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Citation for published version:
Rudan, I, Adeloye, D & Sheikh, A 2022, 'COVID 19: vaccines, efficacy and effects on variants', *Current opinion in pulmonary medicine*, vol. 28, no. 3, pp. 180-191.
https://doi.org/10.1097/MCP.0000000000000868

Digital Object Identifier (DOI):
10.1097/MCP.0000000000000868

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Current opinion in pulmonary medicine

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Download date: 02. Mar. 2023

COVID-19 Vaccines, Efficacy and Effects on Variants

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Abstract

Purpose of review. We focused on three strategies that showed the best results in both being developed remarkably quickly and showing high efficacy and safety against COVID19: mRNA vaccines, adenoviral vector vaccines and recombinant nanoparticles. We also considered the emergence of SARS-CoV-2 variants and their impact on the effectiveness of the most widely implemented vaccines.

Recent findings. We reviewed general properties, efficacy, safety and global uptake of Pfizer/BioNTech's Comirnaty (BNT162b2), Moderna's Spikevax (mRNA-1273), Oxford/AstraZeneca's ChAdOx1 nCoV-19, J&J/Janssen's Ad26.COV2.S and Novavax's NVX-CoV2373 vaccines at the end of the year 2021. We summarized the lessons from vaccine implementation, such as the continued spread of infection, waning of immune protection, the emergence of "cross vaccination" ("mix-and-match") approaches, and the effectiveness against COVID19 infection, severe disease and death. We then focused on important missense mutations acquired by the five variants of concern (VoC): Alpha, Beta, Gamma, Delta and Omicron. We explored the evidence for the effectiveness of the vaccines against those five VoC and the progress towards universal coronavirus vaccine.

Summary. It is very difficult to predict the further development of the COVID-19 pandemic. Clearly, there are reasons for optimism, as the vaccine development pipeline is likely to keep producing vaccines of an increasingly broad spectrum against coronaviruses, more easily deliverable and conferring more durable immune protection. However, the very large number of infections caused by the Omicron variant shows that a new variant could emerge at any time, and some future variants may still be associated with increased virulence and pathogenicity, which would represent a setback in this pandemic. Therefore, at the beginning of 2022, a major goal of the global scientific community will be to develop interventions that will assist governments to control COVID-19 more effectively and enable a safer coexistence with the SARS-CoV-2 virus and its emerging variants.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated in late 2019 in Wuhan, China, where it was shown to cause a disease named COVID-19 which proved lethal in about 1% of those infected, depending on the population age structure [1]. Its genetic sequence was published on 11 January 2020 by Chinese scientists, triggering global efforts to develop COVID-19 vaccines [2,3]. An unprecedented collaboration between the multinational pharmaceutical industry, biotechnological companies, global governments, international organisations and universities emerged as a result [4]. Six months later, massive investments were committed to developing a number of vaccine candidates [5].

The first approved vaccine against COVID-19 was the Chinese replication-defective adenovirus vector vaccine CanSino. It was approved by the Chinese authorities on 24 June 2020 for limited use in the military and for those in high-risk occupational groups [6]. The second was the Russian Sputnik V, approved by the Russian authorities on 11 August 2020 for emergency use [7]. These were followed by Pfizer/BioNTech partnership, which submitted an Emergency Use Authorisation (EUA) request to the United States (US) Food and Drug Administration (FDA) for their mRNA vaccine (Comirnaty, BNT162b2) [8]. Their vaccine was first approved by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) on 2 December 2020 through a temporary regulatory approval [9]. In the US, the FDA granted a EUA for the Pfizer–BioNTech COVID-19 vaccine on 11 December 2020 [10]. Only a week later, they granted a EUA for Spikevax (mRNA-1273) produced by the Moderna [11]. Most of the European Union (EU) countries followed with their authorisations by 21 December 2020 [12]. In parallel, in December 2020, Bahrain and the United Arab Emirates granted full authorisation for the Chinese Sinopharm BIBP vaccine [13,14]. Then, on 29 January 2021, Oxford/AstraZeneca's adenovirus vector-based vaccine (ChAdOx1 nCoV-19) obtained a conditional marketing authorisation (CMA) in the EU for its vaccine [15].

