cause for concern. [25]. Lineage P.1 acquired 17 mutations, associated with increased binding to the human ACE2 (angiotensin-converting enzyme 2) receptor. Molecular clock analysis shows that P.1 emergence occurred around mid-November 2020 and was preceded by a period of faster molecular evolution. This new variant could threaten the efficacy of current monoclonal antibody therapies or vaccines, because it shares mutations at the same three RBD residues with B.1.351, a variant that first emerged from South Africa [26].
- B.1.617: A new variant under investigation (VUI) has been isolated from Maharashtra, India, in a setting of the highly diffusive epidemic with devastating proportions. This variant, identified as B.1.617, carries several non-synonymous mutations. Two of them, the E484Q (or the P478K) and the L452R, are located in the RBD region, and they are critical sites for the binding with ACE2. Currently, B.1.617 comprises three sub variants, B.1.617.1-3, with different distribution of the mutations P478K and E484Q [27]. In just a few weeks this variant have become a dominant strain in India and has spread about 40 nations, including the United Kingdom, Fiji and Singapore. Genomic data indicated that a new variant dubbed B.1.618 was present in West Bengal [28].
- B.1.1.529: More recently a new variant of SARS-CoV-2 was identified again from South Africa. WHO named this newer variant as a variant of concern - Omicron (B.1.1.529) on 26th November 2021. This variant showed more than thirty amino acid mutations in the spike protein. Also the mutation rate is surpassing the other variants with the average of 5-11 times in the receptor-binding motif of the S protein [29]. Omicron is a variant with high transmission rate, evidented from the studies from South Africa and UK reports doubling times of 3.38 days [30].WHO warned that the Omicron variant of SARS-CoV-2 held a very high risk of infection, reigniting anxieties about the economy's recovery from the two-year pandemic [31].

WHO in fraternizing with distinct companion, commission of experts, some national administrates, institutions and inquisitors are keeping an eye on the

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COVID- 19 in as much as Jan 2020. During the late 2020 the emergent of various mutants that possess furthermore elevation in public health risk which are designated as variants of concern and variants of interests [32].

Variant: A variant is usually considered as the virus which constantly changes through the mutation and new strains of the virus are look forward to occur as time follows or passes [33].

Variant of interest

A variant with some precise or distinct genetic markers which are associated with alterations to receptor binding, decrease in neutralization by antibodies made against the previous infection or vaccination, bringing down the treatment effectiveness or foresee an increase in transmission or disease gravity. A variant of interest can be called for one or more sequestrate public health activity.

Example: B.1.427 (next strain)

Variant of concern

A variant for concern is considered in which there is evidence of an increased transmission, more severity (e.g., increased hospitalizations or deaths), and noteworthy depletion of counterbalance the antibodies formed during impetuous infection or vaccination, decreased efficacy of therapy or vaccines, or diagnostic discernment failures. [34].

Epidemiology discussion about transmission and prevalence of different strains

In accordance with the World Health Organization (WHO, 2020a), SARS-CoV-2 is on the whole conveyed through person-to-person close contiguity (<1.5–2.0 m), as well as by aerosol respiratory droplets less than 5 μm in diameter [35]. The delta coronavirus strain is considered a “variant of concern.”

Currently designated variant of concern

WHO Label	Pango lineages	Earliest documented samples	Date of designation
Alpha	B.1.1.7	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351 B.1.351.2 B.1.351.3	South Africa, May-2020	18-Dec-2020
Gamma	P.1 P.1.1 P.1.2	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2 AY.1 AY.2 AY.3	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021
Eta	B.1.525	Multiple countries, Dec-2020	17-Mar-2021
Ota	B.1.526	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	India, Oct-2020	4-Apr-2021
Lambda	C.37	Peru, Dec-2020	14-Jun-2021

Table 2: Currently designated variant of concern (World Health Organisation (www.who.int). Tracking the SARS-CoV variants. Last updated on 13 August 2021)

Because it became apparent to be transmitted easily from one person to another. As of July 2021, the delta variant is considered as the most infectious form of the SARS-CoV-2 at present and is also leading to increase in

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transmission when juxtapose to other strains, even in vaccinated individuals with unvaccinated people it remains one of the greatest unsettlements [36]. VOC B.1.1.7 (also termed Alpha), was first pick out in the United Kingdom, is of somewhat more interest because it has the potentiality to convey productively, it can also spread through populations ghastly, and has also been putatively to have remarkably sky-high mortality rate than non-B.1.1.7 infections [37]. VOCs B.1.351 (β) and P.1 (Gamma), have result in common disease in South Africa and Brazil, respectively that have sequence alterations in spike protein that make their less susceptibility to host and some therapeutic antibodies [38]. The two additional VOIs, B.1.427 and B.1.429 (Epsilon), were conceded by the CDC in part because of their rapid transmission in many California communities [39]. Although comprehensive data are not available from India, the B.1.617, B.1.617.1, B.1.617.2, and B.1.617.3 variants were recently described as causing widespread COVID-19 disease in that country [40]. The SARS-CoV-2 viruses causing infections in the earliest phase of the pandemic affecting Houston had substantial genomic diversity and are progeny of strains derived from several continents, including Europe and Asia [41]. COVID-19 caused by B.1.617.1 (Kappa) or B.1.617.2 (Delta) variants reported to be causing widespread disease and extensive public health problems in India, other Southeast Asian countries, and many regions of the United Kingdom [42].

