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Review

An overview of the ongoing challenges in SARS-CoV-2 global control

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Abstract

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has caused a severe global pandemic with major public health issues. Public health sectors implemented several control strategies, such as social distancing, hygienic measures, and the development of anti-viral drugs and vaccines. However, the situation is still critical due to several challenges facing the global control strategy. SARS-CoV-2 has undergone several mutations that will drive viral evolution, which might impact the virus's transmissibility and pathogenicity and the immune escape and development of resistance to therapeutics. Moreover, although the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved several vaccines, however, some vaccines, especially vector-based vaccines, have rarely induced severe fatal side effects. These side effects led to widespread doubts about the safety of the coronavirus disease-19 (COVID-19) vaccines, which in turn dragged a certain proportion of the public from getting vaccinated. This review highlights some of the ongoing challenges in controlling the COVID-19 pandemic, including side effects of the developed vaccines, potential mechanisms for the development of thrombocytopenia, and the clinical impacts of the emerged SARS-CoV-2 variants on the pathogenesis of the virus and vaccine efficacy. Additionally, we discuss the comorbidity and the potential role of gastrointestinal microbiota in controlling SARS-CoV-2. Finally, we shed light on the substantial collateral health damage and unprecedented economic disaster caused by the lockdown.

Keywords: SARS-CoV-2, Variants, Thrombocytopenia, Lockdown, Comorbidity, Public hesitation, Global control

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Introduction

Many cases of idiopathic pneumonia were reported in Wuhan city, China, in late December 2019. One month later, scientists identified the causative agent as a newly emerged severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) (Zhu et al., 2020). SARS-CoV-2 caused outbreaks of coronavirus disease 2019 (COVID-19) in different cities in China, and then spread globally and later was declared as a pandemic by World Health Organization (WHO) (Wu et al., 2020; Zhou et al., 2020).

SARS-CoV-2 belongs to the family *Coronaviridae*, subfamily *Orthocoronavirinae*, genus *Betacoronavirus*. SARS-CoV-2 is an enveloped virus with a single-stranded positive-sense RNA genome composed of 29,903 nucleotides with 11 open reading frames (ORFs) encoding 29 proteins (Aldaais et al., 2021). The ORF1ab contains the first two-thirds of the viral genome (21,290 nucleotides) and encodes a total of 16 non-structural proteins, designated nsp1–nsp16. The last third of the genome encodes four structural and six accessory proteins. The Spike, Envelope, Matrix,

and Nucleocapsid proteins are the main structural proteins of SARS-CoV-2 (Chan et al., 2020; Helmy et al., 2020). Cell entry requires the Spike protein, the virus attachment glycoprotein. The trimeric Spike protein comprises two subunits, namely S1 and S2, mediating receptor binding and membrane fusion. The S1 subunit contains the receptor-binding domain (RBD), which binds with the angiotensin-converting enzyme 2 (ACE2) (Hoffmann et al., 2020; Letko et al., 2020; Ou et al., 2020; Wan et al., 2020; Zhou et al., 2020).

At the time of writing, 245,602,702 SARS-CoV-2 cases and 4,984,270 deaths were reported worldwide. Scientists made significant efforts to control SARS-CoV-2, including clinical trials to assess the efficacy and safety of anti-viral drugs and developed vaccines, complementary measures such as social distancing, and hygienic measures like hand washing and using chemical disinfectants. Scientists exerted efforts to develop vaccines against SARS-CoV-2, utilizing a fast mode of research and production, including obtaining emergency approval for use. Fortunately, several vaccines were granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) and have shown tremendous effect in decreasing the number of deaths related to COVID-19. The European Medicines Agency (EMA) and national authorities have approved the mRNA vaccines (Pfizer-BioNTech and Moderna) and adenoviral vector-based vaccines (AstraZeneca and Johnson and Johnson/Janssen). However, several challenges in global control remain critical. We aimed to discuss ongoing challenges, such as the safety and efficacy of the developed SARS-CoV-2 vaccines, the emergence of mutations distinct from the ancestral virus, lockdown measures, and social factors.

SARS-CoV-2 vaccine platforms

Scientists needed an urgently effective SARS-CoV-2 vaccine in response to the COVID-19 pandemic to protect humans and minimize the pandemic's economic and societal impacts. The Spike protein has been shown as the most potent antigen for SARS-CoV-2 and has been considered the critical target for SARS-CoV-2 vaccines (Amanat and Krammer, 2020). Developed vaccines encoding the S protein of SARS-CoV-2 elicited both neutralizing antibodies and cellular immune responses (Suthar et al., 2020). Although the standard vaccine development process usually takes several years to be finished with clinical trials and obtaining marketing approval, there are currently 183 COVID-19 vaccine candidates in pre-clinical testing and another 97 vaccine candidates in clinical phases based on different vaccine platforms as of May 7, 2021 (WHO, 2021a). Moreover, three vaccine candidates have recently been granted by the US FDA (for Pfizer/BioNTech, Moderna mRNA vaccines, and Johnson and Johnson viral vector vaccine) and by the UK government (for the University of Oxford/AstraZeneca viral vector vaccine) (Nagy and Alhatlani, 2021). Here, we summarize data about current COVID-19 vaccine platforms, particularly replication-deficient vectors, and genetic vaccines (DNA and RNA vaccines).

Replication-deficient vectors

There are 14 vaccine candidates currently in clinical phases using deficient/non-replicating viral vector platforms as of May 7, 2021 (WHO, 2021a). Some of these candidates are currently in Phase III, such as vaccine candidate that was developed by CanSino Biological Inc./Beijing Institute of Biotechnology (trial numbers NCT04526990 and NCT04540419) and Gamaleya Research Institute developed another candidate vaccine, the Health Ministry of the Russian Federation (trial number NCT04530396) (WHO, 2021a). Generally, replication-deficient vectored vaccines are depending on using attenuated virus vectors generated by the reverse genetics system (Nagy and Alhatlani, 2021). In addition, these vaccines have the advantages of an easy scaling-up process and broad targeted immune responses, including both humoral and cellular responses without the need for adjuvant (Krammer, 2020).

In addition, other vaccines from this platform, such as Ad-26 prime-modified vaccinia Ankara (MVA) boost-based ebolavirus vaccine are licensed (Krammer, 2020). However, some drawbacks are currently associated with the use of vectored vaccines. (i) Pre-existing immunity against the used viral vector may render vaccine ineffective (Nayak and Herzog, 2010); however, this could be minimized or avoided by priming with another type of vaccine, such as a DNA vaccine (Yang et al., 2003). (ii) The used viral vector would induce an immune response that subsequently interferes with future vaccines using the same vector (Nagy and Alhatlani, 2021). Host reactions to the structural proteins of the viral vector become self-limiting after numerous vaccinations with vectored vaccines, resulting in declining responses against the vaccine insert. To overcome this constraint, some clinical trials have used the heterologous prime-boost protocol, in which two distinct viral vectors or a pDNA prime-viral vector boost were explored (Draper and Heeney, 2010; Trovato et al., 2020).

