



Anti-coronavirus vaccines will not accelerate the transition of humanity to a non-pandemic period, but the pandemic will take fewer victims

V. V. Oberemok^{1,2} · O. A. Andreeva^{1,2} · K. V. Laikova^{1,2} · I. A. Novikov¹ · Y. V. Puzanova^{1,2} · A. V. Kubyshekin²

Received: 17 January 2022 / Revised: 17 March 2022 / Accepted: 21 March 2022 / Published online: 10 April 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

The vaccination rate worldwide has reached enormous proportions, and it is likely that at least 75% of the world's population will be vaccinated. The controversy is that, while people aged 65 and older suffer a significantly higher mortality rate from COVID-19, plans are being made to vaccinate young people under the age of 20. Equally thorny is the question of vaccinating people who already have antibodies to SARS-CoV-2, as well as B and T memory cells, because they contracted and survived the virus. The possible consequences of large-scale vaccination are difficult to predict, when some people do not have access to the vaccine at all and others have already received 3 doses of the vaccine. SARS-CoV-2 will circulate through the human population forever and continue to mutate, as viruses do. Therefore, in the coming years, the need to develop and use effective vaccines and medicines for the prevention and treatment of COVID-19 will remain urgent in view of the high mortality rate from this disease. To date, three vaccine platforms have been most used: adenoviral vector, inactivated, and mRNA. There is some concern about the side effects that occur after vaccination. Whether modern anti-coronavirus vaccines can raise the safety threshold, only time will answer. It is obvious that the pandemic will end, but the virus will remain in the human population, leaving behind invaluable experience and tens of millions of victims. This article is based on search retrieves in research articles devoted to COVID-19 mainly published in 2020–2021 and examines the possible consequences of the worldwide vaccination against SARS-CoV-2 and suggests that, while anti-coronavirus vaccines will not magically transport humanity to a non-pandemic world, they may greatly reduce the number of victims of the pandemic and help us learn how to live with COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Pandemic · Vaccine · Immunity · Reinfection · Immunological memory

Introduction

As of 17 March 2022, more than 6 million people have died from COVID-19 worldwide [1]. The COVID-19 pandemic is unprecedented in the twenty-first century and one of the largest pandemics known in human history. Due to the biological characteristics of SARS-CoV-2, such as its short life

cycle, the large number of mutations that arise during the replication of the microorganism genome, and its high infectivity, since March 11, 2020, the COVID-19 pandemic has been the most serious social and economic problem in the entire world.

SARS-CoV-2 is a (+) ssRNA virus of the Sarbecovirus subgenus of the genus Betacoronaviruses of the Coronaviridae family, which was first isolated in the city of Wuhan [2]. The earliest split in the SARS-CoV-2 phylogeny defines two lineages, denoted A and B [3]. Evidence from its genomic structure and the frustrating ongoing evolution of SARS-CoV-2 has led to considerable attention being devoted to claims that SARS-CoV-2 was genetically engineered, or adapted in cell culture or ‘humanized’ animal models, to promote human transmission [4]. These claims lack any kind of supporting evidence. Like all viruses, since its host-hopping evolution into the virus known worldwide, SARS-CoV-2 has experienced

Responsible Editor: John Di Battista.

✉ V. V. Oberemok
genepcr@mail.ru

¹ Department of Molecular Genetics and Biotechnologies, V.I. Vernadsky Crimean Federal University, Simferopol, Crimea

² Department of DNA Technologies of Engineering Center, V.I. Vernadsky Crimean Federal University, Simferopol, Crimea

repeated waves of mutations that have increased its overall viral fitness [5]. This is nothing new, nor did it require human intervention; historically, newly emerging (and re-emerging) infectious diseases have been threatening humans since the Neolithic era 12,000 years ago, when human hunter-gatherers first settled in villages and began to domesticate animals and crops [6].

There are seven types of coronaviruses relevant to humans. Four of these human coronaviruses (HCoV-NL63, HCoV229E, HCoV-OC43, and HKU1) cause limited mild upper respiratory symptoms in immunocompetent populations. The other three are highly pathogenic coronaviruses: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and novel Coronavirus (SARS-CoV-2), all of which cause severe respiratory disease in humans [7]. SARS-CoV-2 is a positive sense, single-stranded RNA virus with a spherically shaped envelope between 80 and 90 nm³ in diameter [8]. Its small genome (~30 kb) is responsible for encoding two sets of proteins. Transcription and replication of the genome are carried out by 16 non-structural proteins, which also produce the structural proteins: envelope spike glycoprotein (S), envelope protein (E), membrane glycoprotein (M), and nucleocapsid protein (N).