The evolution of vaccine

Taking into sight the billions of people, 2020 has been arduous, but has positive stations also with as many as 58 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) be come out and in the trials, accompanied a little vaccine presumably having as much as the 90% advantageous in the battle of COVID-19 in clinical trials [43]. The boundless preponderances of viral vaccines anymore licensed for human beings can be arranged based on virus and proteins. In the instance of SARS-CoV-2, mammoth mass of viruses needed to produce under biodefence level 3 settings for an inactivated vaccine, and capacious safety evaluation is needed to corroborate that they do not retrogress to infective state [44]. All embracing use of the safety and durability of efficacious vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), distinctively in concoction with multiple collateral prevention game plan, would retrench the coronavirus disease 2019 (COVID-19) pandemic [45].

Moderna Covid-19 vaccine (mRNA-1273)

Dated back in December 18, 2020, the U.S. Food and Drug Administration accouter an emergency use authorization (EUA) for the succeeding vaccine for the interception of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus to be disseminated in the U.S for use of population 18 years of age and older [46]. SAGE put forward the usage of the Moderna mRNA-1273 vaccine scheduled in the two doses (100 µg, 0.5 ml each) given at interval of 28 days. If required, the time between the doses can be increased up to 42 days [47]. On august 12, 2021, EUA sanctioning to administer a third dose (0.5 mL) given at least 28 days succeeding the 2-dose regime of mRNA vaccine in population who had history of solid organ transplantation or that are diagnosed with diseases that are presumed to have an equal level in the immunocompromised state [48].

Covaxin (BBV152)

Covaxin was invented by an Indian pharmaceutical company Bharat Biotech in alliance with the Indian

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Council of Medical Research [49]. BBV152 is a whole virion β-propiolactone-inactivated SARS-CoV-2 vaccine [50]. Bharat Biotech's Covid-19 vaccine (COVAXIN) has been authorization for incommodious use in an emergency situation to prevent Covid-19 in the two-dose regimen at 28 days apart initially. The COVAXIN is directly injected in the upper arm into the deltoid muscle [51].

Covishield

Covishield is based on a simian adenoviral vector that is replication- deficit, codes the full-length spike glycoprotein (S) of SARS-CoV-2. The vaccine is to be given in a dose of 0.5 mL scheduled at 2 doses, with the two doses administer at the duration of 4-6 weeks (now revised to 8-12 weeks), the deltoid muscle intramuscularly. The Each mL of the vaccine dose administered contains 5 X10 ^{10} simian adeno-viral particles manufactured in genetically modified human embryonic kidney (HEK) 293 cells [52].

Sputnik

Aug 11, 2020; Russia foretell the introduction of Sputnik V, Russia's home prepared adenovirus-based vaccine contender countering the COVID-19 and by Sept 4, the outcome of its phase 1/2 studies were promulgate in The Lancet [53]. The Sputnik V COVID-19 vaccine belongs to member of the so-called vector vaccines and it uses the two non-contrasting vectors (Ad26 priming and Ad5 boost) to decrease the risk of abatement in the efficacy of the vaccination. Real life data shows the usefulness of the vaccine more than 97% [54]. Sputnik V has become the third most approved vaccine among of any covid-19 vaccine, after the AstraZeneca and Pfizer/Biotech jabs, which got their head nodded in 91 and 82 countries respectively [55].

Pfizer (BNT162b2)

Based on the corroboration from clinical trials in people age 16 years and older, the Pfizer-BioNTech vaccine was found to be 95% efficacious in prevention of laboratory-long standing infection with the virus that give rise to COVID-19 in individuals who received two doses and had no proof of being previously infected with virus [56] Recently, dated May 10, 2021, the FDA enlarged the emergency use authorization for the Pfizer-BioNTech COVID-19 vaccine for the inclusion of adolescents aged 12 through 15 years of the age and on June 25, 2021, the FDA amended the provider and patient fact sheets in regard to the recommended expanded risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) followed by the vaccination. On August 12, 2021, the FDA again made an amendment regarding the Pfizer-BioNTech COVID-19 Vaccine EUA to get allowed for an additional third dose to be given to some of the immunocompromised individuals [57]. Persons aged 12 years and more must receive 2 doses with the time period between 2 doses 21 days apart [58].

Pipeline vaccines

Pipeline vaccines involve the record of some disease-causing microorganisms for which vaccines and/ or monoclonal antibodies (mAbs) are in development stage [59]. Some pipeline vaccine is as follow: [60].

Vaccine Platform	Vaccine Name	Stage of development
Non-Replicating	ChAdOx1-nCoV-19 vaccine	Phase-1
Viral Vector	Ad-5vectored COVID-19 vaccine VXA-CoV2-1 MVA-SARS-2-S	Phase-3 Phase-1 Phase-1

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DNA	INO-4800 AG0301-COVID19	Phase-1/2 Phase-1/2
RNA	BNT162b1 mRNA 1273	Phase-3 Phase-3
Inactivated	Inactivated SARS-CoV-2 vaccine BBV152	Phase-3 Phase-1/2
Replicating Viral Vector	rVSV-SARS-CoV-2-S Vaccine	Phase-1
Protein subunit	Recombinant S protein SCB-2019	Phase-1/2 Phase-1
Virus like particle	Coronavirus-Like Particle COVID-19 Vaccine	Phase-1

Table 3: Some pipeline vaccines in different phases of clinical trials.

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