The Global Trend of COVID-19 Vaccine and Challenges of New Emerging SARS-CoV-2 Variants

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INTRODUCTION

Since Coronavirus Disease (COVID-19) was declared a Public Health Emergency of International Concern on January 30, 2020 [1-4] and later declared a pandemic by the World Health Organization on March 11, 2020 [2], it has claimed over 1,754,000 lives worldwide and over a total of 79,231,000 cases reported [3]. New infection cases are continuously rising as well as deaths and other health complications and cases with new variants are increasing [5,7-9].

Even if SARS-CoV-2 was identified as the virus causing COVID-19, during earlier stages of COVID-19, mutations of the virus have been reported and Chinese researchers identified two SARS-CoV-2 variants. However, by sequencing more SARS-CoV-2 genome, they identified more variants [4,8].

Since then, other mutations have been reported in different countries and some new variants were found to be more transmissible and more virulent [4,8-12]. COVID-19 has also caused other social and economic devastations [5,6].

To mitigate these, scientists worldwide are deploying their time and different resources in developing the urgently needed vaccines [1-3,6] and investigations on how new variants react to the current vaccines are underway. The World Health Organisation (WHO) has launched a COVID-19 Vaccines Global Access (COVAX) initiative for the global and non-discriminatory access to the vaccine [6,7].

NEW EMERGING SARS-CoV-2 VARIANTS

Viruses constantly change through mutation, and new variants of a virus are expected to occur over time. Sometimes new variants emerge and disappear. Other times, new variants emerge and persist. Mutations are common, but the majority of them cause no alteration in the structure of the proteins they encode—these are called "silent" mutations, as they eventually translate to the same amino acids. Another type is "missense" mutation, which could result in an amino acid change.

The failure of current public health measures to contain the spread of SARS-CoV-2 within

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and between countries has given rise to many virus lineages across the world. Open genomic surveillance data sharing and collaborative online platforms have enabled real-time tracking of these lineages' emergence and spread [10–13]. Genomic sequencing has been critical in identifying and responding to new SARS-CoV-2 variants. Increased recognition that viral genome sequencing can contribute to improve public health is driving more laboratories to invest in this area.

The rise of SARS-CoV-2 variants with spike (S)-proteins mutations that are now predominant globally, have raised a concern and call for attention to put in place a program to identify circulating variants in the population in order to strengthen the laboratory and diagnostic and monitoring capacity for SARS-CoV-2. The SARS-CoV-2 virus mutates just like other viruses. To date there have been about 4,000 mutations in its spike protein alone [11,14,15].

Three global variants of interest D614G, N501Y and E484K mutations which occur in the spike (S) protein identified in the UK, in South Africa, and Brazil, respectively, have called to attention to improve the laboratory diagnostic capacity in place.

These mutations mostly occurring in the spike protein that the virus uses to bind to the human angiotensin-converting enzyme 2 (ACE2) receptor increase the ability of the virus to be transmitted [11,14,16,17]. Hence, changes in the receptor-binding domain (RBD), that the virus uses to bind to the human ACE2 receptor can result in the virus changing its ACE2 binding specificity and alter antibody recognition [11].

The COVID-19 Genomics UK (COG-UK) consortium, a partnership of the UK's four public health agencies, as well as the Wellcome Sanger Institute and 12 academic institutions has been created since April 2020, has sequenced 140,000 virus genomes from people infected with COVID-19. It uses the data to track outbreaks, identify variant viruses, and publish a weekly report (https://www.cogconsortium.uk/data/) [7].

According to the most recent report from COVID-19 Genomics UK (COG-UK) consortium a new variant reported in December named VUI-202012/01 (the first "Variant Under Investigation" in December 2020) and is defined by a set of 17 changes or mutations. N501Y mutation is one of the most significant mutations in the spike protein that the virus uses to bind to the human ACE2 receptor. Changes in this part of spike protein may, in theory, result in the virus becoming more infectious and spreading more easily between people [11,16]. Apart from the N501Y mutation, other mutations of importance appeared in the UK are D614G with a high transmissibility rate and , A222V, N439K, Y453F one deletion (del) and co-occurrence of some of these changes are actively being investigated by COG-UK [16].

