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Review

COVID-19 vaccines: evidence, challenges and the future

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Summary

Through an unprecedented research and development process, in early 2021, just one year after the COVID-19 pandemic started devastating the world, there are several vaccines commercially available or in advances phase of testing, each with its own characteristics and challenges. For the first time in the history of vaccination, a global immunization program has started at a time of intense pandemic activity characterized by high virus transmission, facilitating selection of variants potentially able to escape the vaccine-induced antibody response. The reality is that one cannot rely on a single vaccine when dealing with a pandemic emergency: the urgent need of billions of doses clashes with the production capacity of the pharmaceutical industry. There is therefore no ideal vaccine, but there are many good vaccines to be used immediately. The current international debate about COVID-19 vaccines is today the hottest topic in global health whether it relates to technical and scientific issues or to the ethical aspects of access to vaccinations for all. This article aims at reviewing the status of vaccines that are used, or about to be used, in immunization campaigns worldwide.

Introduction

In recent decades, major outbreaks of emerging infectious diseases have become a serious and recurrent problem. According to a study published in Nature, about 40 new pathogens have been identified since the beginning of the new millennium, many of them from animal reservoirs [1]. In fact, most of these new infections are zoonoses, since they may originate in animals, at least in their initial emergence. Among all microorganisms, the ones that best fulfill the role of an emerging pathogen are viruses. In general, the risk of contracting a new virus of animal origin depends on the frequency of contact between humans and the animal species that is infected (the natural host). Measles and smallpox probably passed from livestock to humans with the introduction of farming over 10,000 years ago. In recent years, new viruses have emerged with increasing frequency from the animal context and have become a major global health threat: avian flu, Hendra, Nipah, SARS-CoV, MERS-CoV, Ebola, Zika, Chikungunya are just a few examples [2, 3].

The frequent emergence of zoonoses and their penetration into humans depend on many factors. Economic interests are leading to deforestation and therefore destruction of natural habitats with, as a consequence, greater contact among wild animals, domestic animals and humans. The trade of bushmeat in urban markets, once limited to rural areas, represents another factor that could carry new pathogens to humans. Climate change has also a significant role in facilitating the progressive movement of vectors towards previously un-infested areas. Furthermore, with the multiplicity of aspects of globalization and with the abolition of previous barriers, humans, animals and goods can move over long distances and reach different continents in a few hours. Hence, the conclusion that "a health threat anywhere is a health threat everywhere". Coping with the spread of new infectious diseases therefore requires a worldwide coordinated effort, that is at the same time in the realm of a health response as well as of political and economic nature.

The current international debate about COVID-19 vaccines is today the hottest topic in global health whether it relates to technical and scientific issues or to the ethical aspects of access to vaccinations for all. Through an unprecedented research and development process, in early 2021, just one year after the COVID-19 pandemic started devastating the world, there are several vaccines commercially available or in advances phase of testing, each with its own characteristics and challenges. This article aims at reviewing the status of vaccines that are used, or about to be used, in immunization campaigns worldwide.

An unprecedented research and implementation effort

The remarkable phenomenon one has witnessed in the past several months is that, after the approval of the first vaccines from Pfizer-BioNTech, Moderna and

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AstraZeneca, other pharmaceutical companies have continued their research efforts, and stringent regulatory authorities have not shied away from the preparatory work to approve new vaccines. This is per se something exceptional, as is the recent announcement that two competitor pharmaceutical companies have agreed to cooperate in the production of a vaccine that one of the two has developed [4]. In fact, it would be imprudent to rely on one vaccine only to cope with a major health emergency such as this pandemic that requires a simultaneous response worldwide. The need of billions of doses to be made readily available clashes with the pharmaceutical industry production capacity, and this has prompted an unprecedented intensive response by industry and governments. Indeed, one has little options: several vaccines must be developed, and all those authorized must be rapidly put into use through effective and strategic campaigns in every country. At the moment, clinical trials are being conducted worldwide on over 80 vaccines, half of which have reached the final phase of experimentation, and at least 180 experimental products are currently in preclinical phase of trials and animal testing has started [5]. Nine vaccines were already authorized in some countries for emergency use based on preliminary evidence of their safety and efficacy, and eight of them (Pfizer/BioNTech, Moderna, AstraZeneca, Cansino, Sinovac, Sinopharm Wuhan, Gamaleya, Vector Institute) were approved by regulatory agencies in some other countries after review of the final trial results [6].

The progress carried in the biotechnology field over the past few years has provided an important boost in the development of vaccines produced through the use of less complex and less expensive methods such as genetic engineering techniques. These techniques allow to obtain in a short time massive amounts of vaccines compared to traditional techniques which were based on the isolation followed by the attenuation or inactivation, and finally the purification of the pathogen. Regardless of the technology used in their development, all vaccines approved or still under study were developed to stimulate in the vaccinated individuals an immune response targeting the blockage of the SARS-CoV-2's Spike protein which has a key role in the viral entry into human cells.

