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REVIEW ARTICLE

COVID-19: An update with future urgent priorities and a case study of repurposing drug design

Juliana Silva Novais[1,2], Reinaldo Barros Geraldo[2], Camila Ferreira Mattos[1,2], Victor Gustavo Oliveira Evangelho[2,3], Aldo Rodrigues da Silva[1,2], Nayra Cordeiro da Conceição[2], Marcos da Veiga Kalil[2], Lúcio Mendes Cabral[4], Norman Arthur Ratcliffe[3,5], Carlos Rangel Rodrigues[3,4,*], Helena Carla Castro[1,2,3,*]

[1] *Programa de Pós-graduação em Patologia, Hospital Universitário Antônio Pedro, Universidade Federal Fluminense, Niterói-RJ 24033-900, Brazil*

[2] *Laboratório de Antibióticos, Bioquímica, Ensino e Modelagem Molecular, Universidade Federal Flumi-nense, Niterói-RJ 24210-201, Brazil*

[3] *Programa de Pós-graduação em Ciências e Biotecnologia, Instituto de Biologia, Universidade Federal Fluminense, Niterói-RJ 24210-130, Brazil*

[4] *Laboratório de Modelagem Molecular & QSAR (ModMolQSAR), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro 21941599, Brazil*

[5] *Swansea University, Swansea 821140809, United Kingdom*

*** Correspondence author:** Carlos Rangel Rodri-gues, rangelfarmacia@gmail.com; Helena Carla Castro, hcastrorangel@yahoo.com.br

ABSTRACT

SARS-CoV-2 is highly transmissible and pathogenic, with nearly 6.5 million infected people dying worldwide. A severe acute respiratory syndrome is one of the primary COVID-19 outcomes, often related to bacterial co-infections. In addition, infective variants of SARS-CoV-2 have constantly emerged in different countries, causing recurrent waves of infection. These variants increase the chances of vaccine failure, even in countries with accelerated vaccination programs, such as Israel and the USA. In this brief review, the subjects addressed include aspects of the SARS-CoV-2 variants, vaccines, drug therapy, and new alternative therapies. Finally, this review also discussed articles that addressed the repositioning of drugs against the SarsCov2 MPro enzyme using in silico approaches. In addition, we discussed the repositioning of drugs in silico, which can be a valuable strategy to guide and optimize the selection of elective compounds already approved for human use. Bearing in mind that few drugs, such as nirmatrelvir, ritonavir (Paxlovid), molnupiravir, and some monoclonal antibodies, have received authorization throughout the COVID-19 pandemic, according to Food and Drug Administration guidelines.

Keywords: COVID-19; variants; vaccination; anti-viral drugs; off-label drugs

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1. Introduction

In December 2019, mysterious pneumonia in the city of Wuhan was detected in China, starting the most serious pandemic of the 21st century. The clinical conditions of infected patients quickly evolved into severe acute respiratory syndrome (SARS-CoV-2), leading to a high rate of lethality[1,2].

SARS-CoV-2 showed high and deadly transmissibility, with nearly 6.9 million infected people dying worldwide[3]. As a result, the World Health Organization (WHO, https://covid19.who.int/) announced the Coronavirus Disease 2019 (COVID-19) as a global pandemic[4]. Since then, this virus has led to this current worldwide tragedy in which even the so-called developed countries, such as the UK, USA, and Germany, were not spared[5].

Although vaccine development has dramatically reduced the number of deaths worldwide, SARS-CoV-2 still poses a public health risk. The WHO recently warned of the risk of a new COVID-19 outbreak worldwide due to new variants of SARS-CoV-2 that continue to accumulate new mutations in their genetic material. This alert was followed months later by an epidemic in France, where a subvariant of Omicron already accounts for 35% of new infections. This underscores the need for further studies that can contribute to the ongoing fight against this virus[6,7].

This emergency situation led the WHO to form a group of scientists called the "Technical Advisory Group on Virus Evolution" (TAG-VE). The WHO COVID-19 Reference Laboratory Network was also created and consisted of representatives from GISAID, Next Strain, and Pango[8]. TAG-VE formulated several terms to understand the adaptations and effects of the SARS-CoV-2 variants arising as a result; variants were divided into variants of interest (VOI), variants being monitored (VUM), variants of concern (VOC), and formally monitored variants (FMV)[5,9].

The transmission of infectious diseases depends on three main factors: i) the source of infection, ii) the transmission routes, and iii) the susceptible hosts[8]. The fourth factor, the environmental temperature, was indicated in silico analysis[9] and revealed a correlation of temperature with COVID-19 disease transmission. A temperature of 16.92 °C is the most critical, as it is the point at which the infection rate is highest. This result suggests that ambient temperature may aid in the transmission process of the ongoing COVID-19 pandemic worldwide[10].

Herein, we briefly critically review several aspects of COVID-19, including SARS-CoV-2 variants, vaccines, and antiviral drugs, and the risk of using antibiotics in therapeutic protocols against secondary/co-infections leading to the emergence of new resistant bacterial strains and the failure of treatments. In addition, this work also discusses the continued demand for new treatment options, which include effective SARS-CoV-2 antivirals.

2. Methods

2.1. Bibliographic review

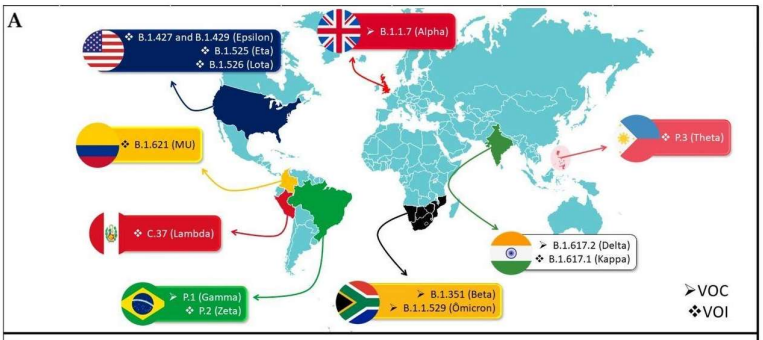
Web of Science, Medline, the World Health Organization (WHO), and the Centers for Disease Control and Prevention (CDC) Websites were searched for relevant publications, and the most recent articles were utilised. PubMed citation indices were also followed in relevant key reference papers to allow the construction of the review of the subject using the keywords SARS-CoV-2, coronavirus, mutant, antibiotics, vaccine, and therapy.

Results

SARS-CoV-2 and variants, in silico approaches:

SARS-CoV-2 is an enveloped RNA virus belonging to the Coronaviridae family and order Nidovirales. The two previous known β-CoVs, SARS-CoV and MERS-CoV, cause severe and potentially fatal infections in the respiratory tract. Genome studies showed that the SARS-CoV-2 genome sequence is 96.2% identical to the Bat coronavirus RaTG13 CoV, a SARS-like betacoronavirus, and 79.5% identity with SARS-CoV[11,12].

WHO recommended the use of letters of the Greek alphabet (e.g., Alpha, Beta, Gamma, and Delta) for designating the variants of previous VOCs[8] (**Figure 1**). The VOC term determined several variants of SARS-CoV-2 identified in England, South Africa, Brazil, and India and classified as alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and Omicron (B.1.1.529) variants, with high transmissibility in the community[13] (**Figure 1**).



