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Human Immunology 83 (2022) 755–767

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Immunogenicity, effectiveness, safety and psychological impact of COVID-19 mRNA vaccines

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ARTICLE INFO

Keywords:
Comirnaty
Spikevax
Immunity
SARS-CoV-2
Vaccination

ABSTRACT

In December 2019, a new single-stranded RNA coronavirus, SARS-CoV-2, appeared in China and quickly spread around the world leading to a pandemic. Infection with SARS-CoV-2 generates symptoms ranging from asymptomatic to severe, occasionally requiring hospitalization in intensive care units, and, in more severe cases, leading to death. Scientists and researchers around the world have made a real race against time to develop various vaccines to slow down and stop the spread of the virus. In addition to conventional viral vector vaccines, new generation mRNA vaccines, BNT152b2 (Comirnaty) and mRNA-1273 (Spikevax), have been developed respectively by Pfizer/BioNTech and Moderna. These vaccines act on immune cells to induce an immune response with the production of specific antibodies against Spike protein of SARS-CoV-2, and to stimulate the differentiation of T and B memory cells. The objective of this review is to provide a detailed picture of the validity of these new vaccines and the safety of vaccination. Not only was the immunogenic effect of mRNA vaccines evaluated, but also the psychosocial impact they had on the population. The data collected show that this type of vaccine can also be an excellent candidate for future treatment and eradication of possible new pathologies with viral and non-viral etiology.

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https://doi.org/10.1016/j.humimm.2022.08.004
Received 3 January 2022; Revised 10 July 2022; Accepted 3 August 2022
Available online 8 August 2022

1. Introduction

Pathologies with viral etiology have always represented a great danger to public health. In recent years several viral diseases have occurred such as Severe Acute Respiratory Syndrome (SARS) in 2003, H1N1 (swine fever) in 2009, and Middle East Respiratory Syndrome (MERS) in 2012 [1]. In December 2019, a newly discovered coronavirus, SARS-CoV-2, began to spread to China from the metropolis of Wuhan, giving rise to a disease known as COVID-19. In a short time, the explosion of contagions forced the World Health Organization (WHO) to proclaim the state of pandemic [2]. Several risk factors such as old age, smoking, and comorbidities may contribute to the increased possibility of infection and the severity of symptoms. Some studies show that lifestyle and eating habits can also affect the severity of symptoms [3]. For example, high alcohol consumption, increased during lockdown periods to cope with a depressive psychological state, plays a role in the worsening of the clinical picture [4]. Symptoms may change from non-existent (asymptomatic) or mild to severe, leading to bilateral interstitial pneumonia and acute respiratory distress syndrome (ARDS) [5]. Globally, 6.249.700 deaths from COVID-19 have been reported by the World Health Organization (WHO) as of May 2022 [6] disrupting social life and the economy, and also causing significant psychological damage. The spread of new strains (Alpha, Beta, Gamma, Delta, Omicron) able to increase the rate of infection and the transmissibility have further aggravated the already unstable social and economic condition, putting even more crisis the health system of the various nations [7]. The Alpha strain (B.1.1.7 lineage) was first identified in the United Kingdom in late 2020 (European Centre for Disease Prevention and Control [8]. Not longer before the Beta variant (B.1.351 lineage), also known as 20H/501Y.V2 has been first identified in South Africa [9]. The Gamma strain (P.1 lineage), also known as 20 J/501Y.V3,was first identified in Japan in December 2020 but mostly widespread in Brazil [10]; simultaneously, the Delta strain (B.1.617.2 lineage), was first identified in India becoming the most prevalent variant worldwide until the emergence of the Omicron variant (2022) [11]. The Omicron strain (B.1.1.529 lineage) was first reported in Botswana, earlier than in South Africa in November 2021 (Omicron (B.1.1.529 lineage). This variant includes BA.1, BA.2, BA.3, BA.4, BA.5 and also recombinant forms such as BA.1/BA.2 (also known as XE) [12].

In addition to licensed drug treatment already undergoing randomized clinical trials (remdesivir, dexamethasone, and bamlanivimab plus etesevimab) [13–15], many studies have shown that different nutraceuticals may play an important role both in the management of clinical symptoms induced by SARS-CoV-2 infection, showing antioxidant (Zinc, Baicalein), anti-inflammatory (Vitamin B3, B6, B12, D, Eucalyptus EO, Baicalein), immunostimulant activity as well as in boosting the immune system before and after the vaccine (Vitamin C, D) [3,16–25].

However, vaccination is the most effective weapon to eradicate this virus and allow the world's population to return to normal daily life. Over the past decade, vaccines have been responsible for improving life expectancy and the economy. Increasingly available and used vaccines have helped to eradicate completely or for the most part many infectious diseases. The management of patients suffering from viral diseases involves an enormous economic and social expenditure. Carrying out widespread vaccination can lower these costs and increase individual and public health security by aiming at the annihilation of the virus [26].