DNA and RNA vaccines

Currently, there are ten DNA-based vaccine candidates and fifteen RNA vaccine candidates in clinical phases as of May 7, 2021 (WHO, 2021a). Some of these DNA vaccine candidates are currently in Phase III, and II (trial numbers NCT04642638 and NCT04655625). On the other hand, an example of RNA vaccine candidates is currently in phase III as the CVnCoV vaccine that was developed by CureVac AG (Tübingen, Germany) (trial number NCT04652102) (WHO, 2021a).

Generally, plasmid DNA vaccines have many advantages, such as targeting and stimulating both humoral and cellular immune responses and flexible and simple scale-up production over short timelines, making them ideal for rapid responses during pandemics and room-temperature storage of the final formulated vaccine. However, there are some disadvantages of this platform. First, DNA vaccines have low immunogenicity in humans, which requires several doses of the vaccine to achieve optimum protection. Second, there is a risk of carcinogenesis due to potential integration in

cellular chromosomes (Frederiksen et al., 2020). The RNA-based vaccines platform has several advantages compared to DNA vaccines. It usually targets both humoral and cellular immune responses, has a high safety profile, does not result in human chromosome integration, and has no anti-vector immunity. However, there are some drawbacks with this kind of vaccines, such as the requirement of temperature storage and the high cost of production, which impedes its use in low-income countries (Frederiksen et al., 2020).

Side effects of currently developed COVID-19 vaccines

SARS-CoV-2 vaccines cause typical side effects like other vaccines, such as fever, local pain at the injection site, fatigue, headache, and myalgias. Resolution of such side effects usually occurs within a few days. Scientists reported more severe side effects in a few cases, such as lymphadenopathy and vaccine-induced immune thrombosis and thrombocytopenia syndrome (TTS) associated with adenovirus vectored vaccines. In the following section we will shed light on the severe side effects that have raised the concern.

Lymphadenopathy

Lymphadenopathy was reported in 0.3 and 1.1% of people vaccinated with Pfizer-BioNTech and Moderna vaccines, respectively (Polack et al., 2020; Lehman et al., 2021). However, the true incidence of lymphadenopathy may be higher since not all cases with axillary lymphadenopathy exhibit clinical symptoms (Tu et al., 2021). Lymphadenopathy commonly affects the axilla as an immune response to SARS-CoV-2 vaccines. Scientists have also reported this side effect in rare cases following vaccination against influenza, and human papillomavirus (Newfield et al., 1990; Shirone et al., 2012; Studdiford et al., 2008). The high number of side effects of mRNA vaccines might be attributed to the higher immunogenic responses to these vaccines (Tu et al., 2021).

COVID-19 vaccination-induced lymphadenopathy is increasingly seen on breast imaging. In general, scientists reported several recommendations to minimize these effects: i) injection of both COVID-19 vaccine doses in the arm contralateral to the primary or suspected malignancy side, with both dosages administered on the same arm. ii) routine image screening for all individuals who present lymphadenopathy followed by COVID-19 vaccination before or 4–6 weeks at least after the second dose of COVID-19 vaccination, or even image examination, in case of urgent clinical indications (Becker et al., 2021; McIntosh et al., 2021; Mortazavi, 2021).

Thrombosis and thrombocytopenia syndrome (TTS)

COVID-19 vaccines also induced thrombocytopenia in some cases 5 to 24 days after initial vaccination with adenovirus vectored vaccines (Greinacher et al., 2021; Muir et al., 2021; Sadoff et al., 2021; Schultz et al., 2021). Although Pfizer-BioNTech and Moderna vaccines usually cause mild to intermediate side effects, TTS associated with adenovirus vectored vaccines was reported after vaccination with AZD1222/Vaxzevria and Johnson and Johnson (Kowarz et al., 2021). Unfortunately, cerebral venous sinus thromboembolic (CVST) events accompany most thrombocytopenia cases. In Australia, the incidence of TTS was <3/100,000 after the first dose, with a case fatality rate of 5-6% (Curtis et al., 2021).

The TTS is associated with high titers of IgG antibodies against the cationic platelet chemokine, platelet factor 4 (PF4) , which trigger platelets to form blood clots (Greinacher et al., 2021). This syndrome is not new; however, it resembles the rare side effect of heparin, called heparin-induced thrombocytopenia (HIT). The immune system develop antibodies to a complex of heparin and platelet factor 4 (PF4) protein, which triggers platelets to form blood clots. However, the mechanism of vaccine-induced TTS is still unclear. Greinacher and others found sucrose, EDTA (approximately 100μM), histidine), and different proteins (i.e., vector proteins, human proteins, and the SARS-CoV-2 Spike protein) within the ChAdOx1 nCov-19 based on 1H-NMR spectrometry and proteomic analysis (Greinacher et al., 2021). The authors suggested that vaccine proteins (unknown protein) and EDTA activate the platelets leading to the release of PF4. In addition, EDTA in the vaccine increases the vascular permeability, which disseminates vaccinal proteins into the blood. This inflammatory response stimulates the production of anti-PF4 antibodies by B-cells. The anti-PF4 antibodies bind with PF4, resulting in PF4/IgG immune complexes, which further activate platelets triggering NETosis with prothrombotic consequences.

More recently, Kowarz and others described the "Vaccine-Induced COVID-19 Mimicry" syndrome that might explain the possible mechanism of TTS (Kowarz et al., 2021). In vectored vaccines, transcription takes place inside the nucleus, however, the RNA of the wild SARS-CoV-2 is translated and replicated only in the cytosol of infected cells. According to the authors, the viral DNA derived from viral RNA is not optimized to transcribe inside the nucleus resulting in arbitrary splice events and soluble Spike protein variants. The authors did not provide data about the spurious splicing events. These soluble proteins could bind with ACE2-expressing endothelial cells in blood vessels and lead to severe side effects. Scientists proposed optimizing codons in vector-based vaccines to prevent undesired splice reactions and promote the safety of these drug products. On the other hand, mRNA vaccines are translated in the endoplasmic reticulum of the cytosol of muscle cells into Spike protein, followed by post-translational modifications in the endoplasmic reticulum (ER) and Golgi apparatus transported to the outer membrane to stimulate both B and T immune cells (Kowarz et al., 2021).