All of these vaccines demonstrated efficacy in reducing the symptomatic COVID-19, but the data for those who studied more serious outcomes were especially promising in relation to reducing severe episodes that required hospitalisation, as well as lethal outcomes caused by COVID-19 [16]. The countries that purchased these have typically prioritised vaccinating healthcare workers, as well as the oldest age groups and those with multiple comorbidities [17]. By the end of 2021, nine billion doses of different vaccines have been administered globally [18]. About half of these were ordered by high-income countries, which have about 14% of the world's population [19].

In this paper, we focus on three strategies that showed the best results in both being developed remarkably quickly and showing high efficacy and safety against COVID19 symptoms, severe disease and death: mRNA vaccines, adenoviral vector vaccines and recombinant nanoparticles. We also consider the emergence of SARS-CoV-2 variants and their impact on the effectiveness of the most widely implemented vaccines.

Accelerated Vaccine Development

The realisation of the inevitability of the spread of SARS-CoV-2 led to massively accelerated development of vaccines that could offer primary prevention against symptomatic infection, severe clinical presentation and death. It was known that vaccines based on inactive or weakened viruses grown in eggs would typically take years to develop [20]. The pandemic brought well-deserved attention to a radically different approach, that was based on decades-long efforts to use mRNA molecules to fight diseases, pioneered by scientists such as Katalin Karikó and Drew Weissman [21]. The US-based Moderna began testing mRNA-based vaccines for humans in 2015 [22]. Other approaches worth exploring, that could yield quick results, were based on viral vector vaccines which rose to prominence as a potentially viable technology after the Ebola outbreak [22]. The pandemic of COVID-19 focused on the accelerated development of vaccines on mRNA-based and viral vector-based technologies. The latter technology, along with recombinant protein-based vaccines and those based on an inactivated SARS-CoV-2 virus, were also expected to use aluminium salts - known as "alum" - as adjuvants to enhance immune defence mechanisms at the molecular level [23].

There were many investors willing to support the development of vaccines against COVID-19 during 2020, but they soon realised that there are no previous examples of such an accelerated vaccine development and that there was considerable uncertainty about which of the technological approaches to support. There were efforts towards attenuating and inactivating the virus and using it to induce an immune response. Other platforms focused on vaccines based on protein or peptide subunits and combined with an adjuvant to enhance immune responses. Some efforts were based on a strategy of using the whole spike protein (S protein), or its parts, such as the receptor-binding domain RBD region. Then, there were strategies based on non-replicating viral vectors, where an adenovirus is often preferred; in contrast, replicating viral vectors did not attract much enthusiasm by the developers and investors [24]

The S-protein was chosen in some approaches because it leads both to specific antibody production and triggers strong B-cell and T-cell immune responses [25] However, this approach was not necessarily ideal, at least in theory, because mutations are most likely to occur in this protein over time because it is critical for the infectivity of SARS-CoV-2. This is why other proteins are also considered for vaccine development, like the nucleocapsid, because they also induce a robust T-cell response and their genetic code mutates less frequently [25]. Platforms also involved nucleic acid technologies, such as nucleoside-modified messenger RNA and DNA, peptides and recombinant proteins [24,26]. The "next-generation" vaccine strategies aim to target COVID-19 infection mechanisms [2], such as using synthetic vaccines with induced mutations to make S-protein deficient in its function and stimulate an adaptive immune response before the virus attaches to a human cell, enabling flexibility for antigen manipulation, or improves effectiveness for protecting specific high-risk groups [2].

In mRNA vaccines, messenger RNA in the vaccine enters human cells and becomes translated into foreign viral proteins, leading to an immune response. This elegant mechanism was used by both Pfizer–BioNTech and Moderna. The introduced mRNA led human cells to express the SARS-CoV-2 spike protein. The genetic code of the mRNA could even be modified. The mRNA molecule is applied in a coformulation with lipid nanoparticles, which protect it and assist its absorption into the cells [27] (**Table 1,2**).