During the outbreaks of SARS and MERS, studies for the development of several vaccines were conducted. In particular, two of these vaccines, one from Sinovac Biotech ltd and one based on DNA, developed by the National Institute of Allergy and Infectious Disease (NIAID) have been processed to Stage I [27]. Almost all studies of vaccines against SARS-CoV have been abandoned, as the virus has never recurred since 2003. In contrast, nine MERS-CoV vaccines reached clinical stage I/II [28,29]. The study of these vaccines served as an advanced starting point for the development of 63 candidate vaccines against SARS-CoV-2. Of all vaccines studied, 11 % are mRNA vaccines, of which two, mRNA 1273 Spikevax (developed by Moderna) and BNT162b Comirnaty (developed by Pfizer-BioNTech ltd), were the first to be approved for emergency use in several countries. Of the viral vector vaccines, which accounted for the remaining percentage of vaccines tested, were approved AstraZeneca (ChAdOx1, developed by Jenner Institute of Oxford University), Johnson & Johnson (JNJ-78436734, developed by Janssen Pharmaceutical companies), and Sputnik-V (Gam-COVID-vac, developed by N. F. Gamaleya Federal Research Center for Epidemiology & Microbiology). They contain recombinant non-replicating DNA within adenovirus (AdV) [30–32]. Both vaccine types aim to code for the SARS-CoV-2 Spike (S) protein to induce a direct immune response against this protein (Fig. 1). Other vaccines developed and used around the world include: NVX-CoV2373 (Novavax), a recombinant protein subunit vaccine composed of trimeric spike glycoproteins and a Matrix-M1 adjuvant [33]. CoronaVac (Sinovac), an inactivated COVID-19 vaccine developed in China [34]. Ad5-based COVID-19 vaccine (CanSino Biologics), based on a replication-incompetent adenovirus 5 vector that expresses the spike protein [35];Covaxin (Bharat Biotech/Indian Council of Medical Research) also called BBV152, an inactivated COVID-19 vaccine that was developed and used in India [36];WIV04 and HB02 (Sinopharm) are inactivated whole-virus vaccines based on two different SARS-CoV-2 isolates from patients in China [37]; ZyCoV-D (Zydus Cadila), the first DNA COVID-19 vaccine available and initially authorized in India [38] (Table 1). mRNA vaccines have many advantages, unlike conventional vaccines. First of all, mRNA vaccines provide a transcript capable of coding for a specific target antigen, whatever it is [39]. Modifying the efficacy of the vaccine is extremely simple, by modifying the mRNA sequence [40]. This type of vaccine also has intrinsic self-adjuvant abilities capable of inducing important and prolonged adaptive immune responses through tumor necrosis factor (TNF), interferon (IFN), and various cytokines secreted by the immune cell system [41]. Importantly, mRNA vaccines resolve in the cytoplasm and are transient molecules that are rapidly degraded after injection [42]. They are more biosecure than DNA-based vaccines because they do not penetrate the nucleus and thus cannot integrate with the host genome [43]. The same mRNA can be recognized by antigen presenting cells (APCs), inducing the activation of pattern recognition receptors (PRRs), such as Toll-like receptors (TLR)-3, TLR-7, TLR-8 [44]. TLRs are evolutionarily conserved receptors that play a key role in the modulation of the immune response [1,45–53,148]. Unfortunately, storage and transport of this type of vaccine require very low temperatures, but with the integration of lipid nanoparticles, mRNA vaccines are more stable and resistant to less rigid temperatures [54].

Our study aims to review the literature on mRNA vaccines, assessing the efficacy and safety but also the immunogenic activity and the social and psychological impact of COVID-19 vaccination, starting from the current state of the art of research in the field.

2. Structure and pathogenicity of SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA (ssRNA) virus contained in an envelope on which S glycoproteins are found, positioned like a "crown". Interestingly, the genome of this coronavirus has 79. 6 % genetic identity with the genome of the previous SARS-CoV [55]. SARS-CoV-2 contains 4 proteins that play a key role in its replication and transmission. In fact, in addition to protein S, proteins nucleocapsid (N), membrane (M), and envelope (E) also contribute to the spread