Due to the presence of a RNA-dependent RNA polymerase in this virus, during genome replication, a large number of mutations form because this polymerase lacks any substantial ability to correct mistakes [9], although high-fidelity replication of the large RNA genome of coronaviruses (CoVs) is mediated by a 30–50 exoribonuclease (ExoN) in nonstructural protein 14 (nsp14), which excises nucleotides including antiviral drugs misincorporated by the low-fidelity viral RNA-dependent RNA polymerase (RdRp) and has also been implicated in viral RNA recombination and resistance to innate immunity [10]. From December 2019 to October 2020, SARS-CoV-2 evolved at a rate consistent with the accretion of approximately two mutations per month across the global population [11]. Currently, comparison of two randomly chosen isolated coronavirus strains would show that with a genome of 30,000 nucleotides, they differ from one another by no more than 18 [12]. That being said, several of the more robust subtypes of coronavirus have been characterized (the most famous are British, South African, Brazilian, Indian and Omicron), because they have made themselves felt worldwide. These subtypes, which vary in presentation, symptoms, and level of infection [13], have made it more difficult to diagnose, treat, and try to prevent COVID-19.

Coronavirus vaccines: great aspirations, but few conclusions

As of 17 March 2022, according to the coronavirus Resource Center of Johns Hopkins University, around the world more than 464 million people have fallen ill with SARS-CoV-2, approximately 1.3% of whom have died [14]. At this point, it is no longer possible to stop the global spread of the virus; the SARS-CoV-2 coronavirus will remain in the human population forever, taking its place with four other circulating non-severe acute respiratory syndrome human coronaviruses: HCoV-NL63, HCoV-HKU1, HCoV-OC43, and HCoV-229E [15]. To control the spread of SARS-CoV-2 and eventually prevent it, vaccines and medicines must be used. Unfortunately, at the moment, we have only begun the first half of this plan; while development of vaccines against the coronavirus has occurred at a fast pace, no effective medicines specific to SARS-CoV-2 have been produced [16].

Most of the vaccines currently used to immunize the majority of the world's population are built using one of three main platforms: inactivated virus, adenoviral preparations, or mRNA (Table 1).

The use of vaccines during a pandemic can be controversial and may lead to a decrease in immunity, which can lead to higher chances of getting sick [17]. In addition, it is possible for some people to develop antibody-dependent enhancement (ADE) infections in response to vaccines. Previous studies of inactivated and live attenuated vaccines for respiratory syncytial virus and dengue virus revealed safety risks related to ADE, which caused the vaccine trials to fail [18, 19]. Attempts to develop vaccines in response to Severe Acute Respiratory Syndrome coronavirus (SARS), Middle East respiratory syndrome coronavirus (MERS-CoV), and other coronaviruses have faced difficulties due to vaccine-induced enhanced disease responses in animal models. With respect to vaccines developed to deal with COVID-19, SARS-CoV-2 antibodies bound to Fc receptors on macrophages and mast cells may represent two different mechanisms for ADE in patients [20]. The fact that the risk of ADE has multiple mechanisms has possible implications for SARS-CoV-2 B-cell vaccines in population subsets based on age, cross-reactive antibodies, variabilities in antibody levels over time, and pregnancy. These models place increased emphasis on the importance of developing safe SARS-CoV-2 T-cell vaccines that are not dependent upon antibodies. So far there have been no verified reports of ADE occurring as a result of injection with COVID-19 vaccines. However, given the emergence of ADE in the past for vaccines against MERS-CoV and SARS-CoV, it is possible that reports will soon emerge for COVID-19 vaccines as well [21].

In response to the coronavirus disease pandemic that began in late 2019 (COVID-19), 20 COVID-19 vaccines

Table 1 Characteristics of the most common SARS-CoV-2 vaccines

Name/company	Country	Vaccine type	Side effects
CoronaVac (Sinovac)	China	Inactivated virus	Pain, swelling, itching, redness and induration at the injection site, headache, fatigue, and myalgia [41]
Vaxzevria (AstraZeneca)	Sweden and UK	Adenovirus vector	Allergic reaction (laryngeal and facial edema, headache with high blood pressure, thrombosis, anemia and thrombocytopenia [42])
Sputnik V (Gamaleya National Research Center for Epidemiology and Microbiology)	Russia	Adenovirus vector	Rise in temperature, "flu-like syndrome", indigestion, nausea and swollen lymph nodes, allergic reactions [43]
Janssen (Johnson & Johnson)	The Netherlands and USA	Adenovirus vector	Pain, skin redness and swelling, headache, feeling very tired, muscle pain, nausea, fever [44]
Comirnaty (Pfizer/BioNTech/Fosun Pharma)	Germany, China and USA	mRNA	Rosacea, hearing impairment, muscle cramps, skin sensitivity disorders, cough, shortness of breath and chest pain, exacerbation of asthma, abdominal pain, bloating, bruising and visual disturbances [45–47]
Spikevax (Moderna)	USA	mRNA	Abdominal pain lasting several days [48, 49]