EMA and FDA approved vaccines

The European Medicines Agency (EMA) is the agency of the European Union (EU) responsible for the evaluation and supervision of medicinal products. As of the end of May 2021, the EMA had approved four COVID-19 vaccines: two of them are mRNA vaccines and two are viral vector vaccines. The other major stringent regulatory authority is the US Food and Drug Administration (FDA) that had approved, as of the end of May 2021, three vaccines: two are the same mRNA-based vaccines approved by EMA, while one is a viral vector vaccine. Table I shows the main characteristics of the EMA and FDA approved vaccines as of the end of May 2021.

mRNA-based vaccines approved by both EMA and FDA

Pfizer/BioNTech (BNT162) and Moderna (mRNA-1273) vaccines were approved by EMA in December 2020 and January 2021 respectively, and by FDA, which issued emergency use authorizations in December 2020 and extended them in May 2021 to include adolescents between 12 and 15 years of age [7].

They are both composed of molecules of messenger ribonucleic acid (mRNA) which contains the instructions for the synthesis of the Spike protein in the cells of the vaccinated subject. Both vaccines were demonstrated to be safe in clinical trials. They require two administrations (at 21 or 28 days from the first administration, with a maximum delay between two doses of 42 days). The Pfizer/BioNTech vaccine phase 3 trial [8] involved 43,998 subjects between 12 and 85 years of age who received both doses, whereas Moderna phase 3 trial [9] included 30,000 participants older than 18 years (3,000 teenagers between 12 and

Tab. I. Characteristics of the four COVID-19 vaccines approved by stringent regulatory authorities and available in Europe as of the end of March 2021.

Vaccine	Type	Efficacy	Indications	Administration	Effect on transmission	Activity against variants	Side effects	Cold chain	Price in EU (€)
Pfizer-BioNTech COMINARTY	mRNA	95%	> 16 Also elderly Pregnancy	2nd dose 21-28d	Unknown	Unclear	Fever, local reaction, allergy	-70°C (2-8°C x 5d)	12.00
Moderna-mRNA 1273 (NIAID)	mRNA	92%	> 18 Also elderly Pregnancy	2nd dose 28d and up to 42d	Unknown	Probable	Fever, local reaction, allergy	-20°C (6 months)	15.30
Oxford-AstraZeneca AZD1222	ChAdOx1	63%	> 18 Also > 65 Pregnancy	2nd dose 8-12w (longer interval increases efficacy)	Unknown	Possible slight reduction of effectiveness on B1.1.1.7	Fever, local reaction, allergy	2-8°C	1.80
Johnson & Johnson Ad26.COV2.S	Ad26	85%	>18	Single dose	Unknown	Unknown	Fatigue, headache, myalgia, fever		7.30

18 years were also included) receiving the two doses. The most common reported side effects related to BNT162 were fatigue (3.8%), headache (2%), together with severe allergic reactions (2/10,000 vaccinated subjects in United Kingdom). Fatigue (9.7%), muscle and joint pain (8.9% and 5.2%), headache and injection site erythema were described for mRNA-1273 vaccine. The efficacy estimated in these trials was 95% (95% CI: 91-98%) for the Pfizer/BioNTech vaccine, with 170 infections reported at 4 weeks from the 2nd administration. For the Moderna vaccine the estimated efficacy was 94% (95% CI: 90-97%) with 196 infections reported at 2 weeks from the 2nd administration. In addition, the Moderna mRNA-1273 vaccine had an efficacy of 86% (95% CI: 61-95%) among patients over 55 years old [10], compared to 95% (95% CI: 67-100%) of the Pfizer/BioNTech product. The major drawback of these two mRNA-based vaccines is the storage requirement at -70°C (or 2-8°C for 5 days) for the Pfizer/BioNTech vaccine and at -20°C (for 6 months) for the Moderna vaccine.

Because of their safety and high efficacy, these two mRNA-based vaccines are now recommended in persons older than 16 years, in particular in high-risk individuals that are more vulnerable to severe forms of COVID-19. At the end of May 2021, EMA and AIFA approved the use of the vaccine from Pfizer/BioNTech in adolescents from 12 to 15 years [11].

Viral vector vaccines approved by EMA and FDA

AstraZeneca/Vaxzevria's vaccine, ChAdOx1 nCoV-19, is the viral vector-based vaccine approved by EMA and filed for FDA approval. It uses a modified version of a chimpanzee's adenovirus which is not able to replicate but can provide the instructions for the Spike protein synthesis. Once the protein is produced, it can stimulate a specific immune response of both cellular and humoral nature. Compared to mRNA-based vaccines, this vaccine has a better stability which does not require excessively cold temperatures for storage and transportation (between -8 and +2°C). The phase 3 trial on the vaccine involved more than 24,000 subjects aged over 18 years from UK, Brazil and South Africa.