Emergence of variants

Coronaviruses undergo continuous evolution to evade host responses and transmit more effectively. SARS-CoV-2 has acquired new mutations as a part of natu-

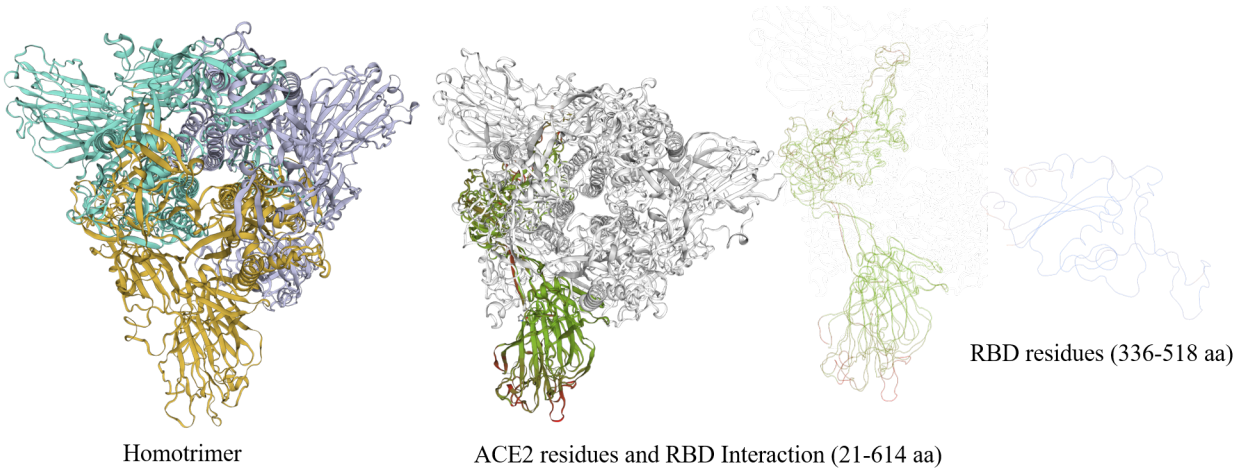

Figure 1: Crystal structure of the Wt SARS-CoV-2 (NC_045512) Spike glycoprotein homo trimer (1270 aa), angiotensin converting enzyme 2 (ACE2) complex (21-614 aa) and ACE2-free conformation of receptor binding site (RBD) (336-518 aa) from left to right orientation. The Wt-homotrimer Spike glycoprotein (NC_045512) was built from the cryo-EM structure, compared with the template 7cwu.1 G available at Swiss-Model (https://swissmodel.expasy.org/interactive) structure. ACE2/RBD complex and separate RBD structure using ACE2 residues 21-614 and RBD residues 336-518 of the respective reference strains, compared with the template 7bbh.1.A and 7kzb.1.C, respectively. Spike glycoprotein homotrimer was depicted as a cartoon chain, and the interaction between ACE2 and RBD was portrayed as a cartoon on chain in a homotrimer backbone and in trace conformation. The free RBD was represented in cartoon trace conformation.

ral evolution, leading to new variants. Although several mutations did not provide a selective advantage to the SARS-CoV-2, some mutations increased transmissibility through an increase in receptor binding or the ability to evade the host immune response by altering those surface structures recognized by antibodies (ECDC, 2021).

Scientists divide the representation of Spike glycoprotein at different conformations into trypsin-cleaved and low pH-treated SARS-CoV-2 Spike glycoprotein homotrimer and ACE2 complex. The conformation of different mutants in receptor binding sites (RBD) that interact with ACE-2 binding might increase or decrease the binding affinity, affecting the virus's pathogenesis. (Figure 1). On the other hand, D614G mutation shows an increase in the transmissibility of SARS-CoV-2 due to conformational changes of the Spike protein, which subsequently favors the binding affinity between S protein and ACE2 (Hou et al., 2020b; Korber et al., 2020; Plante et al., 2021; Yurkovetskiy et al., 2020). In animals, scientists associate D614G with a higher transmission rate and a higher viral load in the upper respiratory tract (Hou et al., 2020a). Scientists have not reported any evidence about increasing the pathogenicity of the virus or increasing the clinical courses in humans (Korber et al., 2020). Weissman and coworkers suggested that these conformational changes induced due to D614G mutation increases the epitope exposure, which subsequently increases the susceptibility to neutralization, with no significant effect on the efficacy of the current vaccines (Weissman et al., 2021).

Variants can be defined as the virus's mutations that can lead to different phenotypes, such as different antigenicity, transmissibility, or virulence (Lauring and Hodcroft, 2021). According to WHO, SARS-CoV-2 is classified as a variant when the virus carries mutation (s) that can cause community transmission, leading to many infected cases in different countries (WHO, 2021a). Generally, scientists classify variants into; variants of interest (VOI), variant-of concern (VOC), and variants of high consequences (VOHC). Only VOI and VOC of SARS-CoV-2 were reported (ECDC., 2021). To date, the B.1.1.7, B.1.351, P.1, and B.1.617 SARS-CoV-2 variants have emerged (Table 1). The emergence of such divergent genetic variants might cause a severe challenge to the therapeutics' efficacy and approved vaccines (Majumdar and Niyogi, 2021). In this section we will shed light on the most important VOC and VOI of SARS-CoV-2.

Variants of Concern (VOC) of SARS-CoV-2

1. B.1.1.7 or VOC202012/01 (VOC-Alpha)

Scientists detected the B.1.1.7 or VOC202012/01 or GRY or 20I/S:501Y.V1 (Alpha) in September 2020 in the UK. The primary mutation in B.1.1.7 is ΔH69/ΔV70 and ΔY144-145 (in N-terminal domain), N501Y (in RBD), A570D and P681H (between RBD and S1/S2 boundary), T716I (in S2 between fusion peptide and HR1), S982A (in HR 1 of S2), and D1118H (in S2) (Akkiz, 2021). The B.1.1.7 variant mutations increased virus transmissibility, and the mutated virus may be associated with an increased risk of death compared to other variants (Davies et al., 2021; Harrington et al., 2021). Generally, the B.1.1.7 variant has higher ACE2 receptor affinity, longer elimination times, and higher viral load based on laboratory diagnosis (Calistri et al., 2021; Kidd et al., 2021; Kissler et al., 2021; Mohandas et al., 2021; Starr et al., 2020; Walker et al., 2021; Zahradník et al., 2021). Scientists found that

N501Y substitution increases the binding of the virus tightly to the ACE2 cellular receptor and subsequently accelerates the spread of the virus (Galloway et al., 2021; Ostrov, 2021; Starr et al., 2020; Zahradník et al., 2021). In addition, P681H mutation in the SARS-CoV-2 B.1.1.7 increased the cleavage of Spike protein by furin-like proteases (Lubinski et al., 2021).