have been developed and approved for use with more than 3.7 billion doses having been administered as of July 20, 2021 [22]. According to the Coronavirus Resource Center of Johns Hopkins University, as of 17 March 2022, 10.8 billion doses have been administered [14], which is almost 3 times as many as eight months previously. When working to develop a vaccine for a new and possibly rapidly spreading virus, the need to reach a large number of people quickly is more problematical than the research and techniques used to create the vaccine [23]. One of the oldest approaches to vaccine development is a platform based on the use of an inactivated virus.

Inactivated vaccines

Inactivated vaccines mirror the micropathogens they are created to prevent because they contain all of the antigens characteristic of a specific pathogen. One of the first vaccines ever created was an inactivated whole-cell anthrax vaccine developed by Pasteur and his colleagues [24, 25]. This classic approach, long used in the practice of virology, has proven itself in the prevention of various viral diseases along with other approaches, such as live-attenuated and protein subunit vaccines [26].

In the past, there have been attempts to create inactivated vaccines against SARS-CoV and MERS-CoV. However, these vaccines were not particularly successful. Experimental animals inoculated with an inactivated vaccine against SARS-CoV developed a Th-2 type immunopathological lung disease, indicative of hypersensitivity to the components of the vaccine [27]. Studies carried out in animal models of vaccines based on a completely inactivated SARS-CoV virus, which is closely related to SARS-CoV-2, have

demonstrated significant antibody formation [28]. However, only a few SARS-CoV vaccines made it to Phase I clinical trials before funding dried up because the virus was eradicated from the human population through non-pharmaceutical interventions when the case numbers were still small [15].

Similarly, the MERS-CoV vaccine was found to cause eosinophilic lung changes in vaccinated animals. Lung pathologies caused by hypersensitivity appear to be common risks of the inactivated MERS-CoV and the inactivated SARS-CoV vaccines [29, 30]. Generally, both the SARS-CoV and MERS-CoV vaccines, inactivated either by gamma-ray or by formalin, induced immunopathologic lung disease in vaccinated animals. This is important to take into account during the development of an inactivated SARS-CoV-2 vaccine.

CoronaVac is one of the successful inactivated SARS-CoV-2 vaccines currently available on the market. Near the beginning of the pandemic, in April 2020, this inactivated virus vaccine was one of the first to begin COVID-19 vaccine trials [9]. Based on its efficacy and the results of Phase I/II trials, the vaccine underwent emergency use approvals (EUA) in a number of countries. The currently available peer-reviewed evidence for CoronaVac confirms its safety and efficacy for short-term use in humans [31, 32], and it has been included in the World Health Organization's emergency use listing [30].

During the Phase I, II, and III trials carried out for these vaccines, no serious side effects were observed. Those reported were minor, predictable side effects with limited occurrence [33]. Of note, when tested in Rhesus monkeys, the inactivated vaccine from Sinovac was shown to be both safe and effective. In addition to producing IgG, it reduced

virus titers and pathological changes in the lungs, without observable antibody-dependent enhancement of infection [7]. While this vaccine performed well overall, one study showed that 62.5% of CoronaVac injections were accompanied by side effects. These included pain at the injection site (41.5%), which was the most common local side effect, and fatigue (23.6%), headache (18.7%), muscle pain (11.2%), and joint pain (5.9%), which were the most common systemic side effects [34].

CoronaVac has been administered in 26 countries and has helped to increase the supply of COVID-19 vaccines through COVAX (COVID-19 Vaccines Global Access). In China, a total of 1.46 billion doses of COVID-19 vaccines have been administered as of July 19, 2021, most of which were CoronaVac [17]. The vaccine has been shown to prevent laboratory-confirmed COVID-19, and to be highly effective at mitigating some of the more severe outcomes [35]. One study demonstrated that the neutralizing antibody level decayed to around the positive cutoff of 8 by 6–8 months after the second dose [36].