It requires 2 administrations. The efficacy in subjects who received two standard doses was 66.7% (95% CI: 57.4-74.0%) and 81 infectious cases were described among vaccinated individuals 2 weeks after the 2nd administration. However, the efficacy was 76% after a single standard dose (from day 22 to day 90). Most participants in the UK received the booster dose more than 12 weeks from the first administration, and the vaccine efficacy was higher in this population (81.3%) compared with those who received the second administration earlier [12]. The primary analysis of a trial conducted on over thirty thousand patients in the US showed an overall efficacy of 76% (95% CI: 68-82%) after the 2nd dose and an efficacy of 85% (95% CI: 58-95%) in adults older than 65 [13].

Its safety and efficacy in older age groups was assessed on a phase 2/3 trial carried out in the UK involving 240 adults older than 70 years. Local and systemic reactions were less frequent in older age groups, with similar humoral and cellular immune responses compared to younger populations [14]. Earlier on, doubts on safety arose due to two cases of transverse myelitis being described following vaccination (at 10 and 14 days from the 2nd administration). Both cases were later reported to be unlikely related to the vaccine. However, later the use of the vaccine was associated with some deaths in different European countries that were attributed to thromboembolic events. These were mainly reported within 14 days from the first dose in individuals younger than 60 years and with a greater frequency in females. This phenomenon has been attributed to a response similar to the one occurring in heparin-induced thrombocytopenia. These adverse events prompted some EU countries (e.g., Austria, Bulgaria, Denmark, Estonia, Germany, Iceland, Italy Latvia, Lithuania, Luxembourg, Norway and Romania) to suspend the administration of the vaccine as a precautionary measure pending further investigations. The EMA's safety committee (PRAC), after reviewing the available information, on 18 March 2021 suggested that "the vaccine's benefits continue to outweigh the risks of side effects", adding that the vaccine is not associated with an increased risk of thromboembolic events nor that specific batches were related to those events. WHO confirmed the recommendations of the EMA stating that the "benefits of the AstraZeneca vaccine outweigh its risks" and therefore recommended that vaccination campaigns continue [15]. However, in April 2021, as further episodes of thromboembolic events (in particular cerebral sinus vein thrombosis: 169 identified cases; and splanchnic vein thrombosis: 53 cases) were described, the European PRAC committee advised that very rare cases of thromboembolism associated to thrombocytopenia should be included as possible side effects of Vaxzevria vaccine [16].

As of May 2021, EMA and WHO still recommend the administration of the vaccine with a careful monitoring of vaccinated individuals, and a preferential use in individuals older than 60 years has been adopted in different countries.

The Johnson & Johnson vaccine, recently approved by the US FDA and by EMA [17], is a viral vector-based vaccine, which uses type 26 human adenovirus administered intramuscularly to adults ≥ 18 years of age. It requires a single administration and its storage temperature does not represent a problem as it can be kept stable for 3 months at +2/+8°C and for 2 years at -20°C. This vaccine was tested in over 43,000 subjects of different age groups (including 34% over age 60) and at different latitudes, from the USA to Latin America and South Africa. It was especially evaluated in patients with comorbidities such as obesity, diabetes, cancers, HIV, obtaining results reaching 100% efficacy in preventing hospitalization or death, and 85% against severe forms of COVID-19 [18]. Furthermore, this vaccine was tested in South Africa when the South African variant was already in circulation. The mean efficacy in moderate to severe forms was 65%, meaning that it has

partial efficacy against the variant. The most common adverse events reported in the trial were injection site reactions, headache, fatigue, myalgia, nausea and fever [19]. Similar to the case of Vaxzevria, some cases of thrombosis with thrombocytopenia were described in patients who received Janssen's vaccine. For this reason, at the end of April 2021, EMA listed these events as a very rare side effect of the vaccine, still recommending, however, its usage [20].

Of relevance, Johnson and Johnson is planning to start testing in children between 2 months and 18 years in different international centers. Based on all these considerations, the US-based company filed phase 3 trial data for a single administration of its anti-COVID-19 vaccine and the US FDA authorized it for use in emergency situations on February 27th, 2021.

Remarkably, a very recent agreement between Johnson & Johnson and its competitor pharmaceutical giant Merck & Co, brokered by the White House, could lead to a faster production of the vaccine in the US. According to this agreement, Merck & Co will be co-manufacturing the Johnson & Johnson vaccine thus allowing production of enough doses sufficient to cover the entire adult population of the United States by the end of May [4]. The EU authorized at the beginning of March the emergency use of the vaccine and already established an agreement for the purchase of 200 million doses together with an option for another 200 million doses.