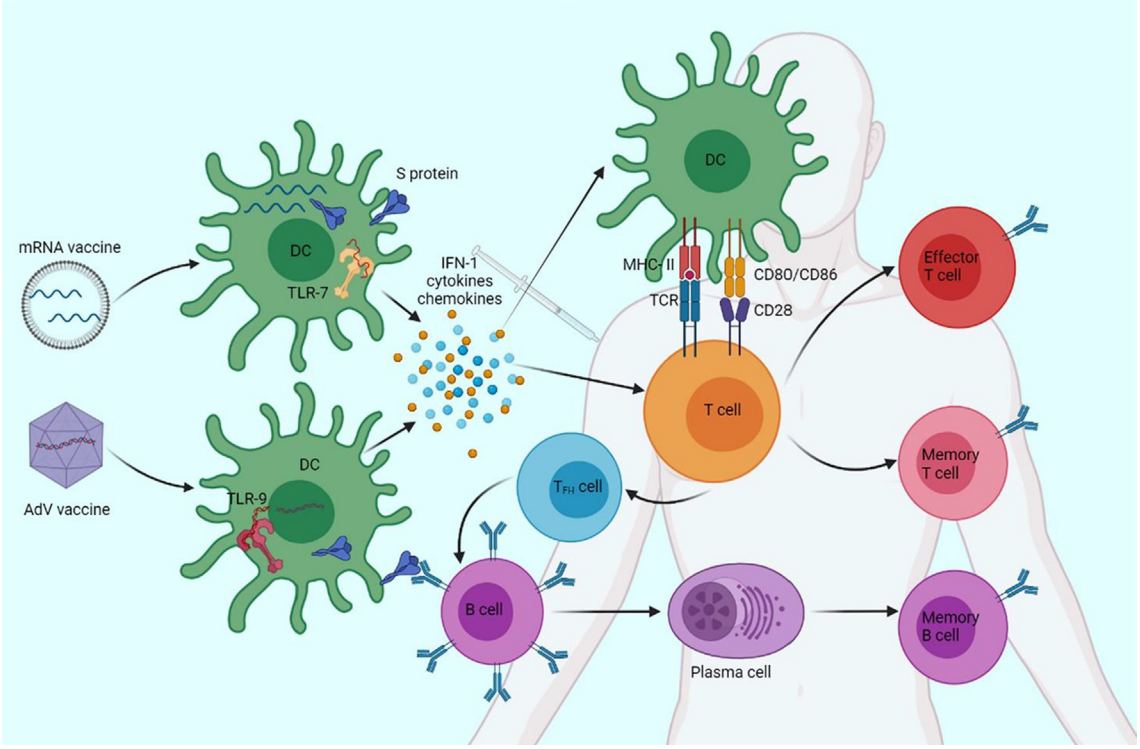

Fig. 1. Vaccines and immune system interaction. Vaccines either penetrate the DCs at the injection site or reach the lymph nodes, producing the S protein. In addition, innate immunity cells are activated by the vaccine's intrinsic adjuvant power, leading to rapid secretion of IFN-1 and pro-inflammatory cytokines. TLRs, in particular, TLR-7 are activated by mRNA vaccines, while TLR-9 is the predominant receptor for AdV vaccines. DCs present the S-protein to naive T cells, through the binding of T cell receptor (TCR) to MHC-II and binding of the CD80/86 and CD28 receptors, which are thus stimulated to differentiate into cytotoxic T lymphocytes and helper T lymphocytes. Follicular *T*-h cells (TFH) induce B cells to differentiate into plasma cells, producing anti-S antibodies. T cells and memory B cells then come into play to prevent future SARS-CoV-2 infection. Created with BioRender.com.

of the virus [56]. Protein S binds to the host cell's angiotensin-converting enzyme (ACE)-2 receptors, present in the respiratory tract, heart, kidneys, intestine [57], activating Transmembrane Protease Serin (TMPRSS)-2 [58]. This protease cleaves the S protein into two subunits, S1 and S2, however, there are also other receptors sensitive to binding to the viral S protein, such as CD-147 on epithelial cells [59] and CD26 [60]. Both S1 and S2 subunits play a key role in host cell penetration: S1 presents the ACE-2 receptor-binding domain (RDB), while S2 shows the cleavage site involved in the fusion of viral membranes and host cell (Fig. 2) [61,62]. Thanks to previous studies on SARS-CoV and MERS-CoV, the S protein has been fully identified, finding in S1 and S2 the epitopes for the induction of neutralizing antibodies [63,64]. Protein N is the most present and highly conserved protein, abundant RNA-binding protein critical for viral genome packaging [65]. Its use in the field of vaccines is still controversial because many studies show that patients have had a strong antibody response against this protein, while others have had almost no response. Protein M, used to stimulate the production of antibodies, has generated a strong immune response, so much so that it is a reference antigen for the development of anti-SARS-CoV-2 vaccines [66]. Finally, protein E, which forms a cation-selective ion channel through host cell lumen release [67] has been shown to induce negligible antibody responses [68].

Following entry of the virus via inhalation, lung epithelial cells recognize SARS-CoV-2 as a foreign pathogen via PRRs and initiate the innate and adaptive immune response [69]. The activation of dendritic cells (DCs), that orchestrates immune response [70–72,147], leads to the presentation of viral antigen to CD8+ and CD4+ cells, with stimulation of naïve T cells in the lymph nodes [26]. Protein S binds to airway epithelial cells via ACE receptors [73]. This binding stimulates TLR-7 and TLR-8 to induce the production of IFN-1, which plays a key role in the management of viral infections, resulting in the production of cytokines and antiviral enzymes by other immune cells [74]. However, SARS-CoV-2 can bypass IFN [75] and this mechanism could be the basis for the development of severe clinical conditions [76]. Within 1–2 days of infection, the virus replicates locally, being detectable by polymerase chain reaction (PCR) with nasal swabs [77]. Often, patients at this stage were asymptomatic but highly infectious. For the next 3–7 days, the virus remains in the upper airway and may cause manageable mild symptoms at home [78]. In about 14 % of cases, however, the virus continues to spread, leading to modest clinical settings that require hospitalization [79]. In about 5 % of patients, the virus infects the alveolar cells, causing a serious pathological condition, increasing the extent of tissue and cell damage. This triggers a chain reaction by macrophages, monocytes, lymphocytes, and neutrophils [80] producing IFN-α, IFN-γ, interleukin (IL)-1β, IL-12, IL-6, IL-18, IL-17, IL-33, TNF-α, transforming growth factor (TGF)-β, chemokine (C—C motif) ligand (CCL)-2, CCL-3, CCL-5, chemokine (C-X-C motif) ligand (CXCL)-8, CXCL-9, CXCL-10, causing a real cytokine storm. This reaction, highly inflammatory, represents one of the main causes of the development of ARDS), bilateral pneumonia leading to death [81].

3. LNPs-mRNA complex immunogenicity

Lipid nanoparticles (LNPs) not only play a key role in the stability of mRNA, but also promote its immunogenic mechanism. LNPs are vectors of approximately 100 nm consisting of phospholipids, cholesterol, polyethylene glycol (PEG) lipids, and ionizable lipids [82]. While phospholipids and cholesterol have a stabilizing and structural function, PEGs promote prolonged circulation [83]. Ionizable lipids

Table 1
Summary chart of vaccine against COVID-19, with way of functioning.