C

3D-Colour	SARs-COV-2 VARIANTS					MUTATION
	Alpha	Beta	Gamma	Delta	Ômicron	CHARACTERISTICS
	(B.1.1.7)	(B.1.351)	(P.1)	(B.1.617.2)	B.1.1.529	
Orange	H69del*, V70del(69), N501Y, D614G	L18F(20), L242del, A243del, L244del, K417N, E84K, N501Y, D614G	L18F(20), K417T, E484K, N501Y, D614G	L452R, T478K, D614G, P681R(674)	H69del, V70del (69), G339D, S371L, S373P, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, D614G, P681H(674), R682G(674), R683S(692), R685S(692)	Interfere with the host cell receptor binding or antigenicity
Blue	A570D,P681H(674), T716I, S982A, D1118H	D80A, D88H, D215G, H245Y, A701V	P26S, D138Y, T1027I	T95I, G142D, D950N	A67V, T95I, G142D, L212I, S375F, T547K, H655Y, N679K(674), N764K, D796Y, N856K, Q954H, N969K, L981F	Identified in more than 100 samples and of epidemiological interest
Cyan	Y144del(143)	-	-	-	V143del, Y144del(143), Y145del(143), N211del, ins214EPE	Insertion or deletion in the original sequence
Magenta	-	-	T20N	T19R(20)	-	Remove or create potential glycosilation sites

Figure 1. The best-known SARS-CoV-2 variants are Alpha, Beta, Gamma, Delta, and Omicron, classified as Variants of Concern (VOC), and Epsilon, Zeta, Eta, Theta, MU, Lota, Kappa, and Lambda, classified as Variants of Interest (VOI). **A)** Countries from which the earliest documented variants were detected (The figure uses vectors verified by Smart.Servier, available under creative commons 3.0 license); **B)** Location of the mutations in the spike protein from SARS-COV-2 variants by using the ViralZone expasy tool. Each color indicates the mutations in the trimeric structure of the Spike protein detailed in the C) part of this figure. The SARS-CoV-2 spike glycoprotein and ACE2 complex deposited in Protein Data Bank (PDB = 6ACC) was used as the three-dimensional (3-D) structure template, whereas the mutations were based on the FASTA sequences predicted using GISAID and the CoVsurver tool; **C)** Comparison of the Spike protein mutations, including the amino acid residues, number location, and characteristics identified for each variant. *del = deleted amino acid.

On November 26, 2021, the TAG-VE convention officially reported a novel SAR-CoV variant (B.1.1.529)[14]. It was the first infection detection described from a specimen collected on 9 November 2021, from South Africa[11]. WHO has designated B.1.1.529 as a VOC with the name Omicron[11]. The Omicron variant (B.1.1.529) is the variant that has the highest number of mutations among all VOCs so far, which paves the way for greater transmissibility and partial resistance to immunity induced by COVID-19 vaccines[15].

The result of mutations in SARS-CoV-2 produced variability in virulence, which seriously impacted global public health. Changes in virus transmission have been studied, described, and shown to be increased for the Alpha, Beta, Gamma, and Delta variants, with 29%, 25%, 38%, and 97% higher transmissibility, respectively[16]. The Omicron variant is even more transmissible, and due to this ability, it has become globally dominant **(Figure 2**).

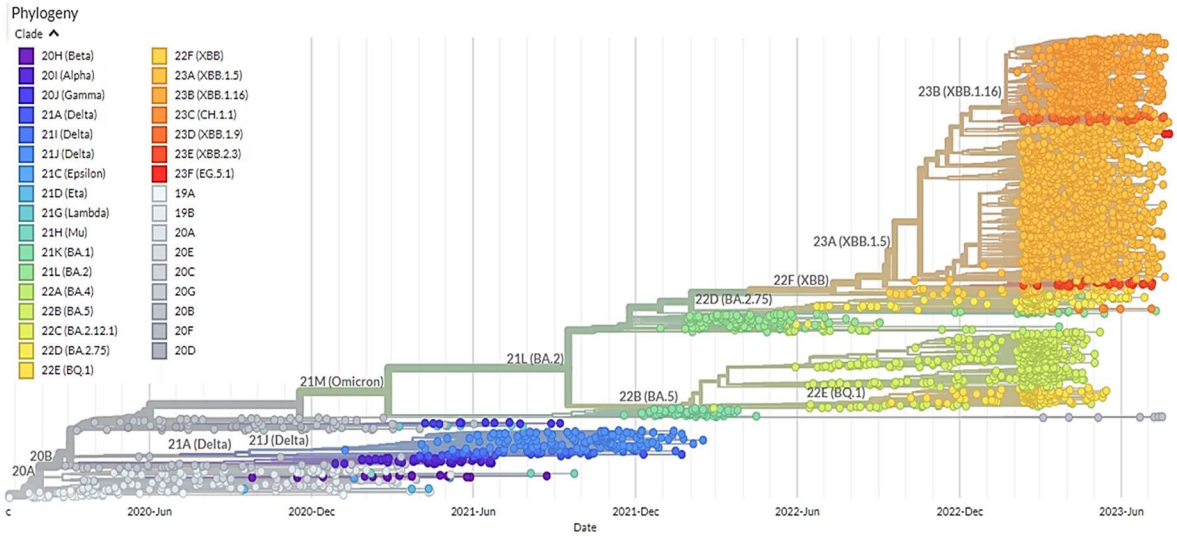


Figure 2. Phylogenetic analysis extracted from the Nextrain tool. The phylogenetic representation is organised by the number of mutations identified in the genomes of each viral variant, representing real-time tracking of pathogen evolution from December 2019 to June 2023. In addition, each new clade is represented by a colour[17].

The Omicron (B.1.1.529) and other sub-variants with the highest number of mutations among all VOCs so far, resulting in greater transmissibility and partial resistance to immunity induced by COVID-19 vaccines[15,18]. Other variants have alert mutations that are being studied. In addition, host genetic variances may impact the susceptibility to milder, moderate, or severe COVID-19 infections (**Table 1**).

Table 1. Summary of updates on SARS-CoV-2 variants.

Authors	Title	Abstract
Liu et al.[19]	The N501Y spike substitution enhances SARS-CoV-2 infection and transmission.	The research concluded that the N501Y substitution recapitulated the viral transmission phenotype, suggesting that it is an important determinant of the increased transmission of the Alpha variant. Mechanistically, the N501Y substitution increased the affinity of the viral spike protein for cellular receptors.
Prathiviraj et al.[20]	Identification of genotypic variants and its proteomic mutations of Brazilian SARS-CoV-2 isolates.	The genotypes of three isolates such as Bra/1236/2021 (G15), Bra/MASP2C844R2/2020 (G11), and Bra/RJ-DCVN5/2020 (G9) have a single mutant in NSP4 (S184N), 2'O-Mutase (R216N), membrane protein (A2V), and Envelope protein (V5A). A mutation in RdRp of SARS-CoV-2, particularly the change from Pro to Leu-at 323 resulted in stabilization of the structure at BRA/CD1739-P4/2020. The protein mutants NSP4, NSP5 are most virulent in genotype 15 and 16. A rapid folding rate of the protein alters structural stability and leads to escape to current antivirals.
Johnson et al.[21]	Nucleocapsid mutations in SARS-CoV-2 augment replication and pathogenesis.	The R203K+G204R mutation was found to be sufficient to enhance the replication, fitness, and pathogenesis of SARS-CoV-2. The R203K+G204R mutant corresponds to increased viral RNA and protein both in vitro and in vivo. The R203K+G204R mutation increases nucleocapsid phosphorylation and confers resistance to GSK-3 kinase inhibition, providing a molecular basis for increased virus replication.

Table 1. (*Continued*).