Vaccines being considered for approval

Sputnik V

The delays in the delivery by Pfizer and the safety concerns arisen by the AstraZeneca vaccine are now prompting the EMA to explore approval of the Russian Sputnik V vaccine which may result in purchasing by the EU Member States. The Sputnik V vaccine was so named from the first Soviet space satellite, Sputnik-1, which was launched in 1957. This event resulted in a new boost to space research all over the world creating the so-called "Sputnik moment" shared by the global community. This viral vector vaccine employs two human adenoviruses (rAd26 and rAd5) which transfer the SARS-CoV-2 Spike protein gene into human cells. Human adenoviruses are considered among the easiest viruses to engineer and therefore became very popular vectors. Sputnik V utilizes these two distinct adenovirus vectors dispensed separately in two administrations at 21 days distance from one another and induces a strong and specific antibody response against SARS-CoV-2. This strategy is conceived to prevent development of immunity against the first adenovirus injected (rAd26) which could impair response to the booster dose if the same virus were used as vector. This vaccine has now been registered in more than 25 countries. The clinical study post Sputnik V registration carried out in Russia involved more than 31,000 volunteers (study population between 18 and 60 years) while phase 3 clinical trials were conducted in United Arab Emirates, India, Venezuela and Belarus. Initially, doubts arose regarding the efficacy of the vaccine lacking assessment by an independent stringent regulatory agency. These doubts however were successfully addressed by a large study finally published in February 2021 [21]. This study showed an efficacy of 91.6% (95% CI: 85.6-95.2%) based on the analysis of data from almost 20.000 volunteers (18-87 years) who received both a first and second administration either of the vaccine or of a placebo.

Starting at 21 days after the first dose of vaccine (the day of dose 2), 16 (0.1%) of 14,964 participants in the vaccine group and 62 (1.3%) of 4,902 in the placebo group developed COVID-19; vaccine efficacy was therefore estimated to be 91.6% (95% CI: 85.6-95.2). Of note, the vaccine efficacy was 91.8% (95% CI: 67.1-98.3) in participants older than 60 years. The study also showed the safety of Sputnik V, the most common adverse events being flu-like illness and local reactions, observed, respectively, in 156 and 56 participants in the vaccine group. The freeze-dried form of the vaccine can be stored at temperatures between +2 and +8°C, which is a strong point in favour of this product since it allows for an easier distribution around the world including in areas which are difficult to reach or when the cold chain cannot be guaranteed. In Moscow, Russia, the vaccine is administered in drugstores and even in some supermarkets.

Novavax

The Novavax NVX-CoV2373 vaccine is a protein-based vaccine composed of SARS-CoV-2 Spike recombinant proteins. It contains an "adjuvant" (saponins), which contributes to strengthen the immune response to the vaccine. Two administrations are planned to be dispensed at 21 days distance from each other. The vaccine target is set to adults between 18 and 84 years of age. Novavax vaccine can be stored between 2 and 8°C and is shipped in a ready-to-use liquid formulation. The company announced an efficacy of 89.3% (95% CI: 75.2-95.4%) following a phase 3 trial conducted in Great Britain (15,000 volunteers, 27% of which were over 65), in a moment in which the UK variant was emerging and circulating widely. Sixty-two COVID-19 cases were described in the trial, 6 of which were among the vaccinated subjects. Of these infections, half were caused by the UK variant, allowing to estimate an efficacy of the vaccine against the Wuhan strain of 95.6% and against the British variant B.1.1.7 of 85.6% [22]. A smaller phase 2b clinical trial conducted in South Africa (4,400 volunteers, 6% of which were HIV-positive) could raise doubts regarding its efficacy on variants. In that context, an antibody-resistant variant was found in a high percentage of infected persons (90%), lowering the overall efficacy of the vaccine to 60% (95% CI: 19.9-80.1%) and to 49% (95% CI: 6.1-72.8%) among HIV-positive volunteers. A phase 3 trial is currently being carried out in the United States and Mexico (30,000 volunteers) to evaluate the efficacy,

safety and immunogenicity of this vaccine in different populations [23]. The vaccine is under rolling review since February 3rd, 2021 [24] and the European Commission is currently negotiating a pre-purchase contract with the company. The rolling review is a regulatory tool that EMA uses to speed up the evaluation of a drug during emergencies, this involves the EMA's human medicines committee (CHMP), which reviews data coming from ongoing studies as soon as they become available.

Valneva

Another vaccine in advanced phase of development is that of Valneva, a French-Austrian company. This vaccine uses inactivated viruses incapable of infecting and multiplying. The virus, despite being killed, maintains all its antigenic properties beyond the Spike protein. This characteristic makes it potentially more immunogenic. Valneva started its phase 1 and 2 trials in December 2020 on patients between 18 and 55 years of age [25].
Once studies are completed, both the Novavax and the Valneva vaccine manufacturers are likely to sign agreements with the EU for the provision of large quantities of vaccines. The negotiations between the EU and Valneva are on an advanced stage for a supply of up to 60 million doses of VLA2001 [26]. The EU is also close to reach a final agreement with Novavax for 100 million doses together with another optional 100 million doses [27].