	Type	Developer	Way of Functioning
BNT162b2	mRNA vaccine	Pfizer-BioNTech	The mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein
mRNA-1273	mRNA vaccine	Moderna	The mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein
ChAdOx1 nCoV-19/AZD1222	Replication-incompetent vector vaccine	University of Oxford, AstraZeneca, the Serum Institute of India	A replication-incompetent chimpanzee adenovirus vector that expresses the spike protein
Ad26.COV2.S	Replication-incompetent vector vaccine	Janssen/Johnson & Johnson	A replication-incompetent adenovirus 26 vector that encodes a stabilized spike protein
Gam-COVID-Vac/Sputnik V	Replication-incompetent vector vaccine	Gamaleya Institute	Two replication-incompetent adenovirus vectors that express a full-length spike glycoprotein
NVX-CoV2373	Recombinant protein vaccine	Novavax	Recombinant protein subunit vaccine composed of trimeric spike glycoproteins and a potent Matrix-M1 adjuvant
CoronaVac	Inactivated vaccine	Sinovac	Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus combined with an aluminum hydroxide adjuvant
Ad5-based COVID-19 vaccine	Replication-incompetent vector vaccine	CanSino	A replication-incompetent adenovirus 5 vector that expresses the spike protein
Covaxin	Inactivated vaccine	Bharat Biotech	Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus combined with an aluminum hydroxide and a toll-like receptor agonist adjuvant
WIBP-CorV	Inactivated vaccine	Sinopharm	Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus combined with an aluminum hydroxide adjuvant
BBIBP-CorV/HB02	Inactivated vaccine	Covilo, Sinopharm	Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus combined with an aluminum hydroxide adjuvant
ZyCoV-D	DNA vaccine	Zydus Cadila	A DNA plasmid vector pVAX1 carrying gene-expressing spikeS protein of SARS-CoV-2 and IgE signal peptide

facilitate the release of mRNA from the endosome into the cytosol to begin translation [84]. Phospholipids and cholesterol are physiologically present in cell membranes, so it is not plausible that they could be involved in the induction of immune responses. However, ionizable lipids can elicit inflammatory responses. Several studies on the LNPs-mRNA complex have shown how the ionizable lipids of this platform can stimulate a powerful immune response [85]. Men who have been given the SARS-CoV-2 LNPs-mRNA vaccine have often experienced the classic symptoms of inflammation: pain, swelling, redness, heat at the injection site, and fever [86]. Specific studies conducted with the administration of LNPs alone or combined with non-coding RNA have demonstrated the inflammatory power of these lipids [87]. This may lead to the conclusion that most of the adverse effects of vaccination are caused by these ionizable lipid nanoparticles.

However, the activation of innate memory could help to modulate both these side effects and the inflammatory response [88]. Moreover, the presence of this complex also allows the repackaging of the mRNA into vesicles which, after expulsion, could reach even sites far from the injection site, increasing the number of cells involved in the antigenic translation and thus increasing the duration of its expression [89,90]. Preclinical animal testing and human clinical studies by Moderna and Pfizer/BioNTech on SARS-CoV-2 to LNPs-mRNA vaccines demonstrated protection rates above 90 %. These vaccines prove to be safer than viral vector vaccines, are highly customizable, self-adjuvant, large-scale products, and easily adaptable to any emerging pathogens [91]. The success of this type of vaccine is mainly due to the improved ability of the mRNA to leave the endosomal compartment to allow translation into cytoplasmic ribosomes. The ionizable component could be protonated in most cells in the acidic environment of the endosome, leading to the release of mRNA. In contrast, the different biology of DCs hinders this release, being able to retain protein antigens for prolonged periods [92].

However, lipid vectors able to merge with the cell membrane release mRNA directly into the cytosol. In the case of mRNA vaccines with complete S protein, it is neutralized and broken down into immunogenic antigenic epitopes and presented to CD8+ cells via the major histocompatibility complex (MHC)-I [91]. DCs transfected by mRNA or immunogenic epitopes involve the MHC-II for immune cell presentation. Activated B cells differentiate into memory B cells and plasma cells (with production of specific antibodies), allowing an immune reaction after a second possible contact, leading to the neutralization of viral antigens. If the amount of antibodies is not sufficient to trigger the response, the inactive memory cells are activated to determine the secondary immune response [93]. The mechanism of mRNA translation and the subsequent presentation of the antigen to trigger the immune response is schematized in Fig. 3.

4. Efficacy and safety of mRNA vaccines

The mass vaccination campaign against SARS-CoV-2 is already active in most of the world. Several articles published during the pandemic described valuable studies aimed at developing an effective and safe vaccine with a reduced number of non-severe secondary effects [94]. During the first phase of the research, the vaccine is administered to humans (both young and elderly) in order to confirm its safety and immunogenic effects, as well as to determine the appropriate dose to be used. In the second stage, randomized clinical trials represent the "gold standard" for evaluating vaccine efficacy (VE). Although, limitations in terms of inclusion criteria (highly restrictive) need to be considered to evaluate its effectiveness [95]. For these and other reasons, the results of the trials may not coincide with those obtained in a mass vaccination.