Authors	Title	Abstract
Giron et al.[22]	Differences between Omicron SARS-CoV-2 RBD and other variants in their ability to interact with cell receptors and monoclonal antibodies.	Of the 32 binders studied, clusters of mAbs with weak to strong binding affinities (e.g., S2K146) were identified. These mAbs with strong binding capacity and especially their combination are amenable to experimentation and clinical trials due to their predicted high binding affinities and possible neutralization potential for currently known virus mutations and a universal coronaviru
Posani et al.[23]	Temporal evolution and adaptation of SARS-CoV-2 codon usage.	The genes encoding the N and S proteins were found to have diverged most rapidly since the outbreak through accumulation of mutations. All genes show a deoptimization of their codon usage relative to the human host. The findings suggest a general evolutionary trend of SARS-CoV-2 evolving toward a suboptimal codon utilization bias to favor host survival and spread. In addition, we found that the S and RdRp proteins are more subject to increasing purifying pressure over time, implying that these proteins will achieve a lower tendency to accept mutations.
Vadgama et al.[24]	SARS-CoV-2 Susceptibility and ACE2 Gene Variations Within Diverse Ethnic Backgrounds.	We identified a variant (rs2285666) associated with increased ACE2 expression with an over-representation in SARS-CoV-2 positive patients relative to 100KGP controls ($p = 0.015$), and in European hospitalized patients relative to outpatients in intra-ethnic comparisons ($p = 0.029$). The eQTL rs12006793 had the largest effect size ($d = 0.91$), which decreases ACE2 expression and is more prevalent in controls, thus potentially reducing the risk of COVID-19. We identified three new non-synonymous variants predicted to alter ACE2 function, and showed that three variants (p. K26R, p. H378R, p. Y515N) alter the affinity of the receptor for the viral Spike (S) protein.
Markosian et al.[25]	Genetic and Structural Analysis of SARS-CoV-2 Spike Protein for Universal Epitope Selection.	The amino acid sequence of the C662-C671 epitope has been found to be entirely conserved in the major SARS-CoV-2 variants observed, in addition to SARS-CoV. Its conformation and accessibility are predicted to be conserved even in the highly mutated Omicron variant. The costly mutation rate in the context of energy expenditure in genome replication and translation may explain this strict conservation. These observations may herald an approach to developing vaccine candidates for universal protection against emerging coronavirus variants.
Alkhatib et al.[26]	Update on SARS-CoV-2 Omicron Variant of Concern and Its Peculiar Mutational Profile.	The definitions and functional characterizations of the mutations that characterize Omicron VOCs were provided. Such mutations, residing mostly in the receptor binding domain, could play a key role in increasing the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (increasing binding affinity for ACE2), compromising spike recognition by therapeutic and vaccine-induced antibodies and causing diagnostic assay failure. To our knowledge, this is one of the first comprehensive descriptions of the newly emerging mutations underlying the Omicron VOC and their biological and clinical implications.
Nunes et al.[27]	Deep phylogenetic-based clustering analysis uncovers new and shared mutations in SARS-CoV-2 variants as a result of directional and convergent evolution.	In this study we described sites with shared mutations under directional evolution in the SARS-CoV-2 spike-encoding protein of VOC and VOI, tracing a described correlation with viral spread in South America, India, and the USA.
Kronstein-Wiedemann et al.[28]	SARS-CoV-2 Infects Red Blood Cell Progenitors and Dysregulates Hemoglobin and Iron Metabolism.	The precursors express the ACE2 receptor and CD147 on the fifth day of differentiation, which makes them susceptible to SARS-CoV-2 infection. qPCR analysis of differentiated RBCs revealed increased mRNA expression levels encoding for hepcidin, which inhibits iron uptake. COVID-19 patients showed impaired hemoglobin biosynthesis, increased zinc-protoporphyrin IX formation and others. It is suggested that SARS-CoV-2-induced dysregulation in hemoglobin and iron metabolism contributes to the severe systemic course of COVID-19. This opens the door to new diagnostic and therapeutic strategies.
Martinez-González et al.[29]	SARS-CoV-2 Point Mutation and Deletion Spectra and Their Association with Different Disease Outcomes.	The location of amino acid substitutions in the three-dimensional structures of nsp12 (polymerase) and S suggest significant structural or functional effects. Thus, patients who develop mild symptoms may be a richer source of SARS-CoV-2 genetic variants than patients with moderate or severe COVID-19.
Sonnleitner et al.[30]	The mutational dynamics of the SARS-CoV-2 virus in serial passages in vitro.	The results identified a number of adaptive genetic alterations ranging from single convergent substitution mutations and previously undescribed insertions. The region encoding for the spike proved to be a mutational hotspot, evolving a number of mutational changes including the already known substitutions at positions S:484 and S:501.
Pellegrina et al.[31]	Human phospho-signaling networks of SARS-CoV-2 infection are rewired by population genetic variants.	It was concluded that SARS-CoV-2 infection diverts signaling pathways and induces protein-protein interactions between human and viral proteins. Human genetic variation may impact SARS-CoV-2 infection and COVID-19 pathology
Ahamad et al.[32]	Insights into the structure and dynamics of SARS-CoV-2 spike glycoprotein double mutant L452R-E484Q.	This study employed various computational algorithms and methods to understand the structural impact of both individual L452R, E484Q variants, and the L452R-E484Q double mutant on the native RBD of the spike glycoprotein. The comparative results of MD simulation parameters showed that the double mutant induces significant conformational changes in the RBD glycoprotein peak, which may alter its biological functions.

Table 1. (*Continued*).

Authors	Title	Abstract
Quaranta et al.[33]	SARS-CoV-2 intra-host evolution during prolonged infection in an immunocompromised patient.	Sequencing of nasopharyngeal swabs at three time points demonstrated dynamic changes in the viral population, with the appearance of 26 amino acid mutations and two deletions, 57% of which were in the Spike protein. The data confirm that persistent infection in certain immunocompromised individuals for a long time may favor the dangerous appearance of new SARS-CoV-2 variants with immune evasion properties.
Mykytyn et al.[34]	Antigenic cartography of SARS-CoV-2 reveals that Omicron BA.1 and BA.2 are antigenically distinct.	Omicron BA.1 and BA.2 evolved as two distinct antigenic outliers. The data show that BA.1 and BA.2 escape vaccine-induced antibody responses as a result of different antigenic characteristics. Thus, antigenic mapping could be used to evaluate the antigenic properties of future SARS-CoV-2 variants that emerge and to decide on the composition of new spike-based vaccines.
Talotta et al.[35]	Sequence complementarity between human noncoding RNAs and SARS-CoV-2 genes: What are the implications for human health?	A total of 252 matches were found between the nucleotide sequence of SARS-CoV-2 genes and human ncRNAs. With the exception of two small nuclear RNAs, all of them were long noncoding RNAs (lnc)RNAs expressed mainly in testis and the central nervous system under physiological conditions. This in silico study shows that SARS-CoV-2 genes have nucleotide complementarity with human ncRNA sequences, potentially disrupting the epigenetic control of ncRNA of the target genes.
Zhang et al.[36]	Impact of natural selection on global patterns of genetic variation and association with clinical phenotypes at genes involved in SARS-CoV-2 infection.	In ACE2, we identified 41 nonsynonymous variants that were rare in most populations, several of which impact protein function. However, three nonsynonymous variants (rs138390800, rs147311723, and rs145437639) are in haplotypes that exhibit positive selection signatures. This signature impacts variation in regulatory regions influencing ACE2 expression in multiple African populations. The study provides insights into global variation in host genes related to SARS-CoV-2 infection, which have been shaped by natural selection in some populations, possibly due to previous viral infections.
Uddin et al.[37]	Genomic diversity and molecular dynamics interaction on mutational variances among RB domains of SARS-CoV-2 interplay drug inactivation.	Phylogenetic analysis, evolutionary modeling, substitution pattern analysis, molecular docking, dynamic simulation, etc. were performed. The genomic sequences showed >99% similarity to the reference sequence from China. In addition, three mutations in the RBD domain, Val/ Phe367, Val/ Leu 382 and Ala/ Val522, were discovered in the genomes of the Netherlands, Bangladesh and the USA, respectively. The molecular and dynamic docking study showed that the RBD with Val/Leu382 mutation had the lowest binding affinity with remdesivir. In conclusion, the SARS-CoV-2 genomes are similar, but varying degrees of transitions and transversions have occurred. The mutations cause significant conformational change, which is needed to be investigated during drug and vaccine development.
Yamamoto et al.[38]	Metalloproteinase-Dependent and TMPRSS2-Independent Cell Surface Entry Pathway of SARS-CoV-2 Requires the Furin Cleavage Site and the S2 Domain of Spike Protein.	Experiments with selective metalloproteinase inhibitors and gene-specific small interfering RNAS (siRNAs) revealed that a disintegrin and metalloproteinase 10 (ADAM10) is partially involved in the metalloproteinase pathway. Consistent with the finding that the pathway is unique to SARS-CoV-2 among highly pathogenic human coronaviruses, both the skin cleavage motif at the S1/S2 boundary and the S2 domain of the SARS-CoV-2 spike protein are essential for metalloproteinase-dependent entry. In contrast, the two elements of SRA-CoV-2 contributed independently to TMPRSS2-dependent S2 priming.
Patil et al.[39]	Receptor binding domain of SARS-CoV-2 from Wuhan strain to Omicron B.1.1.529 attributes increased affinity to variable structures of human ACE2.	ACE2 with the rs961360700 variant showed the lowest binding energy (–895.2 Kcal/mol) upon binding with the Phe160Ser variant RBD compared to the Wuhan RBD complex. Interestingly, the binding energy of the RBD of Omicron B.1.1.529 with the ACE2 structure (rs961360700) showed the minimum binding energy of -1010 Kcal/mol. Furthermore, molecular dynamics showed structural stability for all complexes analyzed with the RMSD (0.22–0.26Â nm), RMSF (0.11–0.13Â nm), and Rg (2.53–2.56 Â nm).
Ahmad et al.[40]	A comprehensive genomic study, mutation screening, phylogenetic and statistical analysis of SARS-CoV-2 and its variant omicron among different countries.	Of the 157 different SARS-CoV-2 strains and their variants, and their complete genome sequences from different countries, it was observed that Corona nucleoca and DUF5515 were the most conserved domains. All genomes obtained changes compared to the Wuhan-Hu-1 strain, mainly in the TRS region (CUAAAC or ACGAAC). We discovered 596 mutations in all genes, with the largest number (321) found in ORF1ab (QHD43415.1), or TRS site mutations found only in ORF7a (1) and ORF10 (2). The Omicron variant has 30 mutations in the Spike protein and has a higher alpha helix shape (23.46%) than the Delta version (22.03%). T478 was also found to be a polymorphism prevalent in the Delta and Omicron variants, as well as genomic gaps ranging from 45 to 65aa.
Hossain et al.[41]	Strategies to tackle SARS-CoV-2 Mu, a newly classified variant of interest likely to resist currently available COVID-19 vaccines.	The SARS-CoV-2 strain B.1.621 (Mu variant) showed approximately ten times greater resistance to neutralizing sera obtained from COVID-19 survivors or from people vaccinated with BNT161b2 than the parenteral B.1 strain.
Magalis et al.[42]	Low-frequency variants in mildly symptomatic vaccine breakthrough infections presents a doubled-edged sword.	Low frequency mutations were observed, which were more recently identified as mutations of interest due to their localization within targeted immune epitopes (P812L) and association with increased replication capacity (L18F).
Zguro et al.[43]	Carriers of ADAMTS13 Rare Variants Are at High Risk of Life-Threatening COVID-19.	Ultra-rare variants in a heterozygous state have been reported to lead to a rare form of COVID-19 characterized by signs of hyperinflammation, which segregates in families as an autosomal dominant disorder conditioned by SARS-CoV-2 infection, sex, and age.