ReiThera

The ReiThera vaccine, developed by the Italian company from the Pomezia's technopole together with the Spallanzani Hospital of Rome and the University of Padova, uses a technology that is very similar to that of AstraZeneca and that takes advantage of a primate's adenovirus (from gorilla) modified so as to express the Spike protein. It recently obtained the green light by AIFA at the end of phase 1 showing safety and immunogenicity, and the testing is now proceeding with phase 2 of trial in different Italian centers [28]. Healthy adults will be included, followed by those over 65 and those affected by chronic conditions [29]. The objective is to rapidly obtain the required registration from both the Italian and EU medicine authorities and swiftly proceed with the large-scale utilization of the vaccine. The Italian Government is financing phase 2 and 3 of the trial which should be completed in June 2021. An effort was requested to the Italian Regional Governments to help finance an early production of the vaccine, trusting in the favorable outcome of the trial, in order to have the first doses readily available as soon as the vaccine is authorized thus shortening the time required to reach full production capacity.

CureVac

Early in February 2021, EMA started a rolling review of CureVac's CVnCoV, a mRNA vaccine, based on preliminary results from laboratory and clinical studies [30]. The results of the rolling review will provide evidence for a possible marketing authorization. Phase 1 study results showed a good tolerability together with a strong antibody and T cell response, reaching titers comparable to those of recovered COVID-19 patients. The vaccine should be administered twice, at day 1 and at day 29 and can be stored at suitable conditions (+5°C for at least three months and 24h at room temperature before administration) [31]. Additionally, a preclinical study on mouse models showed protection against the "South African" SARS-CoV-2 variant. The HERALD study, a phase 2b/3 study initiated in December 2020 has so far recruited 40,000 participants worldwide and will further characterize the efficacy of the vaccine against SARS-CoV-2 and its variants [32].
Of interest, at the beginning of March 2021, the Swiss company signed an agreement with Novartis for the production of CVnCoV, which should start in the 2nd quarter of 2021, with the production of 50 million doses by the end of the year and further 200 million doses in 2022 [32].

Sinovac

At the beginning of May, EMA announced the starting of another rolling review, evaluating the efficacy and safety of the Chinese company Sinovac Life Sciences Co. (Life'On) vaccine, Vero Cell Inactivated [33]. The vaccine was first authorized in China in February 2021 and has since then been authorized by more than 30 countries in adults older than 18 years, with 260 million doses which have been already distributed worldwide [34].
Vero Cell is an inactivated viral vaccine containing inactivated SARS-CoV-2 as antigen, together with an adjuvant. The vaccination schedule consists in two administrations, at 14-28 days distance, and the vaccine can be stored at 2-8°C. Phase 3 studies are taking place in different countries (China, Brazil, Indonesia, Turkey, Chile). As of end of May 2021, the most common adverse events which were described are pain at the injection site, headache, fever and myalgia. In China, where more than 35 million doses have been administered, 49 serious adverse events were reported. These include demyelination, cerebral hemorrhage, Henoch-Schönlein purpura, anaphylaxis and laryngeal edema. Overall, the vaccine showed an efficacy of 67% (95% CI: 65-69%) in preventing the infection and of 85% (95% CI: 83-87%) in preventing hospital admissions [34].

Is there an ideal COVID-19 vaccine?

With several COVID-19 vaccines now available and in an advance phase of the development pipeline, country authorities would be tempted to try and rank them to make a rational decision on which would better fit the needs of a certain country and that therefore should be adopted. However, the reality is that one cannot rely on a single vaccine when dealing with a pandemic emergency: the urgent need of billions of doses clashes with the production capacity of the pharmaceutical industry. There is no alternative therefore to the adoption

of all authorized vaccines and their urgent delivery to people through well-thought strategic campaigns. The development and validation of those still in trial phase is essential, as this is one important way to reduce the circulation of the virus and the potential emergence of new variants. The situation is extremely delicate: for the first time in the history of vaccination, a global immunization programme has started at a time of intense pandemic activity characterized by high virus transmission. This is a very favorable situation for the virus, facilitating selection of variants potentially able to escape the vaccine-induced antibody response. There is therefore no ideal vaccine, but there are many good vaccines to be used immediately. In other words, we do not have the 'luxury' of selecting one ideal product since to vaccinate billions in a very short time requires urgent adoption of all vaccines that are authorized.