4.1. BNT152b2 ("Comirnaty"; Pfizer BioNTech)

BNT152b2 is administered intramuscularly in two doses three weeks apart and has been authorized for use in various locations, including the European Union (EU) [96]. Comparable binding and neutralizing antibodies to the convalescent plasma of patients with asymptomatic or moderate SARS-CoV-2 infection were found in a randomized phase I and II study in healthy adults aged 18 to 85 years [97]. Although the response in participants aged ≥65 years old was generally lower than that of younger participants, it was comparable to the titer present in the convalescent plasma. It was also found that the neutralizing antibody titer in 12–15 years old participants was sig-

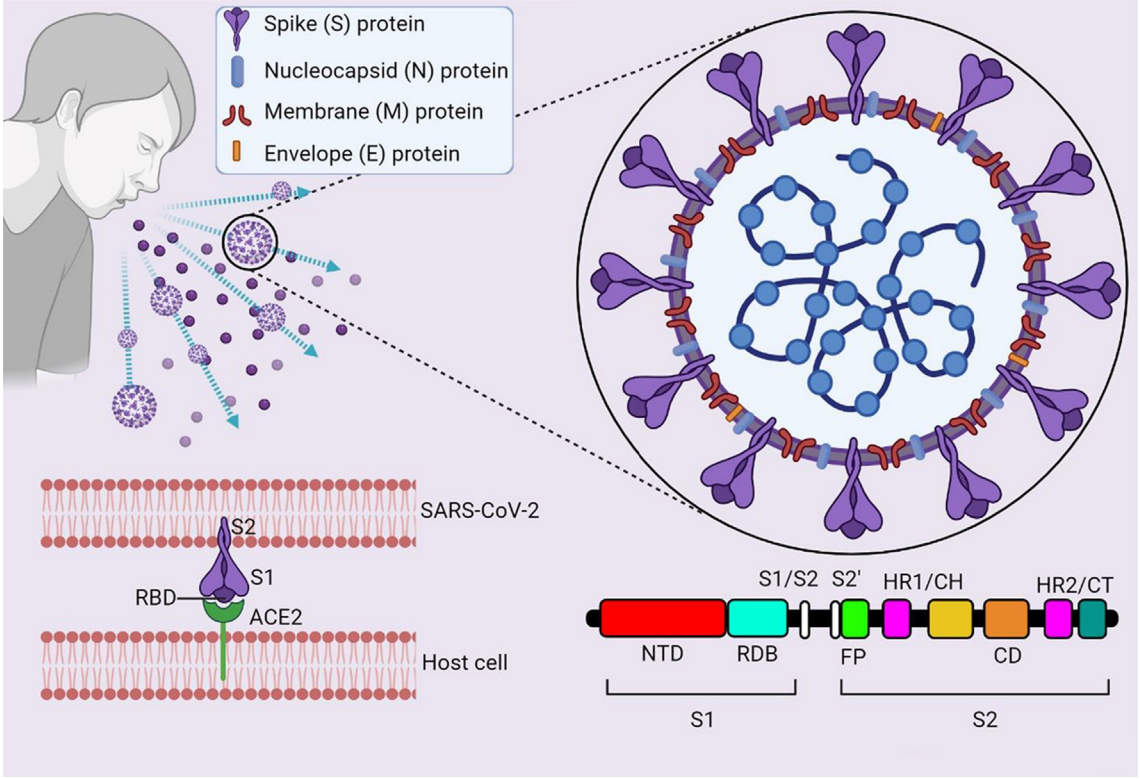

Fig. 2. Structure of SARS-CoV-2 virus. ssRNA shares 79.6% of the sequence identity with SARS-CoV and encodes for the proteins S, M, N, and E. Protein S consists of two subunits: S1 and S2. S1 presents the RBD. RBD is required for binding to the ACE-2 receptor on the surface of host cells. The domain of the S2 subunit forms a trimeric structure and has the fusion peptide (FP) and two heptad repeats (HR1/Central Helics and HR2/Cytoplasmic Tale), which are necessary for the fusion of the virus and the host cell membrane. Protein N wraps the genome into a virion for efficient viral replication, protein M is involved in viral integration, protein E facilitates assembly and compacting. Created with BioRender.com.

nificantly higher than that of 16–25 years old participants [98]. Furthermore, several studies suggest that the neutralizing activity against variants of concern is maintained, despite the level of neutralizing antibodies in the Beta variant (B.1.351) being lower than in the Delta variant (B.1.617.2), if compared with that obtained with other circulating strains [99–102].

In the phase III trial, BNT152b2 showed a capacity of 95 % (Confidence Interval (CI) 90.3–97.6) in preventing a symptomatic form of COVID-19 at or after day 7 after the second dose, calculated after the evaluation of 170 confirmed cases of COVID-19 among more than 36,000 participants ≥16 years, with a median of two months of follow-up after vaccination [103]. In the population ≥65 years old with other comorbidities, the efficacy was 95 % (CI 44.2–99.8). The efficacy of the vaccine was also high in a trial carried out in adolescents 12–15 years without evidence of a previous infection, reaching 95 % (CI 75.3–100) [98]. The data in question have been confirmed by studies carried out at national level in other states. In Israel, the effectiveness observed at ≥7 days after the second dose was 92 % for preventing a SARS-CoV-2 infection, 97 % for hospitalization from COVID-19, 97 % for symptomatic forms of COVID-19, 97 % for death from COVID-19; with high and comparable outcomes in all age groups. It was also found to be effective against the SARS-CoV-2 variants prevalent during the trial in question [104]. Some data not yet published in Israel would suggest that the increasing predominance of the Delta variant on the territory would have led to a temporary reduction of effectiveness, reaching 64 % against a symptomatic infection of SARS-CoV-2, but maintaining very high values of effectiveness against the hospitalization from COVID-19. In the United Kingdom, the estimated effectiveness against the symptomatic form of COVID-19 induced by the Delta variant was 95 % (CI 85–90) compared to 95 % (CI 92–95) for the Alpha variant [105]. A cohort study confirmed the efficacy of vaccination in protecting Delta variant against contagion [106]. The effectiveness may decrease over time. In a follow-up study, the efficacy against the symptomatic form of COVID-19 remained high for 6 months, standing at 96 % from the time of vaccination at 2 months, at 90 % between 2 and 4 months, and 84 % from 4 to 6 months. According to the data in question, only 1 case of severe infection among the 30 observed was recorded in a vaccinated subject [107].