The B.1.1.7 variant is associated with an increased risk of hospitalization (CDC, 2021). However, there is no evidence that this variant impacts the severity of disease or vaccine efficacy (Weisblum et al., 2020; Wu et al., 2020). Interestingly, this variant has minimal or no impacts on virus immune escape (Collier et al., 2021; Edara et al., 2021; Shen et al., 2021; Wang et al., 2021). The ChAdOx1 nCoV-19 vaccine proved to be efficient against the B.1.1.7 variant, similar to the vaccine's efficacy against other lineages (Emary et al., 2021). *In-vitro* studies indicated that the approved mRNA vaccines were effective against viruses of the B.1.1.7 variant (Dagan et al., 2021; Muik et al., 2021; Wang et al., 2021; Wu et al., 2020).

2. B.1.351 or 20H/501Y.V2 (VOC-Beta)

The B.1.351 or 20H/501Y.V2 was first detected in South Africa in December 2020. It contains Spike L18F, D80A, D215G, R246I, K417N, E484K, N501Y, and A701V mutations, which characterize this variant by increased transmissibility (Pearson et al., 2021). In the E484K mutation, a negatively charged amino acid (glutamic acid) substitutes with a positively charged amino acid (lysine). Thus, one can expect that the mutation has a significant impact on viral sustainability and adaptive evolution. The structural analysis revealed a new site for ACE2 binding (amino acid 75) because of the E484K mutation, which appears to create a significantly stronger interaction between ACE2 and the native binding site located at the RBD and ACE2 interface (aa 501). Interestingly, the E484K is not a new mutation or a unique mutation to the South African variant because it was detected earlier in 2020 in an old isolate deposited at GISAID with ID EPI_ISL_528300 that scientists collected on March 20, 2020, from a female in Switzerland and the original sample was not passaged on cell culture.

The B.1.351 variant also presents new challenges for the current monoclonal (mAb) therapy and threatens the protective efficacy of the current vaccine due to E484K mutation (Wang et al., 2020). Scientists suggested that E484 impacts binding and neutralization by polyclonal serum antibodies targeting the RBD (Greaney et al., 2021). In addition, the B.1.351 variant exhibited a significant decrease in the susceptibility to bamlanivimab and etesevimab mAb combinations (Wu et al., 2021). Following mRNA-1273 vaccination, there was a significant reduction of neutralization against the full B.1.351 variant (Wu et al., 2021). A two-dose regimen of the ChAdOx1-nCoV19 vaccine did not show protection against the mild- B.1.351 variant (Madhi et al., 2021).

3. P.1 variant (VOC-Gamma)

The P.1 or 20J/501Y.V3 variant (B.1.1.28) variant emerged in Brazil in April 2020 (Maggi et al., 2021). It contains Spike L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, T1027I, and V1176F mutations. It may increase virus transmissibility and antigenic profile, raising concerns of a potential increase in transmissibility or propensity for SARS-CoV-2 re-infection of individuals. In addition, reduced effectiveness of neutralizing antibodies and increased virulence are also assumed for this variant (Faria et al., 2021). Due to the presence of E484K substitution, these viruses may exhibit a reduction of neutralization by some polyclonal and mAb antibodies (Weisblum et al., 2020; Resende et al., 2021). Moreover, significant resistance of these viruses to antibody neutralization was also reported (Wang et al., 2021).

4. B.1.617.2 (VOC-Delta)

In October 2020, the B.1.617.2 or VOC202104/01, G/452R.V3, 21A/S:478K variant, was first detected in India. It is currently prevalent in the UK. The B.1.617.2 variant is characterized by the mutations (T19R, del157-158, L452R, T478K, D614G, P681R, D950N), associated with reduced effectiveness of the immune response, increased transmissibility, virulence, and immune escape.

5. B.1.1.529 (VOC, Omicron)

More recently, the B.1.1.529 variant was first reported in South Africa on 24 November 2021 (WHO, 2021b). On 26 November 2021, the WHO designated this variant as VOC and named it Omicron (WHO, 2021b). It belongs to Pango lineage B.1.1.529, and is characterized by 30 amino acids mutations (A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F), three small deletions (Δ69-70, Δ143-145, Δ211, and one insertion (ins214EPE) in the Spike protein compared to the original virus (CDC, 2021). So far, the Omicron variant is the most divergent one detected during the COVID-19 pandemic, raising concerns that it might be associated with increased transmissibility, immune evasion, and reduction in vaccine effectiveness (CDC, 2021). However, further experimental studies are urgently required to assess these potential impacts.

Table 1: Summary of the most important SARS-CoV-2 Variants of Concern (VOC).

Variant	WHO description	First detection	Mutation in Spike-Protein	Potential effect*				
				Transmission	Virulence	Binding affinity with ACE2	Immune escape	Susceptibility to antivirals
B.1.1.7 (20I/501Y.V1)	Alpha	UK	ΔH69/ΔV70, ΔY144, N501Y, A570D, P681H, T716I, S982A, D1118H (K1191N)*	↑	↑	501Y: ↑	+/-	-
B.1.351 (20H/501.V2)	Alpha	South Africa	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, A701V	↑	Unknown	501Y & 484K: ↑↑↑	+	+
P.1 alias B.1.1.28.1	Gamma	Brazil/Japan	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, T1027I, V1176F	Unknown	Unknown	501Y & 484K: ↑↑↑	+	+
B.1.617.2	Delta	India	T19R, del157-158, L452R, T478K, D614G, P681R, D950N	↑	↑	501Y: ↑	+	-
B.1.1.529	Omicron	South Africa	A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F, Δ69-70, Δ143-145, Δ211, ins214EPE)	↑	Unknown	501Y↑	Unknown	Unknown

*↑ means high

Variants of Interest (VOI) of SARS-CoV-2

1. B.1.427 or 20C/S:452R (VOI-Epsilon)

The B.1.525 was reported first in the United States/Nigeria in December 2020. It contains the Spike mutations A67V, 69del, 70del, 144del, E484K, D614G, Q677H, and F888L. Potential reduction in neutralization by some mAb antibodies, as well as convalescent and postvaccination sera (Jangra et al., 2021), are characteristic of this virus's variant.

2. B.1.429 or 20C/S:452R (VOI-Epsilon)

The B.1.429 or 20C/S:452R variant first emerged in the United States in March 2021. It contains the Spike mutations S13I, W152C, L452R, and D614. The effect of these mutations on the transmissibility and neutralization by convalescent and post-vaccination sera is similar to the B.1.427 variant (Deng et al., 2021).

3. B.1.526 variant (VOI-Iota)

The B.1.526 or GH 20C/S:484K also emerged in the United States in October 2020. It contains the Spike L5F, T95I, D253G, E484K, D614G, and A701V mutations. Due to the presence of E484K, these viruses might exhibit a reduction in neutralization by convalescent and post-vaccination sera (Jangra et al., 2021).