Current vaccination campaign in Italy

The anti-COVID vaccination campaign in Italy began in late December 2020 and has been structured in 4 phases by the government. The strategy has been subsequently updated in early February 2021 after the approval of the AstraZeneca vaccine, which was shown to be suitable for the target population of phase 3 (school and university staff; armed police forces; prisons; community places) [35]. More than 84 million doses should be administered (2 doses per vaccinated person) to achieve the goal of vaccinating 80% (conventionally established to guarantee herd immunity) of the Italian population by September 2021 [36]. As of 31 May 2021, 34,900,000 doses had been administered and 12,000,000 people had been fully vaccinated (of those, 630,000 were vaccinated with a monodose vaccine), representing 20.38% of the total population [37]. The initial slow coverage has been attributed mainly to delays in supply and distribution of vaccines by pharmaceutical companies, compounded with poor planning and organization of vaccination services in some regions. However, at the current pace and with the current average rate of daily vaccinations, it would take almost 4 additional months to cover 70% of the population. Therefore, the government's target would be reached by end of September 2021 (with a delay of one month with respect to deadline of end of August 2021 set by the government) [38]. This situation could be complicated by the consideration that 70% vaccination coverage may no longer be sufficient to interrupt virus transmission given the new and more transmissible variants already circulating and progressively replacing the original strain of SARS-CoV-2 against which vaccines were produced.

Limitations of current vaccines

While an unprecedented research effort has in one year resulted in the development of numerous vaccine candidates and the introduction of large-scale campaigns of a few of them, there are important and critical limitations that may prevent a successful containment effort of the COVID-19 pandemic: the emergence of variants and the uncertainties around the duration of protection. These factors add to the widespread adverse feelings in some segments of the population that oppose vaccination practices due to ignorance and misinformation.

The appearance of virus variants is an expected event and is part of nature's variability. The identification of variants is possible by applying advanced gene sequencing techniques capable of detecting mutations in the viral genome. These mutations occur more frequently in RNA viruses, including the influenza Orthomyxoviruses, Hepatitis C virus and HIV, especially when they find a way to replicate and widely spread in the population. Neutralizing antibodies are usually induced by infection or vaccination, so that a strong neutralizing antibody response is built up to suppress virus replication. A weak response does little to suppress replication, but neutralizing antibodies that have intermediate potency are thought to cause the virus to evolve and create ways to escape the constraint on its ability to replicate.

Therefore, the occurrence of SARS-CoV-2 mutations capable of producing variants able to replace original wild strains if they become more transmissible, was predictable. Among the SARS-CoV-2 genes that most frequently mutate there is the one encoding for the Spike protein. This protein is a key to transmission as it is involved in binding with the ACE human cell receptors and is also the target of neutralizing antibodies produced as part of the natural response or the vaccine. Data published by WHO on over 10,000 SARS-CoV-2 genomes from 68 countries sequenced to date indicate the appearance of almost 6,000 mutated strains. Not unexpectedly, only a few of those became well established in the population by showing a relevant epidemiological advantage. Hence, the denomination of "variant" [39]. The "English", "South African", "Brazilian" and "Indian" variants are among them. It is known today that all four variants are characterized by a higher transmissibility and the vaccine seems to be protective against the English one, while there are less certainties for the South African, Brazilian and Indian ones. Table II shows the significant variants identified so far.

The most recent identified variant, the Indian one, has 13 mutations, including two notable ones in the Spike protein that the virus uses to bind and infect cells. One of the mutations, E484Q, is similar to that found in the variants identified in South Africa and Brazil (E484K). The other, known as L452R, may boost viral transmission. The two mutations are in important parts of the structure of the Spike protein that is linked to the interaction of the virus with the host.

Scientists are also looking into a third mutation, P681R, which might help the virus replicate more quickly [40].

In laboratory-based studies, the South African variant was found to be partially resistant to neutralizing antibodies induced by 2 doses of the Pfizer mRNA

Tab. II. The main characteristics of the principal variants identified as of the end of March 2021.

Lineage and variant name	Location of first detection	Date of first detection	Mutations	Spread [63]	Clinical significance	Vaccine efficacy
B.1	China	02/2020	D614G (spike protein gene)	Global	More infectious, overgrew wild type strain globally	Pfizer: 95% Moderna: 95% AstraZeneca: 82% Johnson & Johnson: 85-100% Novavax: 95% Sputnik V: 91%
B1.1.7 (VOC 202012/01 or 501Y.V1)	UK	03/2020	P681H (may increase the production of Spike proteins) N501H (not likely to be involved in vaccine resistance) H69-V70 Y144/45 (may help evade antibodies)	Variant reported by 94 countries, sequenced in 102 countries	More infectious, causes more severe infections	AstraZeneca: 74% Novavax: 85%
Cluster 5 ΔFVI-spike	Denmark	09/2020	Y453F 69-70deltaHV	Extinct as the Danish minks' population was culled	Spread from minks to humans, causing an infection not more severe than the B.1 lineage. Causes weaker antibody response	Not known, but mutation may be related to a reduced vaccine response.
B1.351 (501Y.V2)	South Africa	10/2020	N501Y (similar to N501H mutation) K417N E484K (may help evade antibodies)	Variant reported by 48 countries, sequenced in 58 countries	More infectious and more resistant to neutralization	Novavax: 60% Johnson & Johnson: 65%
P.1 (501Y.V3)	Brazil, Japan	12/2020	N501Y K417T E484K	Variant reported and sequenced by 26 countries	More infectious, more severe infections. Escapes neutralization by circulating antibodies	AstraZeneca: preliminary data shows efficacy (results not published)
B.1.427, B.1.429 (CAL.20C)	USA	06/2020	L452R (increases transmissibility)	B.1.427 reported by 14 countries B.1.429 reported by 15 countries	Not yet shown to be more infectious, neither to be related to a more severe infection	Not known
B.1.617	India	10/2020	E484Q (may help evade antibodies) L452R P681R (increases infectivity)	Variant reported by 30 countries	More infectious and reported to be more resistant to neutralization	Bharat's Biotech: preliminary results show efficacy [64]