Most of the variants tracked by COG-UK are mutations occurring in the lineage B.1.1.71 which is of interest and is notable for a higher number of mutations in one lineage than observed previously. COG-UK is actively investigating five amino acid replacements (D614G, A222V, N439K, Y453F and N501Y), one deletion (del) and co-occurrence of some of these changes due to their importance and to their high transmissibility [15]. One of these (the N501Y mutation) occurs in the Spike protein region, the receptor-binding domain (RBD), that the virus uses to bind to the human ACE2 receptor. Changes in this region of the Spike protein can result in the virus changing its ACE2 binding specificity and alter antibody recognition [16]. There is no evidence suggesting that the variant has any impact on the severity of disease or vaccine efficacy.

Recently South Africa also reported new SARS-CoV-2 lineage (501Y.V2) characterized by eight lineage-defining mutations in the spike protein, including three at important residues in the receptor-binding domain (K417N, E484K and N501Y) that may be associated with increased transmissibility [10]. E484 is in the receptor-binding motif (RBM) and interacts with the K31 interaction hotspot residue of hACE2. Studies have shown that E484K mutation may modestly enhance binding affinity [10]. In adition, in Brazil, the lineage P.1 (alias of B.1.1.28.1) an emerging variant that harbors several amino acid mutations including S:K417T, S:E484K, and S:N501Y has been reported. These mutations in the spike (S) protein raises concern about the potential impact on viral infectivity and immune escape [17].

MUTATIONS CHALLENGES AND POSSIBLE IMPACT ON VACCINATION

SARS-CoV-2 is an RNA virus that belongs to coronaviruses and have at least four essential proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The coronavirus

spike (S) protein mediates receptor binding and fusion of the viral and cellular membrane [20]. Mutations in the SARS-CoV-2 genome arise naturally as the virus replicates and accumulate at a rate of about one to two mutations per month in the overall phylogeny. However, only a very small minority are likely to be important and change the virus appreciably. In order words, the majority of mutations observed in SARS-CoV-2 have no apparent effect on the virus, and only a very small minority are likely to be significant and modify the virus appreciably (for example, a change in the ability to infect people; cause a disease of different severity; or become insensitive to the effect of the human immune response, including the response generated by a vaccine) [11]. Because of this ongoing process, several thousand mutations have already appeared in the genome of SARS-CoV-2 since the appearance of the virus in 2019. As mutations continue to appear, new combinations are increasingly observed, and these changes jeopardize the current treatment strategies under construction. Although these mutations present a risk, no studies have proved the variant has any impact on the severity of disease or vaccine efficacy.

Currently, most COVID-19 vaccines target the SARS-CoV-2 spike protein. There are some vaccines, such as inactivated virus vaccines developed in China and India, that target the whole virus. Mutations may reduce vaccine efficacy directed against the spike protein but will not obliterate their effects. This is because the immune responses they induce target more than a single part of the spike protein. Inactivated vaccines target an even greater array of viral proteins, inducing several protective immune responses.

However, scientists are working to learn more about these variants to better understand how easily they might be transmitted and the effectiveness of currently authorized vaccines against them.

RESEARCH AND DEVELOPMENT OF COVID-19 VACCINE

Since the COVID-19 emerged in Wuhan, China, late 2019, significant progress has been made towards developing a vaccine. To date, a number of vaccines have been approved by licensing institutions and are currently being administered to identified high-risk groups [18,19].

Currently, 73 vaccines are still at different developmental stages. Among these, 18 vaccines are in Phase II, under clinical trials, 32 vaccines and 23 vaccines in Phase II and I, respectively [2,6].

There are also 7 vaccines approved for early or limited use and 3 vaccines approved for full use. Pfizer/BioNTech vaccine was approved for use across North America, Europe and the Middle East. The same vaccine is being studied to be approved in many other regions and countries (Figure 1) [1,20].

Developer	Type	Phase	Status
Pfizer-BioNTech	mRNA	II III	Approved in Canada, other countries. Emergency use in U.S., other countries.
Moderna	mRNA	III	Approved in Canada. Emergency use in U.S., Israel.
Gamaleya	Adenovirus	III	Early use in Russia. Emergency use in Belarus, Argentina.
Oxford-AstraZeneca	Adenovirus	II III	Emergency use in Britain, India, Argentina.
CanSino	Adenovirus	III	Limited use in China.
Johnson & Johnson	Adenovirus	III	
Vector Institute	Protein	III	Early use in Russia.
Novavax	Protein	III	
Sinopharm	Inactivated	III	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
Sinovac	Inactivated	III	Limited use in China.
Sinopharm-Wuhan	Inactivated	III	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	III	Emergency use in India.