4. B.1.617.1 variant (VOI-Kappa)

The B.1.617 or UI-21APR-01 or G/452R.V3 or 21A/S:154K variant also emerged in India in April 2021, and three distinct lineages were described (ECDC, 2021; PHE, 2021; WHO, 2021b). The B.1.617.1 (VOI-Kappa) variant is defined by the Spike mutations G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H (some viruses also carry V382L). Additionally, the Spike mutations T19R, Δ157-158, L452R, E484Q, D614G, P681R, and D950N define the B.1.617.3 variant. These variants also potentially reduce neutralization by post-vaccination sera (Deng et al., 2021; Greaney et al., 2021; Yadav et al., 2021).

5. B.1.526 variant (VOI-Iota)

The B.1.527 or GH or 20C/S:484K variant was reported first in the United States (New York) in November 2020. It contains Spike L5F, T95I, D253G, S477N, E484K, D614G, and A701V mutations. These viruses showed reduced susceptibility to bamlanivimab and etesevimab mAb combinations. Additionally, these viruses exhibited a reduced neutralization by convalescent and post-vaccination sera (Annavajhala et al., 2021; Garcia-Beltran et al., 2021).

6. Other VOI variants (WHO, 2021b):

- P2 (VOI-Zeta), B.1.527 or VUI-21JAN-01 or GR 20B/S.484K was reported first in Brazil in April 2020 and contained Spike mutations S477N, E484K, D614G, and V1176F.
- P3 (VOI-Theta), VUI-21MAR-02 GR 20B/S:265C was reported first in the Philippines and contained the Spike mutations del141/143, E484K, N501Y, D614G, P681H, E1092K, H1101Y, and V1176F.
- A.23.1 (not described by WHO) or VUI-21FEB-01 (+E484K) was reported first in Uganda and contains Spike mutations F157L, V367F, Q613H, and P681R.
- A.27 (not described by WHO) was reported first in France and contains Spike mutations L18F, L452R, N501Y, A653V, H655Y, D796Y, and G1219V.
- B.1.1.318 or VUI-202102/04 was reported first in the UK in Feb. 2021 and contain the Spike mutations T95I, del144/145, E484K, D614G, P681H, and D796H.

Significant mutations of SARS-CoV-2

The infection cycle initiates via the binding of SARS-CoV-2 Spike glycoprotein to host ACE2 (Othman et al., 2020). RBD, which promotes host receptor recognition and binding to the ACE2 peptidase domain, mediates the interaction making it a promising vaccine and therapeutic target. All these mutations are directly maintaining the stability of the interface. The E484K/Q mutation is located in the highly versatile loop region of the interface, N501K is located at the second point of high-affinity interaction, whereas K417N and L452R are located in a region with a lower likelihood of contact (Figure 2. E484K/Q and N501K substitutions increase the affinity of the Spike at the interface of the 501Y.V2 variant S RBD - hACE2 interaction (Leung et al., 2021; Nelson et al., 2021). All these naturally occurring mutations in the RBD have been shown to affect infectivity, human-to-human transmission, pathogenesis, and immune escape (Wan et al., 2020). *In-vitro* and *in-vivo* experiments to consider the phenotypic effects of mutant strains are needed. Furthermore, the structural analysis revealed that the two RBD mutations L452R and E484Q, found in recent Indian variant strains, may reduce specific antibodies binding capacity compared to the wild-type strain (Cherian et al., 2021).

According to a recent study, the L452R mutation reduced or eliminated neutralizing activity of mAb (McCallum et al., 2021), demonstrating that the mutation can lead to escape from HLA-24-restricted cellular immunity and can also increase viral infectivity, potentially promoting viral replication (Motozono et al., 2021). As a result, the double or triple mutant combination described in recent reports could result in neutralization escape of specific mAb that needs to be validated by further experiments. Although mutations in

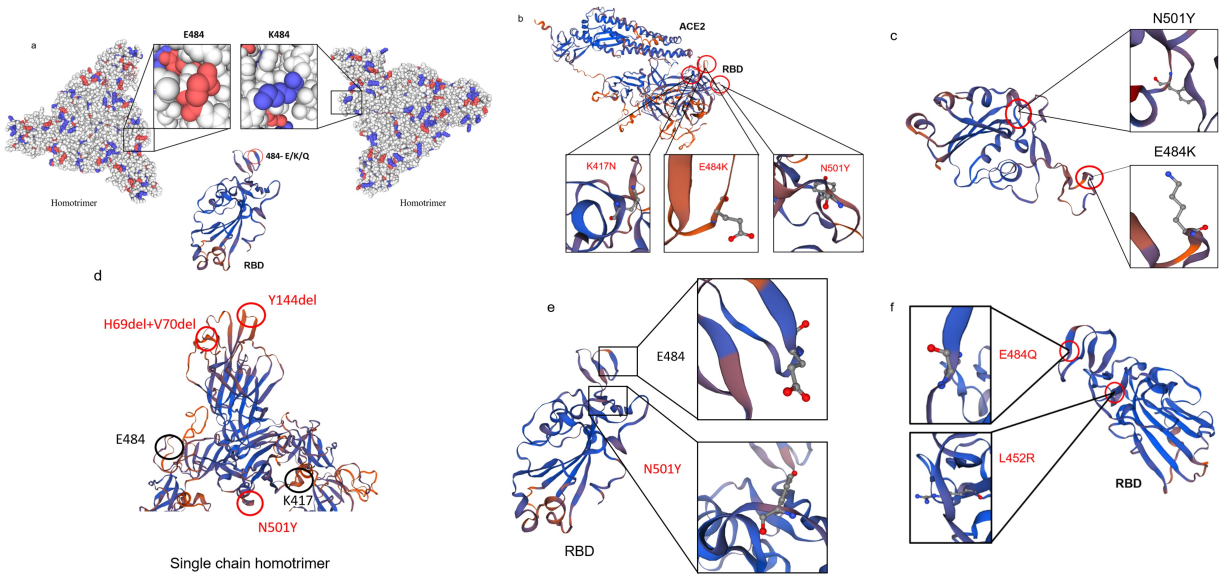

Figure 2: The conformation of different mutants in receptor binding site (RBD) that interact with ACE-2 binding. The recently observed RBD mutations (K417N, L452R, E484K/Q and N501Y) either triple/dual/single mutants were introduced and the crystal structures were created using the SwissModel and DeepView Project Mode (https://swissmodel.expasy.org/interactive) and are shown in Figure 1 (a-f). a) Surface atom representation of Spike glycoprotein homotrimer showing the negatively charged E (wild type) substituted with a positively charged K at Brazilian variant that revealed a new site for ACE2 binding. b) The K417N, E484K and N501K substitution (triple mutant) in the novel South African variant as cartoon chain conformation c) E484K and N501K substitution (dual mutant) found in the UK B.1.429 variant. d) Single chain homotrimer showing H69del, V70del, Y144del at N terminal domain in addition to N501Y single substitution interaction at RBD at B.1.1.7 variant from UK. e) Single mutant (N501Y) interaction in presence of wild type E484 at B.1.1.7 UK variant. f) Dual mutant E484Q and L452R found in the Indian variant B.1.617.1.

the Spike protein are advantageous for the virus till now, it could also make it less fit by enhancing the population-level immunity in the future. Defining virus evolution and its potential impact on vaccine effectiveness require large-scale monitoring of SARS-CoV-2 and host immunity for a long time to come.