The second successful approach were adenovirus vector vaccines, which uses a shell of non-replicating adenovirus that contains genetic material to produce a SARS-CoV-2 protein [28]. The protein then serves as an antigen that stimulates an immune system to respond to it [28]. Examples of this approach were the Oxford/AstraZeneca vaccine [29], Johnson&Johnson (J&J)/Janssen [30], Sputnik V [31] and Convidecia [32]. The J&J/Janssen and Convidecia are interesting because they are one-shot vaccines that can be stored under ordinary refrigeration for several months, which gives them a considerable advantage in global logistic efforts to vaccinate hard-to-reach and underprivileged populations [31-33]. Sputnik V uses two doses: Ad26 for its first dose (also used in Janssen's only dose), and Ad5 for the second dose (also used in Convidecia's only dose) [34]. Its “light” version uses Ad26 alone and it’s been recommended as a booster shot to other types of vaccines, such as mRNA vaccines, in a proposed “mix and match”/”combo” approach, which should – in theory – elicit a more robust and prolonged immune response [31].

The third successful approach was subunit vaccines, which use one or more antigens without introducing whole particles of a virus. These antigens can be protein subunits or any molecules of the virus that stimulate immune response by the host [35]. Examples are the recombinant nanoparticle vaccine by Novavax [36], peptide vaccine EpiVacCorona [37], ZF2001 [26] and MVC-COV1901 [38].

Other approaches use inactivated viral vaccines, where virus particles are grown in culture and then killed using heat or formaldehyde to lose pathogenicity but maintain antigenicity [39]. Chinese CoronaVac [40], Sinopharm BIBP [41] and WIBP, the Indian Covaxin, the Russian CoviVac [42], the Kazakhstani QazVac [43] and the Iranian COVIran Barekat [44] are some examples. Attempts to develop intranasal vaccines, which target mucosal immunity in the nasal mucosa, are also very promising [45]. They aim primarily to stimulate Immunoglobulin A, and their advantage is the ease of administration [45].

Vaccine Trials and Authorisation

Before the COVID-19 pandemic, candidate vaccines would normally progress through several consecutive phases of clinical trials to establish their safety, immunogenicity, efficacy, dosage and adverse side effects [46]. This would normally take years, but in 2020 vaccine trials were compressed so that safety, efficacy, and dosing were investigated in parallel [47], before their population-level uptake, effectiveness and large-scale side effects could be determined through further research. Pre-registration of such trials allows understanding of the number of vaccines against COVID-19 that are undergoing accelerated development and testing. This number was large throughout 2020-2021: nearly 30 vaccines have been authorised for use by national governments, eight have been approved for emergency or full use by the WHO-recognised stringent regulatory authority, and more than 300 further vaccines are undergoing clinical trials. The vaccines formally authorised for use by at least one country include two prominent examples of mRNA vaccines (US/German Pfizer/BioNTech’s and US Moderna’s) and five prominent viral vector vaccines (Chinese Convidecia, Russian Sputnik Light and Sputnik V, UK/Swedish Oxford/AstraZeneca vaccine, and US/Dutch/Belgian Janssen vaccine). In addition to these vaccines, which have contributed to the vast majority of purchased and administered doses in 2020-2021

globally, the vaccines that also gained national authorisation also included eleven conventional inactivated vaccines (Chinese Academy of Medical Sciences, CoronaVac, Covaxin, CoviVac, COVIran Barekat, FAKHRAVAC, Minhai-Kangtai, QazVac, Sinopharm BIBP, WIBP, and Turkovac), one DNA vaccine (ZyCoV-D) and eight subunit vaccines (Abdala, COVAX-19, EpiVacCorona, MVC-COV1901, Novavax, Razi Cov Pars, Soberana 02, and ZF2001) [26]. Therefore, the COVID-19 pandemic has led to an unprecedented development of biomedical research underpinning vaccine development and immunology. **Table 1** shows the general properties of the most commonly used vaccines globally.