SARS-CoV-2 variants present multiple mutations in the spike (S) glycoprotein. In the Delta variant, they are concentrated closer to the regions of contact with the angiotensin-converting enzyme 2, also known as the ACE2 receptor (**Figure 1B**). The Omicron variant corresponds to three lineages: BA.1, BA.2, and BA.3. The most widely prevalent strain globally is BA.1; however, BA.2 is gradually replacing BA.1 in several countries, for instance, Denmark. In contrast, BA.3 presents very limited transmissibility[15]. Omicron BA.4 and lately BA.5 have now taken over with this tremendous ability to adapt to different mutations raising fear about the effectiveness of the vaccines currently produced by different pharmaceutical industries against SARS-CoV-2[13,44,45].

An important study shows the comparison of the antibody responses against these sub-variants with the ancestral SARS-CoV-2 strain bearing the D614G mutation. The neutralizing-antibody titers were four times as low against the BA.4/5 variant and three times as low against the BA.2.12.1 variant ($P < 0.001$ for both comparisons), and approximately 2.8 times as low against the BA.1 and BA.2 variants[46].

BA.4 and BA.5 carry their unique mutations, including changes called L452R and F486V in the viral spike protein. The WHO Weekly Epidemiological Update of COVID-19 (31 week)[47] shows that BA.5 and its descendent lineages correspond to account for 74% of submitted sequences when compared to other lineages, and BA.4 represents 7.8% of submitted sequences. Three BA.5 descent lineages have the most enhanced spreads, including BA.5.1 (present in 99 countries) BA.5.2 (105 countries), and BA.5.2 (104 countries)[48].

Different mutations are involved in these variants in various viral antigen regions and proteins such as N and S proteins (Supplementary material). From one mutation to up to six amino acid deletions, this virus may adapt itself in a very specific way. Structurally, we might expect a lower infective profile, since changes occur in the amino acids` polarity profiles of these proteins but in fact, these mutations made it more infective and with a higher spreading profile.

2.2. Vaccines overview: Almost the way out

Despite simple but important preventative measures (e.g., wearing masks, physical distancing, or hygiene) to slow the pandemic, vaccines are still the most potent tool to fight COVID-19. Currently, there are 38 vaccines in use worldwide, with more than 11 billion doses of vaccine have been applied, and 11 vaccines have been granted Emergency Use Listing (EUL) by WHO. In addition, according to the WHO's COVID-19 vaccine tracker and landscape, there are 364 vaccine studies (198 preclinical and 166 clinical) in different phases involving a range of vaccine methods (**Figure 3**).

In general, there are seven types of vaccines developed to combat COVID-19, which use: (1) live attenuated virus, (2) inactivated virus, (3,4) replicating and non-replicating viral vectors; (5) plasmid DNA containing SARS-CoV-2 gene; (6) messenger RNA (mRNA) to produce the antigenic protein and (7) the antigenic protein itself without any genetic material (**Figure 3**).

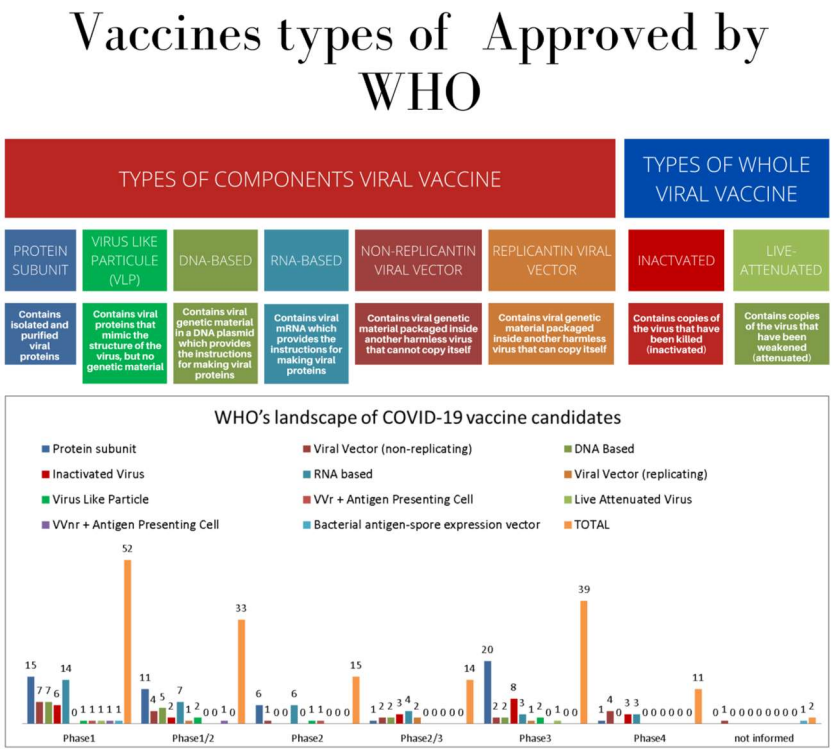


Figure 3. Schematic composition of vaccine types of formulation that received WHO approval. Inbox a WHO's landscape of covid-19 vaccines candidates. Adapted from the World Health Organization, 2023[49].

Among the main vaccines used, ten vaccines stand out, which are:

(1) AstraZeneca–University of Oxford (ChAdOx1-S [recombinant]) based on the phase 3 trials, the AstraZeneca vaccine against COVID-19 has an efficacy of 72% (95% CI: 63–79%) against symptomatic SARS-CoV-2 infection[50,51].

(2) Johnson and Johnson's/Janssen COVID-19 vaccine (Ad26.COV2.S) shows in the Phase 3 efficacy trial that a single dose of Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration efficacy of 67% (adjusted 95% confidence interval CI: 59–73) and at least 28 days after administration efficacy of 66% (adjusted 95% CI: 55–75). Vaccine efficacy against severe-critical Covid-19 was 77% (adjusted 95% CI: 55–89) for onset at ≥14 days and 85% (adjusted 95% CI: 54–97, for onset at ≥28 days)[52,53].

(3) Moderna vaccine (mRNA-1273) showed efficacy in preventing COVID-19 of any severity of COVID-19 of 94%. In adolescents aged 12–17 years (phase 2/3 trial of mRNA-1273), it showed that the vaccine was well tolerated, immunogenic, and efficacious presenting an efficacy against symptomatic illness was 93%[54].