Social challenges

Figure 3 illustrates a summary of the different ongoing challenges of COVID-19.

Public vaccination hesitancy

There is widespread doubt about the safety of the COVID-19 vaccines. This concern may be due to the rapid development of EUA approved vaccines. There are significant misconceptions related to COVID-19 among people, including: i) Severe side effects to the vaccine, ii) Integration of vaccine material into human chromosomes, iii) Use of fetal tissue in the development of the vaccine. iv) Some of the approved vaccines might introduce a microchip or nano transducer into the body.

Psychologists need to create the context in which COVID-19 vaccination, in-office care, and one's psychotherapy practices, which the psychologist discusses clearly. Doing this can help achieve higher public health and patient vaccination levels and less resistance to getting vaccinated. Several steps are essential to achieve high vaccination levels: i) Talking with positive expectations, ii) Stating one's practice procedures clearly, iii) Use active listening skills to hear the core of any patient doubts or fears, iv) Use motivational interviewing skills to correct misunderstanding and increase motivation for getting vaccinated (VandenBos, 2021). v) Including health professionals is essential among those whose opinions and attitudes are monitored, given their influence on patients' decisions, because they are also subject to uncertainty about COVID-19 vaccines (Verger et al., 2021).

Lockdown

Doctors and scientists generally recommend lockdown to control pandemics, especially in the case of the absence of a vaccine or effective treatment. WHO recommended lockdown as an emergency protocol to prevent the spread of SARS-CoV-2, only with essential supplies such as pharmacies, hospitals, banks, and grocery shops allowed opening. In Germany, social distancing and lockdown had a noticeable effect on the dynamics of the COVID-19 pandemic. Scientists reported the first case in Germany on January 27, 2020. Due to the rapid increase of COVID-19 cases, the German authorities enforced strict physical distancing guidelines banning groups of more than two people in public and shutting down some businesses.

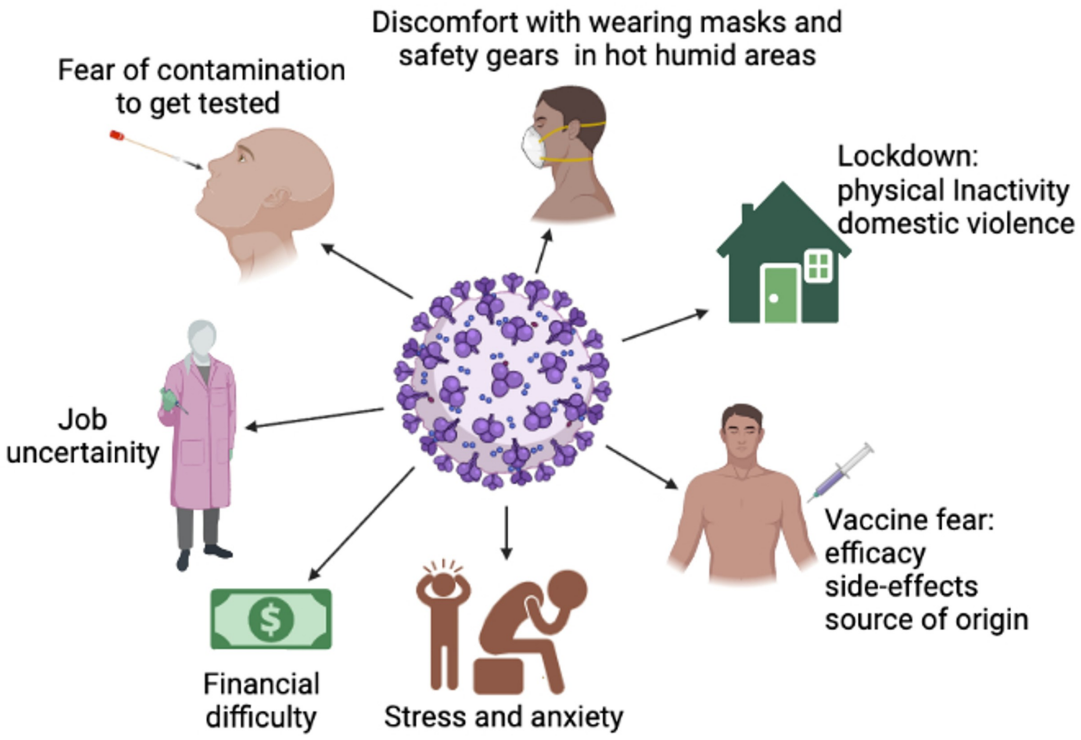

Figure 3: Challenges of COVID-19 (made with www.biorender.com)

There were no restrictions on public life till March 12, 2020, while from March 13, 2020, to April 19, 2020, a lockdown was implemented. New COVID-19 cases began to drop on April 6, 2020. Since the beginning of October, the number of new infections in Germany has increased noticeably. As a result, officials recommended a partial lockdown for Germany at the beginning of November. However, since new infections were still occurring, the lockdown measures were implemented on December 16, 2020, leading to a decline of new COVID-19 cases.

Implementation of lockdown is a significant measure to decrease the virus spread during the pandemic. However, lockdowns might cause substantial collateral health damage. Doctors found that cancer cases decreased during the first lockdown (March 12 and April 19, 2020). According to the Initiative Qualitätsmedizin (2020) (IQM, 2020), breast cancer, bladder cancer, gastric cancer, lung cancer, colon cancer, prostate cancer numbers were decreased by 13.9%, 16.5%, 18.4%, 19.8%. 23.3%, 23.1%, respectively, suggesting that cancers might have been undetected and untreated during this period. Moreover, lockdown might increase the risk of suicide due to severe stress (Reger et al., 2020). Psychologists found that the occurrence of stress, anxiety, and depression increased during the COVID-19 pandemic (Salari et al., 2020). They assessed the impact of the COVID-19 pandemic and the protective measures during the first wave on mental health and self-rated general health (Peters et al., 2020).

They found that depressive and anxiety-related diseases increased relative to baseline in participants less than 60 years of age, particularly young women. The moderate to severe depressive symptoms increased from 6.4% to 8.8%, especially in the young population. Additionally, COVID-19-pandemic significantly worsens mental health, as presented in psychometric scores. Generalized anxiety, depressive symptoms, and perceived distress elevated in individuals with mental illness; these individuals seem to be less affected by explicit COVID-19-related fear than the general population or individuals with chronic somatic diseases (Bäuerle et al., 2020). Moreover, social isolation due to lockdown increased physical inactivity, stress, and, consequently, adverse changes in body composition, cardiorespiratory capacity, muscle strength, physical functionality, and vascular events (Ruberti et al., 2021). These negative impacts highlighted the need to consider all aspects of physical and mental health while controlling COVID-19 (Kampf and Kulldorff, 2021). Moreover, a home-based training protocol could be an effective strategy to remain physically active and safe at home (Ruberti et al., 2021).