Uptake

By the end of 2021, about nine billion COVID-19 vaccine doses have been administered worldwide. About 57% of the global population received at least one dose, this proportion was only 8% in low-income countries. Official reports from national health agencies, collated by "Our World in Data" website [18], which may include vaccination of non-citizens (thus pushing the proportion to very high levels in some instances), suggests that United Arab Emirates achieved 99% coverage with at least 1 dose, Cuba 92%, South Korea 86%, China 85%, Argentina 83%, Canada 83%, Australia 80%, Japan 80%, Vietnam 79%, Brazil 78%, United Kingdom 76%, USA 73%, European Union (as a whole) 72%, Iran 70%, Turkey 67%, Mexico 63%, India 60%, Indonesia 57%, Philippines 55%, Bangladesh 53%, Russia 50%, Pakistan 41%, Ukraine 34%, South Africa 31%, etc. [18]. In Africa, the coverage has been particularly very low, with many countries, including some of the continent's most populous, reporting less than 5% coverage [18]. Only Botswana, Morocco, Rwanda, and Tunisia in mainland Africa have exceeded the WHO target of 40% as of 30 December 2021 [33].

To improve access to vaccines in the poorest countries and global vaccine equity, G20 and WHO announced a joint initiative in April 2020 to enable sharing resources and knowledge on vaccines (so-called "COVAX" initiative), diagnostics, therapeutics, and health systems [48]. The COVAX program mostly relied on the Oxford/AstraZeneca COVID-19 vaccine produced by the Serum Institute of India, which faced supply problems when India's needs increased between March and June 2021. The United Nations International Children's Emergency Fund (UNICEF), Amnesty International, Oxfam and Médecins Sans Frontières (Doctors without Borders) have all criticised vaccine monopolies and repeatedly called for their suspension and for transferring vaccine technologies, noting that otherwise the dose prices are increased several times, making them unaffordable to poor countries [49]. Also, in August 2021, the WHO called for a moratorium on a booster dose at least until the end of September to reduce unequal distribution between rich and poor countries, but a number of countries ignored this request [50].

Table 1: COVID-19 vaccines: General Properties [2,4,12,26,87]

Name	Developer	Type	Transport and storage	Authorised for (age groups)	Recommended dosage	Booster dose(s)
Comirnaty (BNT162b2)	Pfizer/BioNTech	mRNA	-60 to -90°C (or -25 to -15°C, up to 2 weeks)*	≥16 years (later also for 12-15 and 5-11 years)	2 doses, 3 weeks apart*,+	≥6 months after the 2nd dose§
Spikevax (mRNA-1273)	Moderna	mRNA	-50 to -15°C (or 2-8°C, up to 12 hrs)	≥18 years	2 doses, 4 weeks apart	≥6 months after the 2nd dose§
ChAdOx1 nCoV-19	Oxford/ AstraZeneca	Adenovirus vector	2-8°C	≥18 years	2 doses, 4-12 weeks apart	No data
Ad26.COV2.S	J&J/Janssen	Adenovirus vector	2-8°C (up to 4.5 months)	≥18 years	1 dose	≥2 months after the primary (1st) dose§
NVX-CoV2373	Novavax	Recombinant nanoparticle	2-8°C	≥18 years	2 doses, 3 weeks apart	No data

*for people ≥12 years of age, purple cap vials should be used with transport and storage as stated; for children under 12 years, orange cap vials should be used and stored at -60 to -90°C, but transport is possible at -25 to -15°C; dosage for ≥12 yrs: 30 mcg (0.3 mL); for 5-11 yrs: 10 mcg (0.2 mL);
+for immunocompromised: 3rd dose should be given 4 days after the 2nd dose;
§a typical guidance is that anyone ≥18 years old may receive a booster dose; however, persons living in a long-term care facility should receive a booster dose, and this is also extended to older age groups in some countries; thereby, heterologous ("mix and match") boosters are authorized in most countries and even encouraged based on most recent scientific evidence;

Table 2: COVID-19 vaccines: Reported efficacy against the original SARS-CoV-2 variant [88-96]