(4) Pfizer BioNTech vaccine (BNT162b2) presents in the randomized trial of the vaccine, a two-dose regimen of BNT162b2 given 21 days apart conferred 91% protection. Additional studies were performed on children and adolescents. A trial in adolescents aged 12–15 years showed a vaccine efficacy against symptomatic SARS-CoV-2 infection of 100% (95% CI 75–100%) from 7 days after dose 2. Children aged 5–11 years showed similar immunogenicity and reactogenicity as young adults. In children aged 6 months to 4 years vaccine efficacy reveals after 7 days after dose 3 was 80.0%.

(5) Sinopharm vaccine has shown that 2 doses have an efficacy of 79% (95% confidence interval CI: 66–87%) in symptomatic SARS-CoV-2 patients[55].

(6) Sinovac-CoronaVac vaccine show the variable efficacious of this vaccine (i.e., phase 3 trials in Indonesia of 65.3% (95% CI: 20.0–85.1%); in Turkey of 83.5% (95% CI: 65.4–92.1%) against symptomatic SARS-

CoV-2 infection; in Brazil of 51% (95% confidence interval CI: 36–62%) against symptomatic SARS-CoV-2 infection; 100% (95% CI: 17–100%) against severe COVID-19; and 100% (95% CI: 56–100%) against hospitalisation, starting 14 days after the second dose[56].

(7) The Covaxin vaccine (BBV152) presents that adults aged less than 60 years showed vaccine efficacy of 79% (95% CI: 66–88%); and in those aged 60 years and older it was 68% (95% CI: 8–91%).

(8) Nuvaxovid (NVX-CoV2373) vaccine against COVID-19 and

(9) Covovax (NVX-CoV2373) vaccine against COVID-19 for emergency use on 20 December 2021 and 17 December 2021, respectively. Both vaccines were developed by Novavax and Serum Institute of India using the Novavax platform of recombinant protein nanoparticles formulated with the adjuvant Matrix M (NVX-CoV2373). This vaccine consists of a recombinant SARS-CoV-2 spike protein nanoparticle administered as a co-formulation with the adjuvant Matrix-M. The recommended primary vaccine series is two doses (5 µg of recombinant spike protein with 50 µg of Matrix-M adjuvant per 0.5 mL dose) given intramuscularly, in persons aged 18 and above. For moderately and severely immunocompromised persons is necessary an additional dose[57].

(10) CanSino vaccine, demonstrating that the vaccine had an efficacy of 58% against symptomatic disease and 92% against severe COVID-19[58].

A comprehensive panel of vaccines listed above against Omicron's sublineages (BA.1, BA.2, BA.2.12, and BA.⅘) reveals that mutations on spike proteins showed an improvement in interaction with the angiotensin-converting enzyme 2 (ACE2), although cell-cell fusion was decreased and also a reduction occurred in the activity of neutralization of plasma that presents antibodies from an ancestral virus[59].

In a recent study published in the Lancet Journal, a meta-regression analysis reveals that the primary series vaccine effectiveness against severe disease when the Omicron variant was predominant was lower than that observed pre-omicron but showed a little decline after vaccination[60].

As a way to combat the new waves caused by the variants, vaccine manufacturers have been updating vaccine protocols. The first boost vaccine to be approved is Moderna's bivalent vaccine, which targets two strains simultaneously, the original variant and Omicron[61]. In the COV-BOOST trial, the heterologous boost after either a two-dose of AZD1222 or BNT162b2 prime showed an increased humoral and cell-mediated immune response compared to homologous booster vaccination, although the reactivity was increased in some heterologous boosted combinations[62]. Initial studies have shown that the combination of vaccines has shown promising results and will therefore be valuable in ensuring that people at higher risk of serious illness remain protected from hospitalization and death. Currently, Pfizer's bivalent vaccine, which provides protection against SARS-CoV-2 Original, and the omicron variants BA.4/ BA.5 are authorized.

Several studies demonstrated the next generation of COVID-19 vaccines are in demand and the intranasal (IN) vaccination method has been demonstrated to be potent in inducing both mucosal and systemic immune responses in animals[63–67]. Some important preclinical studies of COVID-19 vaccines have indicated that IN vaccines have the potential to induce sterilizing immunity against mucosal pathogens[67]. Another advantage of nasal vaccines is demonstrated in preventing SARS-CoV-2 infection in both the upper and lower respiratory tracts[68].

The emergence of SARS-CoV-2 variants further limits the success of vaccines and natural immunity as they contain genomic alterations. This is observed particularly in the coding regions of the Spike protein, isolated initially from the original Wuhan virus, which increases its molecular interaction with the ACE receptors compared to the original virus[69]. The continuity of infections by Omicron BA.1 can result in substantial evasion of antibodies, through the formation of several mutations in the spike protein, including in the receptor binding domain (RBD) and in the N-terminal domain, which correspond to new subvariants. After

vaccination, BA.1 infections predominantly develop a humoral immune memory directed against ancestral (hereafter referred to as wild-type (WT) SARS-CoV-2 spike protein. These antibodies could neutralize both WT SARS-CoV-2 and BA.1. According to vaccine developers, an adaptation of the vaccine to a new variant virus strain would be necessary for the future, and such adaptation would be facilitated by the flexibility of mRNA-based vaccine technology[70].

3. Antiviral drugs

During the COVID-19 pandemic, safe and effective drugs that could be used in the treatment as soon as possible were widely explored, especially with the emergence of the coronavirus variants. Therefore, drug repurposing for antiviral action of compounds already available on the market for other diseases has been one of the main strategies used in the COVID-19 pandemic scenario[71].

Drug repurposing strategy, also called "off-label", has several advantages, including a) testing these drugs directly in clinical studies since all the safety studies are already approved by regulatory authorities such as Food and Drugs Administration (FDA), European Medicines Agency (EMA) and the Brazilian National Health Surveillance Agency (ANVISA); b) lower costs to access markets since the pharmaceutical supply chain is ready for large-scale formulation and distribution; c) combination therapy in association with other drugs, which may be more effective than monotherapy; d) the discovery of new mechanisms of action against other similar diseases to these drugs, improving health worldwide[72].

Following FDA advice, it is possible to use medications outside their specific indication in emergency cases, for instance: a) when there is no approved drug to treat the illness or medical condition; b) if all approved treatments have been tried without any apparent benefit; c) with the consent of the patient and guardian. However, this information should not be interpreted as a free license to prescribe any drug by the health care providers and governments since the decision about repurposing use involves many other considerations fully described by the FDA[73].

One example that raised concern at the beginning of the pandemic was the use of hydroxychloroquine/chloroquine against SARS-CoV-2. Several studies for use alone or in combination with azithromycin have shown that neither mortality is reduced in hospitalized COVID-19 patients nor SARS-CoV-2 infection is prevented[74–76]. Therefore, WHO has strongly recommended against the use of hydroxychloroquine/ chloroquine in any COVID-19 patients[71,77–79].

Drugs can be allocated into eight groups (anti-inflammatory, antibiotics, anti-neoplasic, antiviral, antiparasitic, anticoagulant, anti-depressive, and immunosuppressant)[80,81]. According to guidelines published by the National Institute of Health[81] and WHO (**Table S1**)[82], by the time this search was performed, Remdesivir has been the only drug approved by FDA against COVID-19[83].

4. National Institutes of Health (NIH), antiviral therapy summary recommendations

To date, a plethora of drugs has been tested and proposed for the treatment of COVID-19. However, few have proven effective in clinical treatment. Apart from remdesivir, other drugs such as nirmatrelvir, ritonavir (Paxlovid), molnupiravir, and some monoclonal antibodies have received emergency clearance for use (**Table 2**). The FDA sets guidelines for the use of some of these drugs, varying according to the patient's condition and response to treatments (**Table 2**).

Table 2. FDA-guided treatments, based on data from COVID-19 Treatment Guidelines of the National Institutes of Health (NIH)[81].

Non-hospitalized patients	Nirmatrelvir along with Ritonavir (Paxlovid)
	Remdesivir
Hospitalized patient (Does not require oxygen supplementation)	Remdesivir
Hospitalized patient (Requires conventional oxygen)	Remdesivir
	Dexamethasone in combination with Remdesivir
Alternative treatments for COVID-19	Bebtelovimabe (CIII)
	Molnupiravir

The above scenario is encouraging with the antiviral drugs, including monoclonal antibodies. Throughout the pandemic, several monoclonal antibodies were developed, tested in vitro, clinically, and approved by the FDA demonstrating a good alternative against COVID. These include, Bamlanivimab (BAM); Bebtelovimab (BEB); Casirivimab (CAS); Cilgavimab (CIL); Etesevimab (ETE); Imdevimab (IMD); Sotrovimab (SOT) and Tixagevima (TIX) (**Table 3**)[84]. all of which are very expensive and excessive for poorer countries.