Additionally, officials should consider the unprecedented economic disaster and the increased unemployment due to the COVID-19 lockdown. Several arguments have been advanced against lockdown during the COVID-19 pandemic. The main arguments include that stay-at-home orders are unnecessary, illegal, unpopular, unenforceable, and worse than pandemic it-

self. However, strict measures are necessary to slow down this pandemic. Otherwise, this situation triggers the intensive care units to be at their maximum level in these countries.

On the other hand, strict lockdowns are enforceable only in those countries that can provide some economic assistance to the needy during lockdowns, when work and salary are not available. In most low-income countries (LICs) and low-middle-income countries (LMICs), there is no compensation for lost incomes, and a substantial number of people depend on their manual labor to earn their daily income. Since there is no social safety net for people in these countries, the efficacy of lockdowns is debatable, and lockdowns are practically unenforceable. A report on low and middle-income residents of Dhaka city, Bangladesh, found that only 11% maintained economic savings, and 75% said they would not be able to survive the lockdown-induced economic shock beyond one month (LightCastle-Partners, 2020).

Challenges related to the development and efficacy of therapeutics

Even after eighteen months following the emergence of SARS-CoV-2, there has been no discovery of conventional medicines, which can prove to be used to control the virus. Instead, even as of this date, scientists are not so sure that they know all the routes of viral transmission; conspiracy theories are abounding as to whether the virus has been 'laboratory-made' or natural. The conventional medicines advocated for the treatment of COVID-19 therapy are stop-gap treatments and primarily symptomatic. Scientists need to discover the ideal anti-SARS-CoV-2 yet.

Comorbidity

Comorbidities in people can lead to a weakened ability to fight infections, making such people more susceptible to being infected with COVID-19. Patients with COVID-19 with underlying comorbidities such as hypertension and diabetes mellitus and the elderly have more chances of their disease progressing to more severe conditions and eventually death (Sanyaolu et al., 2020; Wang et al., 2020). A meta-analysis study with 1786 COVID-19 patients with a mean age of 41 years showed that the significant comorbidities were hypertension (15.8%), cardiovascular and cerebrovascular conditions (11.7%), and diabetes mellitus (9.4%) (Paudel, 2020). CDC has reported that people with "diabetes; hypertension; lung, liver, and kidney disease; cancer patients on chemotherapy; smokers; transplant recipients; and patients chronically taking steroids are at increased risk of COVID-19 infection" (CDC, 2019).

A further problem with comorbidity is the choice of drugs. In some cases, a conventional drug that may be used simultaneously against both diseases is COVID-19 and comorbidity like diabetes mellitus. For instance, besides controlling blood glucose levels, the anti-diabetic drug Metformin may also attenuate endothelial dysfunction and viral entry and subsequent infection. Recent studies have also shown that the drug has an anti-inflammatory effect against the SARS-CoV-2 induced cytokine storm and boosts immune functions (Samuel et al., 2021). On the other hand, the anti-viral drug Remdesivir, which doctors increasingly use in COVID-19 patients, cannot be used in patients with renal impairment (Adamsick et al., 2020). This poses a conundrum to the doctors treating COVID-19 patients regarding which drug to use during COVID-19 with comorbidity, when the drug(s) against the two diseases may have adverse effects and compromise one disease at the expense of bettering the other. This conundrum opens up a window for traditional medicines, a position recently endorsed by WHO.

Gut microbiome dysbiosis in COVID-19

While SARS-CoV-2 primarily causes lung infection through the binding of ACE2 receptors expressed on the alveolar epithelial cells (Zhou et al., 2020), earlier studies have reported that the intestinal epithelial cells of the small intestine also express ACE2 receptors and might be another target for this virus (Dhar and Mohanty, 2020; Leung et al., 2003). These studies somehow explained the detection of SARS-CoV-2 RNA fragments in stool samples of COVID-19 patients (Wu et al., 2021), along with the observation that gastrointestinal symptoms, such as vomiting, diarrhea, or ulcerative colitis throughout different phases of the disease (Villapol, 2020). Interestingly, patients with gastrointestinal symptoms had more severe respiratory disorders (Wan et al., 2020), which indicated an association between microbial dysbiosis and SARS-CoV-2 infection.

Scientists define dysbiosis as any disturbance to the composition of resident commensal microbial communities relative to the community found in healthy individuals (Petersen and Round, 2014). Typical phenotypes would include the decreases in microbiome diversity and functions (de Oliveira et al., 2021; Zhang et al., 2021) or the decline in beneficial microbes such as Lactobacillus and Bifidobacterium under disease situations (Din et al., 2021). It remains to be determined whether there are "real" compositional or functional changes in the gut microbiome during COVID disease, given the limited number of studies in the air, notably that not all of them included convincing sample sets or proper controls. Scientists reported a higher abundance of *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii* in fecal samples from people with high SARS-CoV-2 infectivity, while people with less virus load were found enriched with short-chain fatty acids producing bacteria

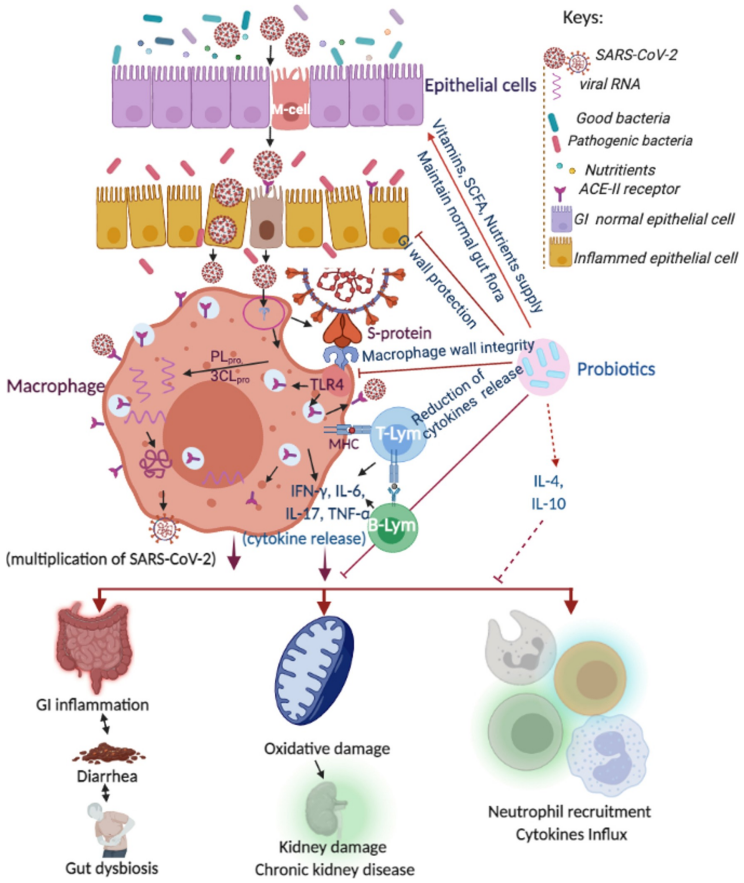

Figure 4: Potential role of probiotics against COVID-19 infection (made with www.biorender.com).