Name	Developer	Preventing COVID-19	Preventing Severe Form of Disease	Preventing Lethal Outcome
Comirnaty (BNT162b2)	Pfizer/BioNTech	95% (1 week after 2nd dose) 91% (6 months after 2nd dose)	88-97%	100%
Spikevax (mRNA-1273)	Moderna	94% (2 weeks after 2nd dose)	84-100%	100%
ChAdOx1 nCoV-19	Oxford / AstraZeneca	67% (>2 weeks after 2nd dose)	100%	100%
Ad26.COV2.S	J&J (Janssen)	66% (overall)	71-88%	100%
NVX-CoV2373	Novavax	90% (1 week after 2nd dose)	100%	100%

Table 3: SARS-CoV-2 Variants of Concern (VoC): General properties [65-70,77-78,98-100]

SARS-CoV-2 variant label	First sample and location	Declared VoC by the WHO	Increase in transmissibility	Effect on hospitalisations	Effect on mortality	Evasion of immunity
Alpha (B.1.1.7; VOC 20DEC-01; 20I (V1))	Sep 2020; UK	18 Dec 2020	+29% (24–33%)	+52% (47–57%)	+59% (44–74%)	Minimal
Beta (B.1.351; VOC 20DEC-02; 20H (V2))	May 2020; South Africa	14 Jan 2021	+25% (20–30%)	Under study	Possibly increased	Reduced for non-severe disease
Gamma (P.1 or B.1.1.28.1; VOC 21JAN-02; 20J (V3))	Nov 2020; Brazil	15 Jan 2021	+38% (29–48%)	Possibly increased	+50% (20–90%)	Reduced after natural infection
Delta (B.1.617.2; VOC 21APR-02; 21A)	Oct, 2020; India	6 May 2021	+97% (76–117%)	+85% (39–147%) relative to Alpha	+137% (50–230%)	Reduced for non-severe disease
Omicron (B.1.1.529; VOC 21NOV-01; 21K)	Nov 2021; South Africa	26 Nov 2021	Likely high	−41% (37–45%) relative to Delta	Under investigation	Likely considerable evasion

Table 4: SARS-CoV-2 Variants: Missense mutations found in SARS-CoV-2 variants and their suspected effects [65-70,77-78,83,98-110]

Mutation	Alpha	Beta	Gamma	Delta	Omicron	Suspected effect
N501Y	Yes	Yes	Yes		Yes	Asparagine (N) is replaced by tyrosine (Y) in amino-acid position 501; this may increase binding affinity because it is inside the spike glycoprotein's receptor-binding domain (RBD) that binds ACE2 in human cells;
del106–108	Yes	Yes	Yes			Deletion in nsp6 gene may alter interferon (IFN) antagonism in multiple variants of SARS-CoV-2, assisting immune evasion;
del69–70[e]	Yes				Yes	Deletion of amino acid at position 69 to 70 may lead to "spike gene target failure" and result in false negative result in PCR virus test;
P681H/P681R	Yes				Yes	Proline (P) is replaced by histidine (H) or arginine (R) at position 681; the presence of the S1/S2 “furin site” enhances virus transmissibility, and P681H may provide an additional basic residue and modulate S1/S2 cleavability by furin, and hence virus infection properties, especially at low pH;
E484K/E484A		Yes	Yes			Glutamic acid (E) is replaced by lysine (K) or alanine (A) at position 484; It may improve ability of SARS-CoV-2 to evade the host's immune system by changing antigenicity; Monoclonal and serum-derived antibodies may be 10-60 times less effective in neutralising virus with this mutation;
K417N		Yes	Yes			Lysine (K) is replaced by asparagine (N) at position 417; it may help the virus avoid neutralising antibodies generated through vaccination or previous infection; it may also increase binding by disfavouring complex formation between RBD and hACE2;
L452R				Yes		Leucine (L) is replaced by arginine (R) at position 452. This may enhance ACE2 receptor binding ability and reduce vaccine-stimulated antibodies from attaching to this altered spike protein; it may even make SARS-CoV-2 resistant to T cells;
T478K				Yes		Threonine (T) is replaced by Lysine (K) at position 478; this mutation is in the RBD region which is affecting the spike binding domain with human receptor ACE2, increasing the electrostatic potential on the interface and assisting immune evasion;
N440K					Yes	Asparagine (N) is replaced by lysine (K) at position 440. In cell cultures, 10 times more infective compared to the previously widespread A2a strain (A97V substitution in RdRP sequence), so it likely increases infectivity
S371L/S373P[f]					Yes	Serine (S) is replaced by leucine (L) or proline (P) at position 447; confers greater antibody resistance
S447N					Yes	Serine (S) is replaced by asparagine (N) at position 447; a mutation that increases Spike-ACE2 binding