Some adverse effects are quite frequent, especially after the administration of the second dose. Most are of moderate or mild severity and are usually limited to the first two days after vaccination [108,109]. In post-vaccination questionnaires collected in the 16-years-or-older US population a local reaction at the injection site (pain, redness, itching, and swelling) was reported in 65 % of cases after the first and second dose; myalgia, headache, and fatigue respectively in 17 %, 25 %, and 29 % of cases after the first dose, and 37 %, 40 %, and 48 % after the second dose [108]. In addition, about one in five participants reported symptoms such as chills, joint pain, and fever. Reactions were mainly reported within the first day of vaccination, especially in the 12–15-years-old group after the second dose. Specifically, myalgia (32 %), chills (42 %), headache (65 %), and fatigue (65 %) were reported. These reactions, while quite common, occurred less frequently in subjects aged 65 years or older [98]. Anaphylaxis after vaccination has been reported with a ratio of about 5 cases per 1 million doses. In about 4 out of 5 cases, anaphylaxis occurs in subjects with a history of allergic reactions and in 9 out of 10 cases within 30 min of inoculation. Other reported cases of allergic reactions were rash, itchy throat sensation, and mild respiratory symptoms. Rare cases of Bell's palsy were recorded in phase III trials, but the percentage did not exceed

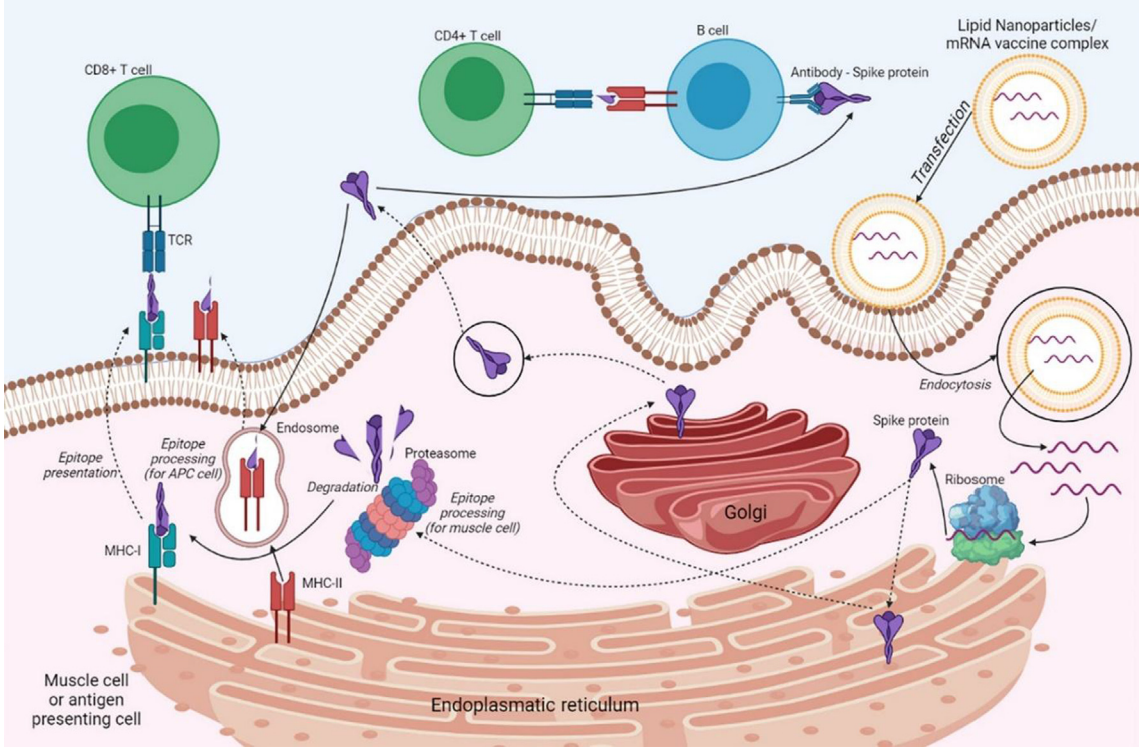

Fig. 3. Immunogenic mechanism of mRNA vaccines. Through endocytosis, the vaccine enters a muscle cell or an antigen-presenting cell. LNP-free mRNA is translated into Spike protein at the ribosome level. The newly synthesized S protein is secreted into the extracellular space [cit] and through endocytosis enters an APC cell and is incorporated as part of the MHC-II to present the antigen to immune T and B cells. Protein antigens partially degraded by the proteasome are incorporated into MHC-I complexes and presented to immune cells. Created with BioRender.com.

the one recorded in the general population. Furthermore, post-vaccine monitoring did not identify an association between vaccination and Bell's palsy [110] (Table 2).