The results of another study showed that, in older adults, 6 months after receiving two doses of CoronaVac, the titers of neutralizing antibody had declined significantly. Vaccination of these patients with a booster dose was found to reverse this by quickly inducing robust immune responses [37].

In addition to traditional approaches, the pandemic has given impetus to the development of innovative platforms for the creation of vaccines with good indicators of immunogenicity and efficacy. Adenoviral vectors based on human and primate adenoviruses, which have been used previously to create vaccines against other viral diseases, are one of the other platforms used to create anti-coronavirus vaccines.

Adenoviral vectors

Many of the first replication-defective adenovirus vectors in the early 1980s were vaccines. The original adenoviral vaccine design was relatively simple: delete a region of the viral genome the virus needs to propagate, support these functions via transcomplementing cells (e.g., Frank Graham's 293 cells) to grow the vaccine, and then insert an expression cassette encoding the targeted epitopes into the virus genome [38]. Several innate features of adenovirus vectors make them ideal vaccine candidates compared to other viral vectors. The eventual disposition of the viral genome after the virus has performed its job as a vector is important. Viral vectors based on retroviruses and the related lentiviruses have been associated with viral-vector mediated insertional mutagenesis, leading to genotoxicity [39].

Unlike retroviruses, adenoviral DNA does not integrate with the host genome, nor does it replicate during cell division. This is one of several reasons adenoviral vectors have

been explored for use in vaccines against many infectious diseases. When used in vaccines, they reliably induce potent, balanced immune responses, with fewer negative consequences, which makes them an excellent choice when creating a vaccine to address COVID-19 [40].

Adenoviruses circulate year round (unlike influenza, they do not infect seasonally) through a variety of vertebrate populations, from humans to fish, and are responsible for mild infections, such as pink eye and the common cold, and for serious diseases that threaten multiple organ systems [50]. The adenoviruses that occur among mammals are specific to each species; the serotypes found in humans (51) and simians (27) include 7 found in chimpanzees, with whom humans share almost 99% DNA. This is important, since humans are less likely to have developed neutralizing antibodies against adenoviruses specific to chimpanzees or other simians. Three of the human serotypes (1, 2, and 5) cause upper respiratory infections, while two others (4 and 7) cause severe pneumonia; owing to their prevalence, close to 80% of humans have antibodies against HAd5 (human serotype 5).

Unlike enveloped viruses, which are protected from degradation within the cell by a wrapping formed from the host cell's plasma membrane, adenoviruses are non-enveloped viruses whose double-stranded DNA genome (~33–34 kb) is contained within an icosahedral protein capsid. Although the viral genome is small, adenoviruses employ a strategy that encodes polypeptides from both strands of DNA, alternatively spliced mRNAs, and the ability to switch between the available poly(A) sites. Inverted sequence repeats (~150 bp in length) found at the ends of the viral genome are responsible for DNA replication. At the genome level, adenoviruses comprise transcription units that may encode multiple proteins with related functions. These eight transcription units, which are transcribed by RNA polymerase II, are divided into three sections: the early units (E1A, E1B, E2, E3, E4, and E5), several units transcribed at the onset of DNA replication (IX and IVa2), and one late transcription unit (L), which generates mRNAs L1–L5 [51].

The cell receptor to which an adenovirus binds depends on its serotype. When initiating entry into a cell, adenoviruses with the B serotype bind to CD46; all others bind to the coxsackievirus and adenovirus receptor (CAR). For instance, when the common HAd5 virus binds to CAR in the epithelium of the respiratory tract, it activates an inflammatory reaction. This reaction causes induction of the ERK1/2 and p38MAPK signaling pathways and the expression of pro-inflammatory cytokines, including IL-6, IL-8, and IP-10, and the chemokine RANTES [52]. Adenoviruses evoke strong immunoreactive responses, which is good when the body is fighting off a viral infection, but less useful when using the adenovirus in a vaccine. Small molecular motifs highly conserved in the adenoviral genome, currently

referred to as pathogen-associated molecular patterns (PAMP), activate immune responses. When PAMP bind to the host cell's pathogen recognition receptors, particularly the Toll-like receptors of the innate immune system, they induce pro-inflammatory cytokines and cause immature dendritic cells to differentiate into professional antigen-presenting cells. These cells internalize the antigen, break it up into fragments, and present these to T-cells to activate them [53]. Because adenoviruses induce strong CD8⁺ as well as CD4⁺ T-cell responses, circumventing these innate immune responses is vital when repurposing adenoviruses for use in vaccines.