Table 5: COVID-19 vaccines: Reported effectiveness against SARS-CoV-2 variants [81,87,93,95,97,111-120]

Name	Developer	Alpha	Beta	Gamma	Delta	Omicron
Comirnaty (BNT162b2)	Pfizer/BioNTech	85-94% 2nd dose; 49% 1st dose only	75-100% 2nd dose	84% 2nd dose	64-88%	Under investigation
Spikevax (mRNA-1273)	Moderna	92%	77% 1st dose only	77% 1st dose only	39-95% 72% 1st dose only	Under investigation
ChAdOx1 nCoV-19	Oxford / AstraZeneca	64-75%	48% 1st dose only	48% 1st dose only	60-92% 67% 1st dose only	Under investigation
Ad26.COV2.S	J&J (Janssen)	60-75%	64%	68%	78%	Under investigation
NVX-CoV2373	Novavax	86%	43%	Under investigation	Under investigation	Under investigation

Efficacy and Safety

Table 2 shows the reported efficacy of the most important early vaccines against the original SARS-CoV-2 variant. They all showed very high efficacy against symptomatic COVID-19 infection, but particularly against severe forms of the disease, including mortality. In terms of safety, an intramuscular injection was expected to cause local soreness, redness, rash or inflammation, with an accompanying fatigue, headache, muscle and joint pain [51]. In less than 1 in each 1,000 vaccinated people, allergic hypersensitivity to vaccine's ingredients may happen. The most extreme form is anaphylaxis, affecting about 2-5 people per million vaccinated [52]. In nearly two million first doses of Pfizer-BioNTech vaccine, there were 175 severe allergic reactions and 21 case of anaphylaxis reported [53], while in the four million of Moderna COVID-19 vaccine doses there were only 10 cases of anaphylaxis, most likely caused by lipid nanoparticles [53]. Reports of very rare (about 1 in 100,000) and potentially lethal thrombosis events in mainly younger female patients attracted more attention, and they were associated with J&J/Janssen [54] and Oxford/Astra Zeneca COVID-19 vaccines [55]. Adverse effects on [56-58].

Lessons from Vaccine Implementation

By the summer of 2021, it became apparent from the population-level implementation that COVID-19 vaccines were both highly effective and safe [59]. Studies found that those fully vaccinated were 5-6 times less likely to become infected with SARS-CoV-2, 10-37 times less likely to be hospitalised, and 11-67 times less likely to die from COVID-19 [59,60]. However, it became apparent that it was still possible for fully vaccinated people to contract and spread COVID-19 [61]. Another unwelcome discovery was that neither fully vaccinated individuals, nor those previously infected with SARS-CoV-2, maintained long-term immunity. They were found to have reduced risk of infection for about six months [62], but with wide individual variation and the titer levels required for individual protection are still being investigated. The emergence of new variants of the virus further complicated the situation towards the end of 2021 [63]. Combinations of two different COVID-19 vaccines (so-called “cross vaccination” or “mix-and-match”) were increasingly studied to gain better protection [64].

The Emergence of SARS-CoV-2 Variants of Concern (VoC)

Large number of infections globally gave rise to mutations of SARS-CoV-2. From the start of the pandemic, scientists were concerned that random mutations may increase transmissibility [65], pathogenic effects on humans, or enable the virus to evade immune response [66]. Mutations with significant effects on some of these properties would be termed “new variants”, and when their frequency among other variants is growing, they could be labelled "emerging variants" [67]. When new properties acquired by mutations are verified, they could be termed "variants under investigation" or "variants of interest" (VoI). When it also becomes very prevalent at national level, these were referred to as a "variant of concern" (VoC) [68,69]. Finally, if it can be confirmed that the effectiveness of prevention or intervention measures against the new variant is substantially reduced, it becomes a “variant of high consequence" [70]. During the first two years of the COVID-19 pandemic,

five SARS-CoV-2 variants have been designated as variants of concern by the WHO: the Alpha, Beta, Gamma, Delta, and Omicron variants (**Box 1**). **Table 3** shows their alternative nomenclature and properties.