4.2. mRNA-1273 ("Spikevax"; Moderna)

mRNA-1273 is administered intramuscularly in two doses four weeks apart and has been authorized for use in various locations, including the European Union [111]. In the phase I trial, it demonstrated the ability to produce neutralizing antibodies in values comparable to those present in convalescent plasma in a healthy population aged 18–55, and a response with CD4 cells with a T helper (Th)-1 bias, as well as an immune response in subjects 55 years old and older comparable to that of younger subjects [86,112]. The binding and neutralizable antibodies decrease slightly after six months in all population groups, but the antibody titer maintains a high value and the neutralizing capacity persists for this time [113]. In addition, induced immunity was found in subjects between 12 and 17 years old that was comparable if not higher than that of young adults [114]. The studies carried out on the plasma of subjects vaccinated with the mRNA-1273 show that the neutralizing antibody activity is effective against the variants of concern, but the number of neutralizing antibodies against the variant Beta (B.1.351) and Delta (B.1.617.2) is lower if compared with that obtained with other circulating strains [99,115,116].

In a phase III study, mRNA-1273 showed an efficacy of 95 % CI 89.3–96.8 in preventing a symptomatic form of COVID-19 at ≥ 14 days after the second dose [30]. In subjects aged ≥ 65, on the other hand, the efficacy was 95 % (CI 61.4–95.5). About 5 months after follow-up, the effectiveness of the vaccine was 93.2 % in preventing a symptomatic form of COVID-19 and 98.2 % in preventing a severe form of COVID-19 [117]. The data collected in the aforementioned trial were confirmed by several observational studies on the effectiveness of the vaccine [118–121]. In addition, a study carried out on hospitalized subjects (40,000) and in the context of urgent care and emergency (20,000) found that mRNA-1273 has a 91–92 % effectiveness in protecting emergency-, urgent care-, and hospitalization-related cases of COVID-19 [121].

Some adverse effects are quite common, especially after the second dose. Most are mild or moderate, do not require the interruption of daily activities or the use of painkillers, and in any case are generally limited to the first two days after vaccination [108,109]. In post-vaccination questionnaires collected in the US population, pain, redness, itching, and swelling were reported between 74 and 82 % of the participants both after the first and second dose. Myalgia (21 %), headache (27 %), and fatigue (33 %) were also reported after the first dose, and respectively in 51 %, 53 %, and 60 % after the second dose. In addition, fever and chills (40 %) and joint pain (32 %) were reported. Reactions generally occurred within the first day after vaccination, and to a lesser extent but still frequently in subjects ≥ 65 years of age [108]. Anaphylaxis has been reported following vaccination at 2.8 events per million doses. In 86 % of cases, anaphylaxis was reported in subjects with a history of allergic reactions, and in 90 % of cases, it occurred within 30 min of administration [122]. Rare cases of Bell's paralysis have been reported following vaccination, but the percentage did not exceed that of the general population and post-marketing monitoring did not identify an association with vaccination [110]. The report by the Advisory Committee on Immunization Practices (ACIP) on May 12, 2021 found a total of 8 cases following the administration of the mRNA-1273 dose, of which only 6 cases could be potentially incidental and none were found to have thrombocytopenia. To date, the scientific community strongly suggests that the benefits far outweigh the potential harm [123,124] (Table 2).

Table 2
Summary table of mRNA vaccines safety and efficacy.

Name of the vaccine	NT162b2	mRNA-1273
Company developer	Pfizer/BioNTech	Moderna
Type	mRNA	mRNA
Doses and suggested interval	2 doses 3 weeks apart	2 doses 4 weeks apart
	Booster dose 6 months following primary series for the following: Adults 65 years or older Adults 18 years or older at high risk for severe COVID-19 because of comorbidities Adults 18 years or older at occupational or institutional risk of exposure	
Efficacy against symptomatic COVID-19 (in clinical trials)	95 % (95 % CI 90–98) after a median of 2 months follow-up 91 % (95 % CI 89–93) after median of 6 months follow-up	94 % (95 % CI 89–97) after median of 2 months follow-up
Effectiveness in observational studies when Delta variant prevalent	Symptomatic infection: 41 to 88 %	Symptomatic infection: 85 to 88 %
	Severe disease/ hospitalization: 86 to 95 %	Severe disease/ hospitalization: 89 to 96 %
Storage requirements	Ultracold freezer (–90 to –60 °C) then freezer (–25 to –15 °C) for up to 2 weeks cumulative time then refrigerated (2 to 8 °C) for up to 1 month	Freezer (–25 to –15 °C) then refrigerated (2 to 8 °C) for up to 30 days
Common side effects	Local injection site reactions	Local injection site reactions
	Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	Systemic symptoms (fevers, chills, fatigue, myalgias, headache)
Rare adverse effects	Anaphylaxis (approximately 5 per million)	Anaphylaxis (approximately 2.8 per million)
	Myocarditis/pericarditis (approximately 16 per million among 16–39-year-olds)	Myocarditis/pericarditis (approximately 16 per million among 16–39-year-olds)

4.3. Booster vaccinations

Some data from observational studies indicates that protection against SARS-CoV-2 infection could decrease over time. However, protection against hospitalization from COVID-19 as well as protection against severe forms of COVID-19 would be guaranteed [107,125]. As a result, several countries have already started to administer booster vaccinations to individuals who have been fully vaccinated. The Centers for Disease Control and Prevention (CDC) recommends a booster dose of BNT162b2 six months after the last dose for some high-risk groups. Taking into account several studies that confirm an increased ability to produce antibodies neutralizing agents in subjects undergoing transplants with a weakening of the immune system, European Medicines Agency (EMA)'s human medicines committee (CHMP) recommends administering an extra dose of COVID-19 mRNA vaccines to subjects with severe immunosuppression at least 29 days after the second dose [126–128]. In an observational study conducted in Israel, individuals who received the booster dose at least 5 months after the previous one had an 11 times lower rate of infection than those who did not and a 20 times lower rate of severe disease. Due to the design of the study, it is unclear whether some of the differences are attributable to other factors [129]. Following the evaluation of these data, the CHMP concluded that it is possible to evaluate the administration of booster doses at least 6 months after the second dose in the population aged 18 and over.