Table 3. Effect of monoclonal antibodies on SARS-COV-2 variants, based on the COVID-19 Treatment Guidelines of the National Institutes of Health (NIH)[81].

Variants	**BEB**		**TIX Plus CIL**		**BAM Plus ETE**		**CAS Plus IMD**		**SOT**	
	In vitro susceptibilitya	Clinical activity	In vitro susceptibilitya	Clinical activity	In vitro susceptibilitya	Clinical activity	In vitro susceptibilitya	Clinical activity	In vitro susceptibilitya	Clinical activity
Omicron BA.2	No change	Active	No change	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron BA.4	No change	Active	Moderate reduction	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron BA.5	No change	Active	Moderate reduction	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Alpha B.1.1.7	No change	Active	No change	Active	No change	Active	No change	Active	No change	Active
Beta B.1.351	No change	Active	No change	Active	Marked reduction	Unlikely to be active	No change	Active	No change	Active
Gamma P.1	No change	Active	No change	Active	Marked reduction	Unlikely to be active	No change	Active	No change	Active
Delta B.1.617.2 , non-AY.1/AY .2	No change	Active	No change	Active	No change	Active	No change	Active	No change	Active
Omicron B.1.1.529 / BA.1	No change	Active	Moderate reduction	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active
Omicron BA.1.1	No change	Active	Moderate reduction	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active

Other treatments such as corticosteroids (Dexamethasone, Methylprednisolone) therapy improved clinical outcomes and reduced mortality rates in hospitalized patients whereas Baricitinib, a Janus kinase inhibitor, along with corticosteroids, could be administered in patients with critical COVID-19. Anticoagulants and antiplatelet therapy can be used only in hospitalized patients suspected of having a thromboembolic disease. The other drugs, even those not approved by FDA and not recommended by the guidelines, are still under investigation in clinical trials (**Table S1**).

According to the Pan American Journal of Public Health[85], several clinical trials are still in progress using a drug repurposing strategy against COVID-19[86]. Some of them involve medicines currently in use for treating Hepatitis C (denoprevir)[87]; rheumatoid arthritis (tocilizumab)[88], parasitic diseases (ivermectin)[77] as

well as those used against infection caused by influenza (umifenovir and favipiravir) (NCT04260594), HIV (lopinavir-ritonavir) virus[72] and bacteria (azithromycin)[89]. update dexamethasone and heparin (**Table S1**).

Overall, the issues from the FDA regarding the off-label use of a drug should be considered to establish clinical conduct based on scientific evidence and consistent parameters aiming at safety in its application[90]. The need for new specific targeting drugs to treat COVID-19 is the final message pointed directly or indirectly by most recently published articles about COVID-19 treatment. A serious debate is still in need, including the view of some political perspectives[71,73,78,79,88–92].

Notably, the main via by which people are infected with SARS-CoV-2 is through the upper airways, mainly by inhalation of respiratory droplets and aerosol, deposition of small respiratory particles in the mouth and nose[93]. Therefore, drugs target for intranasal therapy needs to be prioritized not only by the possibility of block the interaction with host epithelial cells in respiratory tract but also to accelerate nasal virus clearance[94,95]. Intranasal drugs candidates including povidone-iodine[96], nitric oxide[97], hydrochloride[98], astrodimer sodium (SPL7013)[99], iota-carrageenan[100], LNA-ASO[101] are being investigated. These strategies can stop the development of infection and act by prophylactic way, avoiding future infection by new variants[102].

Recently, studies involving COVID-19 and alkaloids have pointed to several potential molecules that should be explored (**Figure 4**).

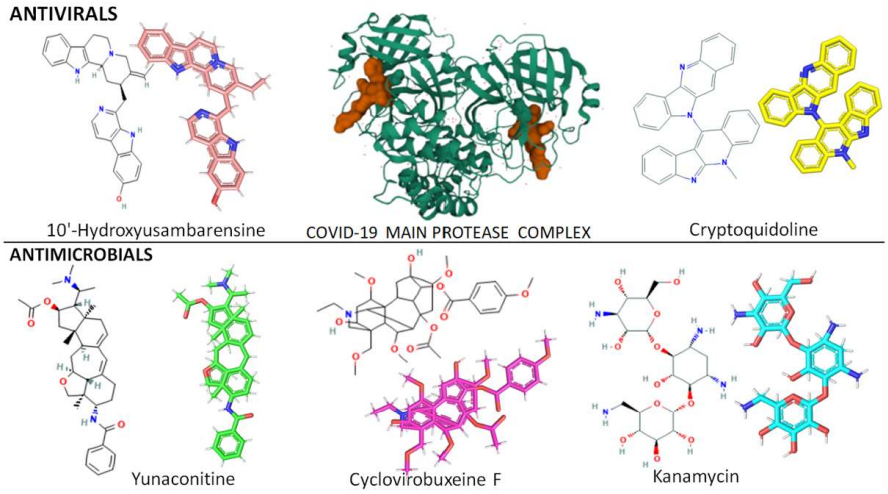


Figure 4. Some examples of different structures (3D and 2D representation) of molecules with antiviral activity against SARS-CoV-2 protease (10-hydroxyusambarensine and cryptoquindoline) and antimicrobial activities (Kanamycin, Yunaconitine, Cyclovirobuxeine F). The COVID main protease has two binding sites that are targets for in silico studies. The figure shows the enzyme with the inhibitor N3 occupying both sites (PDB ID = 6LU7). The representation of the complex was created using Mol* (https://www.rcsb.org/3d-view/6LU7/1)[103,104]. Whereas the other molecules were from the PubChem, the National Institutes of Health open chemistry databank (https://pubchem.ncbi.nlm.nih.gov).

Thus, the class of alkaloids can serve as templates for bioinformatics studies because of strategies based on ligand structural optimization based on its antibacterial and antiviral activities reports[105]. For example, Topçu et al.[106] evaluated within 20 years of literature on the anti-coronaviral profile of 20 alkaloids from African plants and reported 10-hydroxyusambarensine and cryptoquindoline as inhibitors of the 3-chymotrypsin-like protease (3CLpro) of SARS-CoV-2 and SARS-CoV. Gyebi et al.[107] had previously explored these two molecules using molecular modeling tools and identified 10-hydroxyusambarensine interacting with SARS-CoV-2 $3CL^{pro}$ His-Cys catalytic dyad (His41 and Cys145), Phe294 and Pro293, and the Domain II (Val104 and Asp153). According to these authors, cryptoquindoline interacts with Cys145 and Met49 of this enzyme.

Structure-assisted drug design, virtual drug screening, and high-throughput screening approaches have been explored to propose bioactive molecules to treat COVID-19[85]. Moreover, recently, two alkaloid compounds (ajmalicine and yohimbine) were identified as the most potent inhibitors among several natural alkaloids as new potential inhibitors for SARS-CoV-2 M^{pro} (main protease (Mpro) of SARS-CoV-2)[107,108]. This illustrates the importance of using these techniques to learn more about this disease. However, a lot still has to be done regarding COVID-19, so the time distance between the in silico environment, the clinical trials, and the market will decrease and new treatment options may emerge. Other strategies also may help and are still being evaluated for the treatment of COVID-19 (**Table 4**).

Table 4. Summary of therapeutic alternatives for COVID-19.