The WHO announced Greek-letter names for important strains on 31 May 2021, so they could be easily referred to in a simple and non-stigmatising fashion [71]. Three main, generally used nomenclatures have been proposed [72]: (i) GISAID records eight global clades (S, O, L, V, G, GH, GR, and GV) [73]; (ii) Nextstrain, founded "for real-time tracking of pathogen evolution" [74], records 13 major clades[d] (19A–B, 20A–20J and 21A) [75]; and the Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) software team proposes [76] 1340 lineages. Public Health England (PHE) designated each tracked variant by year, month and number in the format [YY] [MMM]-[NN], prefixing 'VUI' or 'VOC' for a variant under investigation or a variant of concern [77] (**Table 3**).

Box1: Summary of Research on Five Variants of Concern (VoC) [65-70,77-78,83,98-100,121-131]

Alpha (lineage B.1.1.7)
First detected in October 2020 during the COVID-19 pandemic in the UK from a sample taken the previous month in Kent, lineage B.1.1.7. From October to December 2020, its prevalence doubled every 6.5 days, the presumed generational interval. It carries N501Y mutation and increased transmissibility, and possibly increased pathogenicity. It has now been verified in 192 locations worldwide. It acquired an N501Y mutation, which improves spike protein binding to cellular receptors making the virus more contagious. It also contains a D614G mutation, thought to enhance viral replication and a P681H mutation. Fortunately, COVID-19 vaccines and monoclonal antibody treatments remain highly effective against it. The WHO is also monitoring the spread of an Alpha variant that contains an additional E484K mutation, which may help the virus to slip past the body's immune defences.

Beta (lineage B.1.351)
On 18 December 2020, the Beta variant was first detected in South Africa. Its prevalence was higher among young people with no underlying health conditions, and it resulted more frequently in serious illness. It acquired several mutations in the receptor-binding domain (RBD) that allowed it to attach more easily to human cells: N501Y, D614G, E484K and K417N – the latter possibly helping SARS-CoV-2 to avoid neutralising antibodies generated through vaccination or previous infection. It has been verified in 139 locations worldwide (as of 3 Dec 2021). It is thought to be around 50% more transmissible than previous variants, but there's little evidence that Beta is associated with more severe disease. The main concern is reduced neutralisation by antibodies generated through vaccination or as a result of a previous infection.

Gamma (lineage P.1)
The Gamma variant or lineage P.1 was detected in Tokyo on 6 January 2021 among four travellers from the Brazilian Amazonas. Days later, the Brazil-UK CADDE Centre confirmed 13 local cases in the Amazon rainforest. It has been named P.1, a descendant of B.1.1.28. It has 17 unique amino acid changes, 10 of which are in its spike protein, including the three concerning mutations: N501Y, E484K and K417T. Gamma variant was absent in samples collected from March to November 2020 in Manaus, Brazil, but its frequency among other variants rose to 85% in early January 2021. It seems that Gamma can produce much larger viral loads and it has about 2 times higher transmissibility than the original strain. It may also be capable of evading 25–61% of inherited immunity from previous coronavirus diseases, and it might be 10–80% more lethal. It has now been verified in 98

locations worldwide. It also contains E484K, N501Y, D614G and K417T mutations, helping it to bind to human cells. It also carries H655Y mutation.

Delta (lineage B.1.617.2)
The Delta variant was first discovered in India in October 2020. It then became a globally dominant variant in the second half of 2021, spreading to at least 185 countries. It carries L452R and P681R mutations in Spike protein. In June 2021, Public Health England raised concerns as 12 of the 42 deaths from the Delta variant were among the fully vaccinated. Then, reports began to appear of a variant of Delta with the K417N mutation, so-called "Delta plus", which may reduce the effectiveness of vaccines and antibody treatments. In July 2021, further mutations were associated with "Delta plus" - AY.4.2, Y145H and A222V. It also contains the D614G mutation; then, T478K mutation, which is thought to help it avoid recognition by the immune system; and a P681R mutation, which may trigger the severe disease. It may be 40-60% more transmissible than the Alpha variant, and roughly twice as transmissible as the original Wuhan strain of SARS-CoV-2. It has a higher risk of hospitalisation compared with Alpha, and vaccines may be slightly less effective.