Cases of pericarditis and myocarditis have been reported in a percentage worthy of attention following vaccination with BNT162b2 and mRNA-1273, generally within the first week after vaccine shot and after the second shot, especially in males, adolescents and/or young adults. However, given the rarity and moderate effects found, the benefits obtained from an mRNA vaccination far outweigh the slightly increased risk [130]. The CDC suggests that those who develop pericarditis or myocarditis after the first dose of an mRNA vaccine should postpone the second dose until the episode has completely resolved, in case the risk of a severe form of COVID-19 is high [131].

5. Covid vaccination psychological impact

The COVID-19 pandemic has had a strong impact on public emotion because of isolation and loneliness due in part to social distancing measures and the lockdown imposed to prevent the spread of infection, but also to fear of contracting the virus, financial difficulties, and fear of vaccine safety, causing an increase in the population of anxious and depressive states [132,133]. Long before the COVID-19 pandemic took hold, vaccination has always been a matter of debate, thanks in particular to anti-vaccination groups on social media and the internet promoting disinformation and conspiracy theories about vaccines, often creating confusion and division [134]. These sites and social accounts play on the subject's emotions, citing mandatory vaccination as a violation of civil rights, or hyperbolizing the dangerous side effects of vaccines [135], and the conspiracy theories mentioned by these groups are aimed at sowing mistrust of scientists, experts and government organizations [134]. This, compounded by the emotional issues of the pandemic, has caused confusion, nervousness, hesitancy, and apathy about the vaccine decision [136].

A recent study by Murphy et al. showed that among a sample of 1041 Irish adults and 2025 British adults, 35 % and 31 % respectively were hesitant/resistant to the vaccine. Despite different social backgrounds and economic, political, cultural, and geographic differences, both hesitant populations shared a similar psychological profile: they were more self-interested, more distrustful of expert figures, more impulsive, and with more religious, conspiracy, and paranoid beliefs [137]. These results coincide with those of other European nations [138], and in the United States, where 33 % of the population report resistance or hesitation to the vaccine [139,140]. An interesting cross-sectional study carried out in Italy during the different phases of the pandemic showed that the perception of the risk of COVID-19 increased during the lockdown phase and decreased during the reopening phase, with the result that during the lockdown a higher percentage of the population was interested in vaccinating against COVID-19, even hesitant people [141]. This can be explained by the "hot–cold empathy bias": in fact, people tend to give less importance to their emotional reactions during "cold" decisions than "hot", thus leading to an asymmetry between their beliefs and choices [142]. This type of bias is also found in people who, before receiving the anti-COVID-19 vaccination, have already undergone tests to determine whether they are positive or negative for the disease. These subjects are more likely and less resistant to receive the vaccination than those who have not taken any kind of COVID-test [143]. Another reason why people are so hesitant about vaccination is its potential negative effect

on fertility [144]. A recent study by Gonzalez et al., which measured sperm levels before and after two doses of COVID-19 mRNA vaccine, showed that there were no significant decreases, and in many cases, there were also increases in sperm parameters. This is because these vaccines contain mRNA and not the live virus, so they are unlikely to alter sperm values [145].

Reaching out to those who are still hesitant or resistant about COVID vaccination is certainly important to ensure public health, however, the distrust these individuals show about the established authority does not make the task any easier. One strategy could be to involve authoritative figures not linked to vaccine authority or competence (such as religious leaders), or to emphasize, given the lack of altruism and the internal locus of control, the personal benefits these individuals could receive with COVID vaccination, and unconventional communication channels could be used to support the vaccine campaign, such as social media [137]. Also, misinformation about the consequences of vaccination is an often widespread and difficult occurrence to control. Vaccine information campaigns could be helpful in this regard, by trying to identify which doubt afflicts a hesitant or resistant subject, and by focusing the discussion on that area [146].

6. Conclusions

The data collected demonstrate the efficacy of mRNA vaccines in stimulating immune cells to produce specific antibodies against SARS-CoV-2. Vaccination is the most effective weapon to combat and contain the COVID-19 pandemic. Therefore, it would be useful to further encourage vaccination, trying to overcome the insecurities and doubts of a minority of people who have not yet been vaccinated. These molecules are more biosecure than traditional viral vector vaccines, suggesting their possible use also in the management of diseases of broad global health interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Alessio Alesci: Conceptualization, Writing – original draft, Writing – review & editing, Data curation, Visualization. **Marco Gitto:** Writing – original draft. **Magdalena Kotańska:** Data curation, Visualization. **Patrizia Lo Cascio:** Data curation, Visualization. **Anthea Miller:** Data curation. **Noemi Nicosia:** Writing – original draft. **Angelo Fumia:** Writing – original draft, Data curation, Visualization. **Simona Pergolizzi:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful to all the researchers whom we cited in this review for their significant and valuable research.

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