such as *Parabacteroides merdae*, *Bacteroides stercoris*, and *Lachnospiraceae* (Zuo et al., 2020b). Alternatively, the baseline abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* were reportedly correlated with the severity of the COVID-19. At the same time, an anti-inflammatory bacterium, *Faecalibacterium prausnitzii*, was inversely related to the disease's progress (Zuo et al., 2020a). The change in microbial composition could precipitate in the progression of COVID-19 via the bidirectional immunomodulation between the respiratory mucosa and the gut microbial community, known as the gut-lung axis (Budden et al., 2017; de Oliveira et al., 2021).

However, it should be noted that while compositional changes signify dysbiosis, they do not necessarily result from the effects of SARS-CoV-2 or a definite offshoot of COVID-19. Dysbiosis in COVID-19 (in all the heterostasis-causing diseases) exacerbated inflammation or weakened the regulation of anti-inflammatory reactions in the gut environment. Inflammatory response induction in SARS-CoV-2 in the gut is possible since SARS-CoV-2 vRNA has been detected in feces. As a result, it could eventually contribute to the mass inflammation during the later phase of COVID-19, where the gastrointestinal symptoms ameliorated, acute respiratory distress syndrome appeared followed by cytokines storm that affected multiple systems (Villapol, 2020; de Oliveira et al., 2021).

Potential use of probiotics in COVID-19 treatment

Among various therapeutic options against COVID-19, doctors propose probiotics as a supplement in some places (Jin et al., 2020). Figure 4 shows the potential role of probiotics against COVID-19 infection. Probiotics have their potential in terms of restoring a healthy gut microbiome (Hemarajata and Versalovic, 2013), boosting the anti-inflammatory reacts (Kekkonen et al., 2008), enhancing epithelial barrier function (Ohland and Macnaughton, 2010), or strengthening anti-viral effects of other treatments (Anwar et al., 2021).

Scientists report that the application of probiotics decreases inflammatory factors such as IL-6 and C-reactive protein (Morshedi et al., 2019) or reduces the systemic pro-inflammatory biomarkers in models of autoimmunity (Plaza-Díaz et al., 2017). Similarly, clinical works have proven that supplementation of probiotics during virus infections such as influenzas was effective in immunity enhancement and inflammation amelioration (D'Angelo et al., 2017; Kechaou et al., 2013; Kekkonen et al., 2008; Leyer et al., 2009; Morshedi et al., 2019). In human immunodeficiency virus (HIV) infections, probiotic administration, mainly Lac-

tobacillus rhamnosus, showed protective effects on the gut epithelial surface and were correlated with the increase of CD4+ cell (Irvine et al., 2010). The successful implementation of probiotics in virus infections could be a valuable reference for their potential applications against COVID-19 related inflammation.

In addition to suppressing inflammation and improving the gut immune responses, probiotics also can act indirectly as anti-viral. In brief, probiotic bacteria, such as *Lactobacilli* and *Bifidobacteria*, produce bacteriocins – peptides with anti-microbial properties that are effective against various intestinal viruses (Dobson et al., 2012). *Lactococcus lactis* strain JCM 5805 was found with the potency to directly stimulate plasmacyotoid dendritic cells via toll-Like receptor 9 (Suzuki et al., 2016), which in turn boosts interferon production and control viral replication and spread (Akour, 2020; Kanauchi et al., 2018). The effect of probiotic strain *Bacillus subtilis* was identified against the influenza virus by producing a new peptide, P18, which exhibited complete inhibition of the virus *in-vitro* and significant anti-viral effect in mice (Starosila et al., 2017).

A recent study using computational predictions showed that bacteria of *Plantaricin* genera produced metabolites that targeted ACE2, which could competitively block this receptor when the SARS-COV2 virus was present (Anwar et al., 2021). These shreds of evidence would indicate promising therapeutic applications of probiotics to alleviate COVID-19 and its associated inflammatory tangles, either through its anti-inflammatory potential or direct participation in the battle against the SARS-CoV-2 virus.

The local immunity in the gut environment is also dependent on the equilibrium of the gut microbiota, while an impaired mucosal barrier and dysbiosis may deteriorate the inflammation, thus favoring the progression of infections. Therefore, the mediation of gut microbiota using probiotics is expected to be a promising therapeutic approach for tailoring COVID-19 symptoms via modulating gut-lung axis immunity, restoring homeostasis, and direct anti-viral potency. As a result, further studies are still required to unravel the efficacy of these microbial-based interventions in well-designed randomized controlled clinical trials to establish their efficacy and safety.

Challenges in low- and middle-income countries

Challenges in Implementing Surveillance Tools of High-Income Countries (HICs) in Low Middle-Income Countries (LMICs) include: i) Development of potential vaccine candidates to provide protection and interrupt the transmission of SARS-CoV-2, ii) To ensure enough supplies for hospitals and their homogeneous distribution among the countries with the highest numbers of severe cases, iii) There is a need for more studies to identify potential treatments that are effective for the control of this viral infection.

Scientists may add to these studies recognition of various 'stressors' arising from long-term confinement at home, loss of employment, lack of adequate finances, and a sense of uncertainty arising from lack of knowledge about when scientists can control the virus, and this pandemic will end. COVID-19 patients and relatives or friends face the additional stress of treatment costs and the uncertainty of whether a close one will live or die. Psychosomatic stress can be a factor leading to other bodily stresses in relatives, friends, and well-wishers of a COVID-19 patient and can lead to the development of comorbidities in the patient himself or herself.

Conclusions

Although scientists have tried to control the COVID-19 pandemic, the situation is still critical due to several global control strategy challenges. It is vital to investigate the epidemiological situation of SARS-CoV-2 variants worldwide; whole-genome sequencing must be used continuously in the future in order to detect further, previously unknown, emerging, or introduced SARS-CoV-2 variants. Still, there is an urgent need to develop/improve efficient and safe anti-viral drugs and vaccines. In addition, nations across the globe must cooperate in combating COVID-19 and be prepared for future pandemics.

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