Omicron (lineage B.1.1.529)
The Omicron was declared a variant of concern by the WHO on 26 November 2021 after it started increasing in Gauteng province in South Africa. Then, it was rapidly identified in numerous countries in November, 2021. In early December 2021, it had been confirmed in 22 locations globally, on all continents. It also carries N501Y, D614G, K417N and T478K mutations, but it also has a larger number of other mutations, the effects of which are still unclear. It seems highly likely that it is the most transmissible variant yet, and also that it can evade the immune response, but also that it may have less affinity for the lungs and therefore be less deadly.

Important Missense Mutations acquired by Variants of Concern

Table 4 shows important missense mutations acquired by the five variants of concern and their likely significance [78]. Clearly, some mutations make the SARS-CoV-2 more infectious, others are associated with immune response evasion, while some may even lead to a more severe clinical picture. Besides these mutations, there are also many others identified in various other clades of SARS-CoV-2 that are causing some concern. One is del246-252, where all amino acids from the position of 246 to 252 in the N-terminal domain of spike protein are deleted, and the aspartic acid (D) at position 253 is replaced by asparagine (N) [79]. This unique mutation is found in the Lambda variant, and it may assist the evasion of antibodies [79]. Another monitored Lambda variant is F490S, where phenylalanine (F) is replaced by serine (S) at position 490, likely resulting in a less effective antibody treatment [79]. Other mutations under investigation include D614G, G446V, S477G/N, Q677P/H, A701V and others [78].

Effectiveness Against Variants and Universal Coronavirus vaccine

Table 5 shows the current knowledge of the effectiveness of the five vaccines that were produced to prevent the infection with the original Wuhan strain of SARS-CoV-2 against the five VoCs that emerged over the two years of the pandemic. US-based Center for Disease Control and other research groups reported that, generally, vaccine effectiveness fell from about 91% against Alpha to about 66% against Delta [80-83]. Then, one dose of the Oxford-

Oxford/AstraZeneca vaccine was 82% effective against hospitalisation or death caused by either the Beta or Gamma variants in Canada, while two doses of the Pfizer/BioNTech and Moderna mRNA vaccines appear to offer strong protection against all variants. Data from Brazil implied that the initial dose of the Sinovac's Coronavac Vaccine had approximately 50% efficacy against the Gamma variant, and was expected to increase further after the 2nd dose [78]. Oxford/AstraZeneca vaccine is expected to show effectiveness against the Gamma variant [84]. As for Omicron, a possible 20- to 40-fold reduction in neutralising activity for Omicron by sera from Pfizer/BioNTech 2-dose vaccinees was reported relative to earlier strains, but a booster dose increases vaccine effectiveness against symptomatic disease back to 70–75%, while it should be even higher against severe forms of the disease [85]. Because of these setbacks caused by the new variants, there is now much interest in a universal coronavirus vaccine (or so-called “pan coronavirus vaccine”), which would be effective against all coronavirus strains. Such a vaccine would also be able to prevent future coronavirus epidemics and pandemics [86], while research in heterologous vaccination is likely to proliferate and lead to new knowledge on immune system functioning.

In conclusion, it is very difficult to predict the further development of the COVID-19 pandemic. Clearly, there are reasons for optimism, as the vaccine development pipeline is likely to keep producing vaccines of an increasingly broad spectrum against coronaviruses, more easily deliverable and conferring more durable immune protection. On the other hand, the very large number of infections caused by the Omicron variant reminds us that a new variant could emerge at any time, and some may be associated with increased virulence and pathogenicity, which would represent yet another major setback in this pandemic. Therefore, at the beginning of 2022, a major goal of the global scientific community will be to develop interventions that will assist governments to control COVID-19 more effectively and enable a safer coexistence with the SARS-CoV-2 virus and its emerging variants.

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