Therapeutic alternatives	Efficacy	Reference
Oxygen therapy	Supraglottic jet oxygenation and ventilation is a promising alternative for High flow nasal cannula oxygen with potential benefits.	Jiang and Wei[109]
Stem cell therapy	Use of stem cells for critically ill COVID-19 patients in a small group of patients in China and subsequent Emergency Use Authorization of stem cells by Food and Drug Administration to Global Institute of Stem Cell Therapy and Research and Athersys has created excitement among the medical community	Choudhery and Harris[110]
Antiviral plants	The ethnopharmacological knowledge about plants has provided food supplements and nutraceuticals as a promise for prevention and treatment of the current pandemic.	Bhuta et al.[111]
Inhalation monoclonal antibody therapy	Passive transfer of antibodies via the intranasal or mucosal route for the prevention and treatment of SARS-CoV-2 and as a prophylactic is a promising alternative approach for a large population, particularly for developing countries. It provides a promising strategy to prevent SARS-CoV-2 infection and control disease severity, to be used as a standalone antiviral prophylaxis tool, complementary to future vaccination programs.	Parray et al.[112]
Complementary and alternative medicine therapies	Different interventions (acupuncture, Traditional Chinese medicine [relaxation and Qigong) significantly improved various psychological symptoms (depression, anxiety, stress, sleep quality, negative emotions, quality of life) and physical symptoms (inflammatory factors, physical activity, chest pain, and respiratory function) in COVID-19 patients.	Badakhsh et al.[113]
Ozone therapy	The beneficial effect of ozone in the management of COVID-19 appears to be limited to improvements in laboratory parameters in critically ill patients. Mortality, length of stay, and ICU admission did not improve after ozone therapy, although this may be partially due to a shorter duration of viral shedding.	Setyo et al.[114]
Enzyme therapy	Currently, promising therapeutic alternatives using the angiotensin-converting enzyme 2 (ACE2) are being studied to treat COVID-19.	Fuente et al.[115]
Phage therapy	Phages are recognized as promising alternatives to antibiotics in treating pulmonary bacterial infections, however, little is known about their use for treating secondary bacterial infections during virus pandemics such as COVID-19	Wu et al.[116]
Flavonoids	Flavonoids are efficacious and safe in treating respiratory tract infections including the common cold, influenza, COVID-19, acute non-streptococcal tonsillopharyngitis, acute rhinosinusitis, acute bronchitis, bronchial pneumonia, and upper respiratory tract infection	Yao et al.[117]

The nasal therapy is one of these strategies. The use of intranasal vaccines is being developed and results showed that this vaccination method is promising to induce mucosal and systematic immune responses[67]. Intranasal antibody-based therapy in mice showed that 0.044 mg per kg body weight of IgM-14 provides prophylactic effects against at least three SARS-CoV-2 variants – B.1.1.7 (Alpha), P.1 (Gamma) and B.1.351

(Beta). The same study revealed that a single dose at 0.4 mg per kg offers therapeutic efficacy against SARS-CoV-2[118].

Another strategy involves nasal therapy candidates that block virus attachment in situ avoiding the progress of infection[94]. A randomized phase III clinical trial evaluated the action of nitric oxide (NO) to eliminate nasal SARS-CoV-2. Interestingly, adults that self-administrate for 7 days, six times daily two sprays per nostril (0.45 mL/dose) accelerated nasal virus clearance[95]. Nasal therapy is investigated not only against SARS-CoV-2 infections directly, but also to treat anosmia, one of COVID-19 consequences. The study conducted by Kasiri et al.[119] in non-hospitalized adult patients with COVID-19, showed that 100 mcg of mometasone furoate nasal spray for 4 weeks associated with olfactory training were able to improve severe chronic anosmia by COVID-19.

5. COVID-19 and secondary microbial co-infections

COVID-19 was and still is a big challenge to the international medical-scientific community and researchers worldwide. The risk of a secondary bacterial or fungal infection or coinfection in patients affected by COVID-19 becomes a critical issue, mainly due to increased morbidity and mortality rates associated with these conditions[120–124].

It is estimated that without vaccination, 1 in 7 patients hospitalised with COVID-19 developed secondary bacterial infections with a 50% risk of death[125]. In addition, severe acute respiratory syndrome (SARS) is among the most death-threatening complications of COVID-19 (17–29%), followed by acute heart injury (12%) and secondary infections (10%)[126]. Therefore, mechanical pulmonary ventilation is generally necessary in the cases of this syndrome[127].

The almost 15% co-infection or secondary infection rates historically detected contributed to morbidity and mortality in other pandemics such as influenza. For example, in the case of SARS-CoV-2 infections, a systematic review[128], revealed that 19% of patients with COVID-19 have coinfection, and about 24% have secondary infections with a 50% death rate[50].

Furthermore, in a recent Lancet report, it found that among the patients surveyed, 8.4% had viral coinfections and the most prevalent viral infections were by influenza viruses[50,105]. Thus, the COVID-19 pandemic continuously reinforces the need for vaccines, antivirals, and antimicrobials to reduce the number of COVID-19 deaths, aggravation, and hospitalisation time. Among the described microbiological co-infections, viral, bacterial and fungal pathogens stand out. Among them, respiratory viruses including hRV, hMPV and RSV are associated with increased respiratory viral coinfections. In addition, immunosuppressive and immunodeficiency conditions such as HIV infection can affect enhance COVID-19[129].

With the highest prevalence, bacterial infections are considered the most important co-infection agents based on their previous records with viral outbreaks and pandemics. People with bacterial coinfection have also been reported to have a high mortality rate. Critically ill patients had a higher percentage of co-infection compared to hospitalized patients[130]. It is important in assess the prevalence of bacterial co-infections prior to the application of empirical antibiotic treatment in patients with SARS-CoV-2. However, attention should be paid to the extensive use of antibiotics, which can lead to various problems such as antibacterial resistance[130]. Some of the respiratory bacterial pathogens such as *Pneumococcus, Staphylococcus,* and *Klebsiella* with SARS-CoV-2 have a common clinical manifestation; therefore, antibiotic treatment would be more difficult than the normal situation[130,131].

Importantly, fungal infections have been a major threat to the life of patients in intensive care units. In this way, fungal co-infections such as *Mucormycosis, Aspergillus*, and *Candida* species can increase the

mortality rate, especially in critically ill patients[132]. One of the great challenges for doctors is their detection since fungal co-infections can remain undetectable even after patients die[133].

6. The way out

In 2023 the situation remains challenging. despite the rapid development, and uptake of vaccines, projected to have saved 10 s of millions of lives, nothing seems to change with new cycles continuing and inducing inconsistent health mandates reflecting many missed opportunities to stem transmission using vaccines, antiviral drugs, and innovative therapies[134,135]. Meanwhile, the virus evolution has rapidly accelerated with transmissibility increasing alarmingly due to new Omicron variants[136].

COVID-19 has confounded most experts who predicted that it would become endemic and seasonal, but instead, the times between cycles are accelerating and in mid-June/July new waves arrived. There are many reasons for this:

Political interventions: Vaccines have significantly lowered the chances of hospitalizations and death resulting in many governments reducing COVID-19 safety mandates. The fact that transmission rates have not been halted at the same time was ignored. Hospitalizations and deaths are now creeping up as Omicron BA.4/5 compose 50 % or more of infections. Reductions in safety mandates misled people to believe that masks were no longer necessary in crowded venues. Just consider the sporting events televised in June/July 2022 from Roland Garros (France), Wimbledon (UK), World Athletics Championships (USA), and Pan American Gymnastics (Brazil), to see very few supporters wearing masks. Omicron BA.4/5 have therefore had great opportunities to break through these crowded audiences in which many probably had waning immunity.

In addition, although 70% of people in mainly high-income countries have been vaccinated, in low-income countries, particularly in Africa, only 28% of older people and 37% of health workers have received the vaccination. About 30% of the global population has yet to receive a single vaccine dose[137]. Without a significant reduction in transmission and circulation of COVID-19, new variants will continue to emerge and challenge vaccine efficiency. The above situation has not been widely accepted by governments who have been pressurized, often by misinformation, to ease safety mandates. Just look at news coverage of awful examples by Trump and Bolsonaro regarding mask-wearing. The damage has been done with inconsistent advice, loss of trust, and COVID-19 fatigue major barriers to change now.

Approximately, 46 million people have yet to take a booster shot in Brazil while the uptick in cases correlates to the abandonment of safety measures like masks[138]. In the real world, we doubt that most people, even if requested, would readily revert to previous safety mandates unless a truly, monstrous killing variant close family and friends should arrive.

7. COVID-19 elimination

There are many who believe that the elimination of COVID-19 is unlikely, and we need to learn to live with the virus. This is not an acceptable scenario, and the solution to this dilemma might be solved with innovative therapy to both prevent transmission and treat infected individuals. A combination of vaccines and antiviral drugs, together with governmental support, should eventually succeed.