vaccine, the Moderna mRNA vaccine, and the Novavax protein vaccine [41, 42]. Moreover, single-dose Pfizer vaccine serum antibodies were shown to be completely ineffective in neutralizing this particular variant. At present, most scientists active in this area are reasonably optimistic that the efficacy of the mRNA vaccines will

not be substantially compromised by the South African and Brazilian variants, but there is a clear need for a definitive, national testing program to determine the properties of virus variants. Neutralizing antibodies induced by the AstraZeneca adenovirus vaccine had very low activity against the South African variant and the vaccine was ineffective at protecting against this strain [43].

Two doses of the Pfizer, Moderna, and Novavax vaccines are widely thought to be required for maximal efficacy, given that neutralizing antibodies can be detected after the first vaccine dose, but their titers are strongly boosted by the second one. Accordingly, the vaccines are less effective during the interdose period than after the second dose administration. Increased efficacy is not the only advantage of administering the second dose. In fact, when people are infected after the first dose but before the second dose, the virus can replicate in the setting of a suboptimal level of neutralizing antibodies, a situation in which resistant variants may emerge [44].

Another issue with significant implications involves what happens when a mRNA vaccine is given to a person who has recovered from COVID-19. Recent studies seemed to demonstrate that a single mRNA vaccine dose rapidly boosts neutralizing antibody titers to very high levels. Moreover, antibody responses against South African and Brazilian variants seems to be reduced in patients who had been infected with the Wuhan strain or United Kingdom variant but a single dose of Pfizer/BioNTech vaccine seems to increase neutralizing activity against them [45].

Considering the number of people in the world who have had COVID-19 and the possibility to only administer one dose to those who recovered from COVID-19, there is a potential to save a huge number of vaccine doses. A related issue is that the mRNA vaccines appear to trigger stronger adverse effects (headaches and mild fever) in people who have previously been infected with COVID-19. One potential solution to the adverse effect problem might be the administration of the Novavax protein vaccine. This vaccine seems to boost antibody levels in previously infected patients, particularly in younger individuals and to elicit fewer adverse effects than the mRNA vaccines with a similar efficacy. However, data from carefully designed clinical trials are needed to address these issues and inform the best decisions [46].

In conclusion, the more the virus changes and additional variants emerge and spread in the population, the more it will be necessary to adapt the vaccine formulations to obtain adequate protection for the population. However, anti-SARS-CoV-2 vaccines are able to elicit SARS-CoV-2-specific CD4+ and CD8+ T cell responses [47] which do not seem to be impaired in the response to the variants [48].

Therefore, a major concern is that of the durability and duration of current vaccines which on the basis of the various clinical trials has been estimated to be in the range of 10-12 months. Continuous monitoring of circulating viral strains is therefore essential to assess the impact of variants on the efficacy of vaccines, besides the performance of diagnostic tests. Only through quick adaptation of diagnostic methods and vaccine composition can one hope to keep the pace with the rapid evolving of SARS-CoV-2. Modern technology should be able to cope with this natural phenomenon [49]. Initiatives such as that recently proposed by the European Commission and consisting in a bio-defense preparedness plan against COVID-19 variants called "HERA Incubator", are necessary. This emergency program will tackle the short to medium-term threat and simultaneously prepare for the future. It will serve as the vanguard for the European Health Emergency Preparedness and Response Authority (HERA). HERA would provide a structural system to enable the EU to anticipate and tackle better future pandemics. In particular, work with researchers, biotechnology companies, manufacturers and public authorities has been planned to rapidly detect and analyze new variants, provide incentives to develop new and adapted vaccines, speed up the approval process and ensure scaling up of manufacturing capacities [50].

What's the future of COVID-19?