Figure 1: *Leading vaccines (Adapted from Covid-19 Vaccine Tracker - The New York Times, December 27, 2020).*

VACCINE RESERVATIONS

Since the early development of COVID-19 vaccines, different countries have entered a race to ensure accessibility to an effective vaccine [21-23]. High-income countries have premarket purchased majority of doses while their populations represent only 14% of the global population [7,24,25]. By the end of December 2020, up to 8.25 billion doses were already reserved mostly by high-income countries, with Canada securing more doses than three times (303.5%) its population size (Figure 2) [7,22,23]. This is contrary to the WHO commitment to ensure fair and equitable distribution of COVID-19 vaccines among its member states [25].

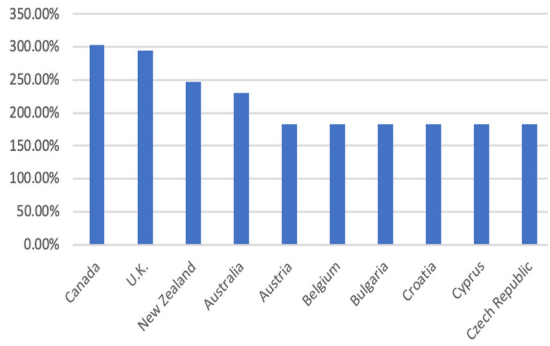

Figure 2: *Top 10 countries with the most Covid-19 vaccine reservations by percentage of the population as of December 30 2020.*

GLOBAL COVID-19 VACCINE COMPAIGN

By the end of December 2020, more than 12 million COVID-19 vaccines were already administered in 35 countries with China leading in numbers of administered doses with over 4.5 million doses (0.32% of population covered), followed by the United States of America with over 4.2 million administered doses (1.30% of population covered). Israel was ahead with a cumulative percentage of 10.5% of the total population vaccinated (Figure 3) [26].

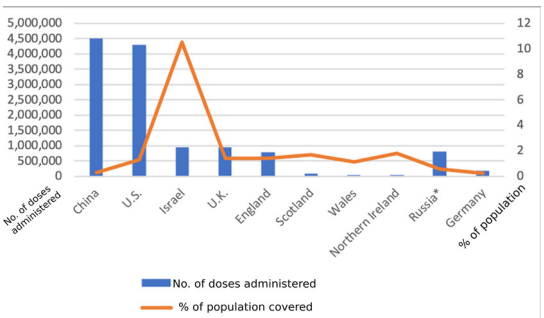

Figure 3: *Top 10 countries with the highest number of COVID-19 vaccines administered as of December 31, 2020.*

Both Pfizer/BioNTech and Moderna vaccines (the two leading COVID-19 vaccines) are mRNA based and 2 doses are given with 21 days apart for Pfizer/BioNTech vaccine and 28 days apart for Moderna vaccine [25].

However, the required freezing temperatures for storage make these vaccines vulnerable, and hence their distribution and storage are expected to be highly challenging, especially in low-income countries [16]. Pfizer/BioNtech vaccine needs to be kept at minus 70 degrees Celcius and Moderna's vaccine at minus 20 degrees Celcius for 6 months for both vaccines [23,24].

COVID-19 VACCINATION IN RWANDA

The government of Rwanda plans to acquire the COVID-19 vaccine in the first quarter of 2021 [27]. Vaccination will start with people at high risk such as health professionals, people with comorbidity, and the elderly 65 years and above [27,28].
Rwanda has already applied for different vaccines including Pfizer/BioNTech, Moderna and AstraZeneca vaccines among others. Rwanda has also submitted all required documents to COVAX; a framework aimed to ensure equitable access and fair allocation of COVID-19 health products [27].

ACCEPTANCE OF A COVID-19 VACCINE

In a survey done by Nature Medicine in 19 countries, over 70% of the respondents agreed that they would accept the vaccine if available. The highest acceptance rate was reported in China (90%). In contrast, the lowest acceptance rate was found in Russia [1] while in Rwanda, the Ministry of Health forecasts good acceptance of the vaccine among Rwandan citizens [28].

In conclusion, COVID-19 remains a global pandemic, keeps claiming more lives and causing devastating social and economic impacts. There are still no effective treatments or cures for COVID-19 and prevention measures should be maintained. Continuous efforts should continue to be deployed to educate the population about the vaccines to ensure acceptance and successful vaccination. Governments and manufacturers of the vaccines will have to fully collaborate to ensure fair and equitable distribution of COVID-19 vaccines to the entire world population to fight and eradicate the COVID-19 pandemic.

Surveillance of SARS-CoV-2 and its variants requires proper identification of each strain to guide preventive measures, and to help inform development of future treatments.

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