Vaccines are therefore under development for treating new variants, although uncertainty exists as to whether we should continue to work behind viral evolution and chase our own tails or develop pan-corona, broad-spectrum vaccines and anticipate future variants[139]. The latest COVID-19 variants BA.4/5 show enhanced breakthroughs of antibodies induced by vaccination[140] so some urgency is required. Various vaccine

strategies are being researched, involving vaccine combinations and targeting viral antigens outside the spike proteins[141].

What is needed is to prevent COVID-19 from entering the body in the first place, i.e., blocking transmission in the nose and upper airways. Injected vaccines are not optimal for raising high levels of antiviral IgA antibodies against virus attachment in the nasal mucosa and mainly produce IgG to protect the lower respiratory system[94,142,143]. Therapeutically, therefore, intranasal vaccines are being intensively researched, although this could be problematic since the autoimmune nasal vaccination clinical trial was recently terminated and virus neutralisation is shown to be compromised by Beta and Omicron variants[125].

Hopefully, successful clinical trials of nasal vaccination will be reported soon, and this will allow the transport and application of vaccines to poorer and more remote regions as well as be more acceptable to vaccine-resistant people. In addition, various combinations of nasal and injected vaccinations, together with new antivirals such as Paxlinoid, designed against early-stage infections, would provide new and powerful tools for controlling COVID-19 and preventing the current destructive waves of infection.

The development of new approaches that seek alternatives for the control of COVID-19 must be considered. The combination of non-vaccinal intranasal strategies targeting host proteins is one possibility. In this regard, the small molecular protease inhibitor (N-0385), a blocker of TMPRSS2 (involved in viral entry) into host cells, and subsequent in vivo infection by a broad spectrum of human coronaviruses, including the Omicron B.1 variant and other viruses, have been tested. There are some advantages to seeking to develop new non-vaccine nasal therapies. They largely reduce the potential side effects of vaccines. They tend to have more stable, low-cost compounds and still have broad-spectrum activity.

Following the potential of nasal therapies without using vaccine molecules but simpler compounds. Such as nasal application of nitric oxide, which was recently demonstrated in a randomised, double-blind, placebo-controlled phase III clinical trial, to rapidly eradicate SARS-CoV-2 in newly infected patients[95]. Several molecules have been tested although with few appropriate clinical trials associated. The potential value of such nasal sprays is enormous, although they must be approved and widely accepted.

Importantly, it is worth noting that several studies demonstrate that SARS-CoV-2 patients have co-infections and super-infections by viruses, bacteria, fungi, and other additional pathogens[125] (14). These infections can affect the severity of COVID-19. Furthermore, as many patients are treated early with antibiotics, this fact needs to be considered in planned treatments to avoid the possible generation of antibiotic resistance. The recommendation is that any bacterial co-infections be identified immediately upon admission of patients with pneumonia. In some cases, these have been treated with antibiotics according to recommendations from the Health Services of several countries, such as the United Kingdom[142], the Netherlands[143], and South Africa[144].

Author contributions

Conceptualization, JSN and HCC; methodology, ARdS and RBG; software, VGOE, JSN and CFM; validation, NCdC and RBG; formal analysis, RBG, MdVK, CRR, NAR and HCC; investigation, VGOE, JSN and CFM; validation, NCdC and RBG; resources, VGOE, JSN, LMC and CFM; validation, NCdC, ARdS and RBG; data curation, VGOE, JSN and CFM; writing—original draft preparation, VGOE and RBG; writing—review and editing, ARdS, RBG, MdVK, CRR, NAR and HCC; visualization, JSN and RBG; supervision, NAR and HCC; project administration, HCC; funding acquisition, HCC. All authors have read and agreed to the published version of the manuscript.

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Consent to participate

All authors have agreed to participate in the manuscript.

Consent for publication

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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Supplementary materials

Table S1. Summary of drug repurposing tested for COVID-19 treatment.

Repurposed drug	Original approved terapeutic use	Status against COVID-19 patients	References
ASA	Pain, fever, inflammation, cardiovascular events	ASA was not associated with reductions in the risk of progressing to invasive mechanical ventilation or death.	Abani et al.[145]
Amantadine	Parkinson's disease; Influenza A	Potential to reduce the severity of respiratory insufficiency and neurological effects.	Rejdak et al.[146]
Azithromycin	Bacterial infections	Azithromycin was not associated with reduced mortality in hospitalized COVID-19 patients.	Kamel et al.[147]
Baricitinib	Rheumatoid arthritis	Reduce mortality hospitalised patients with COVID-19 who were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation.	Ely et al.[148]
Bevacizumab	Cancer	Improved oxygenation and shortening oxygen-support duration for patients with severe Covid-19.	Pang et al.[149]
CM	Pancreatitis and reflux disease	Not found to be effective against SARS-CoV-2.	Tobback et al.[150]
HCQ	Malaria and amebiais	Associated with increased mortality in COVID-19 patients.	Axfors et al.[151]
Dexamethasone	Anti-inflammatory	Reduced mortality among patients thar were receiving either invasive mechanical ventilation or oxygen alone.	The RECOVERY Collaborative Group[152]
Favipiravir	Influenza	Option for moderate COVID-19 pneumonia treatment. The risk of adverse events, including hyperuricemia, should be considered.	Shinkai et al.[153]
Fluvoxamine	Depression	No significant effect on the rates of hospitalization, mechanical ventilation, and mortality of patients with COVID-19 infection.	Bhuta et al.[111]
Heparin	Anticoagulant	No effect on survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support in critically COVID-19 patients.	The ATTACC, ACTIV-4a, and REMAP-CAP Investigators[154]
IFN-β-1a	Multiple sclerosis	IFN-β 1a did not improve the median time to clinical improvement in hospitalized patients with moderate to severe COVID-19.	Alavi et al.[155]
Imatinib	Cancer	There was no reduction in time to discontinuation of ventilation and supplemental oxygen in patients with COVID-19.	Aman et al.[156]
Ivermectin	Antiparasitic, onchocerciasis, strongyloidiasis, ascariasis, trichuriasis and enterobiasis	Not showed efficacy to reduce viral load. Treatment during early illness did not prevent progression to severe disease.	Buonfrate et al.[157]
Lopinavir/ritonavir	HIV infection	In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care.	Cao et al.[158]
MP	Immunosuppressant, anti-inflammatory, antiallergic	Early administration was associated with a significantly lower hazard of death and decreased ventilator dependence in patients with severe COVID-19 pneumonia.	Salton et al.[159]
Nafamostat mesylate	Anticoagulant	Clinical improvement in a small group of high-risk COVID-19 patients requiring oxygen treatment.	Zhuravel et al.[160]
Niclosamide	Antihelminthic	No significant difference in oropharyngeal clearance of SARS-CoV-2 at day 3 between placebo and niclosamide groups.	Cairns et al.[161]
Nitazoxanide	Antiprotozoal	Nitazoxanide did not prevent admission to the intensive care unit for patients hospitalized with COVID-19 pneumonia.	Rocco et al.[162]
Pirfenidone	Idiopathic pulmonary fibrosis	Viable drug to treat patients with severe COVID-19. Showed good tolerability profile without safety alert.	Zhang et al.[163]
Remdesivir	Ebola virus	No significant effect on patients with COVID-19 who are already being ventilated. Among other hospitalised patients, it has a small effect against death or progression to ventilation (or both).	WHO[164]

Table S1. (*Continued*).

Repurposed drug	Original approved terapeutic use	Status against COVID-19 patients	References
Ribavirin	Hepatitis C	Ribavirin is well tolerated in critically ill patients with COVID-19 and may benefit COVID-19 patients through increasing the virus clearance.	Xu et al.[165]
Sofosbuvir	Hepatitis C	Showed no protective effects against severe illness in patients with COVID-19.	Kow et al.[166]
Tocilizumab	Rheumatoid arthritis, other autoimmune rheumatic diseases	Reduced the risk of disease progression among high-risk patients with mild-to-moderate COVID-19.	Broman et al.[167]
Umifenovir	Influenza	No effective in shortening the duration of SARS-CoV-2 in severe patients and improving the prognosis in non-ICU patients and mortality.	Alavi Dazaram et al.[155]

ASA = Acetylsalicylic acid; CM = Camostat mesylate; HCQ = Hydroxychloroquine; MP = Methylprednisolone.