The current COVID-19 pandemic has undoubtedly raised awareness of the impact infectious diseases may have on health, economy and society as a whole. The valuable lessons to learn from this situation can be summed up in three words: speed, preparedness and public health response. First, speed has characterized not only the spread of the pandemic but also the deployment of all the efforts to counter it as well expressed by the rapid development of several diagnostic tests and vaccines which were authorized for use in less than a year. Secondly, preparedness is the key when fighting epidemics. To successfully organize a response and control effort while the epidemic is ongoing is a difficult task. Health systems and services need to be in place before an epidemic outbreak occurs. Preparedness is an essential requirement of the International Health Regulations (IHR) and signatory countries should implement a proper monitoring system based on the State Party self-assessment annual reporting tool and on joint external evaluations as recommended by WHO [51, 52]. Thirdly, the considerable impact of COVID-19 on society and the economy has abruptly brought the concept of an adequate public health response to the top of priorities of the contemporary highly inter-connected world: surveillance of new infections, rapid detection of epidemics, and ability to interrupt the transmission chain of the virus through pharmaceutical and non-pharmaceutical tools are crucial interventions to be implement at local, national and global level.

Vaccines have an established role in preventing pandemics and in curbing the spread of a disease like COVID-19. However, ensuring worldwide access to COVID-19 vaccines remains a major concern. Authorizing the use of a product in a country does not automatically translate into wide access to all and especially the poorest and

most marginalized [53]. The price needs to be affordable and effective health systems must be in place to guarantee access at-scale. Crucially important are negotiations with industry that are crucial to facilitate access for the poorest countries. An initiative named COVAX has been established through an agreement among the Coalition for Epidemic Preparedness Innovations (CEPI), the GAVI Vaccine Alliance and WHO, jointly with the delivery partner UNICEF, with the aim to "accelerate the development and manufacture of COVID-19 vaccines, and guarantee fair and equitable access for every country in the world" [54]. However, it has been previously reported that entities representing only 16% of the worldwide population secured 70% of the doses of vaccines available [54]. More recently, at the end of May 2021, high- and upper-middle income countries that include 50% of the worldwide population had administered 85% of all vaccines available, while low-income countries, mostly in Africa, could access less than 1% of vaccines available worldwide [55]. COVAX has tried to address the inequity by shipping 76 million vaccines to 126 participants [56], in what is considered "the largest vaccine roll-out in history" [57]. While this is progress, it is far from sufficient to address the needs of the poorest countries. In the month of January 2021, WHO issued a call open to anybody in any country, including public health and political authorities as well as pharmaceutical companies, to build a global sense of solidarity and ensure that as soon as possible vaccination for the highest-risk people, especially the elderly and health workers, becomes possible everywhere [58].

Lately, several activist organizations have voiced their frustrations about the lack of access to vaccines in the poorest countries and issued calls to stakeholders to urgently find a solution. MSF, for instance, has applauded "the US government's bold decision to support the waiving of intellectual property on COVID-19 vaccines during this time of unprecedented global need" [59]. Likewise, the International Federation of the Red Cross has requested an acceleration, under the World Trade Organization (WTO) umbrella, of negotiations related to intellectual property and other barriers to a rapid scaling up of vaccine production all over the world [60]. A political debate has thus ensued. Already in October 2020, India and South Africa proposed a temporary waiver of certain Trade-Related Intellectual Property Rights (TRIPS) Agreement provisions to the WTO. Recently, this call has been backed by most low and middle-income countries as well as by the WHO. Despite the call, high-income countries, including the UK and the European Union where many pharmaceutical companies are located, have blocked negotiations and progress of the initiative. The political debate has thus created a divide between those for whom access to COVID-19 vaccines is a needed humanitarian gesture towards the poorer and those who instead are concerned about the consequences for the pharmaceutical industry that, deprived of the patent benefits, may reduce future involvement in research and development and loose motivation to invest in innovations. The political discussion continued during the Global Health Summit held in Rome on 21 May 2021 in the context of the G20 Italian Presidency. Leaders of the G20 and several international organizations issued a document called "Rome Declaration" where, besides strong support to the prevention and preparedness efforts to be undertaken by all countries, a statement was made to be "working consistently within the TRIPS agreement and the 2001 Doha Declaration on the TRIPS agreement and Public Health; and Promoting the use of tools such as voluntary licencing agreements of intellectual property, voluntary technology and know-how transfers, and patent pooling on mutually-agreed terms" [61]. Hopefully, this development will be the basis for a definitive solution to the issue of access to COVID-19 vaccines for all countries worldwide.

In conclusion, as the WHO declaration spells out, "distributing COVID-19 vaccines quickly and equitably is essential to end this pandemic, restart our economies and begin to tackle the other great challenges of our time, like food insecurity, inequality and the climate crisis" [62].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

ET wrote the manuscript; CG, MT, CF performed the bibliographic research, revised and updated the manuscript; MCR and AA conceived the design and critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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