The desire to use adenoviral vectors in creating new vaccines for human diseases is not confined to vectors developed from human serotypes, such as human serotype 5 adenovirus (AdHu5). As mentioned above, adenoviruses from nonhuman sources, such as chimpanzees, are being evaluated for use in the development of vaccines [54]. In mice given an experimental adenovirus-vector vaccine against H5N1, both intramuscular and intranasal immunization provided protection from the disease, due in part to resident memory T-cells generated in the lungs [55]. Intranasal immunization is faster and more convenient than receiving an injection and has been shown to induce IgA antibodies in the mucosa. However, it has also been shown that delivery of a vaccine with an adenoviral vector in the proximity of the olfactory bulb during intranasal application carries a real risk of viral infection of the central nervous system [56].

When using adenoviruses as vaccine vectors, it is worth noting that their efficacy is directly affected by the widespread pre-existing immunity that results from their prevalence in human populations [50]. Almost all children are infected with ubiquitous human adenovirus serotypes during early infancy and develop immune responses to them. Two of the most common human serotypes, AdHu5 and AdHu2 viruses, have been exhaustively studied. Given that children contract and recover from these early in life, it is not surprising that, depending on the region, 45–80% of adults have been found to carry AdHu5-neutralizing antibodies [57]. A major scientific focus of adenoviral vector vaccinologists is the circumvention of adenovirus-specific neutralizing antibodies. The sheer variety of adenovirus serotypes, including serotypes from nonhuman primates, as well as their versatility, makes them valuable. As we develop vaccines against new pathogens in an effort to contain them, knowing that more as yet undiscovered are coming, we need every tool available to us, including the adaptable adenovirus [51]. Unfortunately, even as SARS-CoV-2 and all its variants has become a global pandemic, little has been done to create an innovative adenovirus vector vaccine for it. As mentioned above, AdHu5 is well studied, precisely because so many people have already been infected with it, so some have used this as the basis for a vaccine. Other researchers have opted

for adenovirus serotypes either human (e.g., Ad26) or simian (monkey and gorilla) with low seroprevalence in Europe and North America, which is of limited utility, since this may not be the case in the much larger areas of Africa, Asia, or South America. This approach has been in use for the last 30–40 years; at this point, researchers should investigate some other angles as well [38].

While some space remains within the adenovirus protein capsid for insertion of additional non-viral material, the creation of effective vaccines is usually accomplished by deleting transcription units [58]. In addition to providing more space (~7.5 kb), deletion of the E1 unit (most often) and sometimes the E3 transcription unit as well modifies the viral vector and renders it replication defective. Because they express viral gene products, but lack the ability to replicate and form more viruses, vectors with these deletions deliver the desired vaccine material without killing the host cells. The E1 transcription unit encodes the polypeptides responsible for the initiation of viral transcription. Since E1 is essential, growing viruses from which E1 has been deleted in cells lines that transcomplement E1 has made this deletion possible [59]. E1-deleted vectors have been used most frequently because they are successful; they remain immunogenic without activating the innate immune system. In addition, after inducing the maturation of immature dendritic cells into antigen-presenting cells [60], they go on to achieve long-lasting antigen presentation without inducing apoptosis of these cells, and to express high levels of transgene products. Most vaccines reduce or prevent infections by inducing neutralizing antibodies against their target pathogen's surface antigens. Studies of an AdHu5 vector used in a rabies vaccine has shown that, after a single injection, it swiftly induced protective neutralizing antibody titers against the transgene product [61].

One of the adenovirus vaccines now available against SARS-CoV-2 is VaxZevria (CoviShield, ChAdOx1 nCoV-19 vaccine (AZD1222)). It was co-invented by the University of Oxford and its spin-off company, Vaccitech [42, 43]. The adenoviral vector used for this vaccine, which contains the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene, was developed using the replication-deficient chimpanzee adenovirus ChAdOx1. In a study comprising four trials carried out among populations on three continents, this vaccine was shown to provide protection (64.1%) from symptomatic disease after one dose and to have significant efficacy after two scheduled doses (70.4%). No safety concerns were noted in any of these studies. The European Medicines Agency (EMA) authorized use of VaxZevria[®], the AstraZeneca adenovirus vector vaccine directed against SARS-CoV-2, on January 29th, 2021 [62].

According to relevant current guidelines, genotoxicity and carcinogenicity studies are normally not required for viral vaccines; none were carried out for these studies (in

addition, no adjuvants or novel excipients were used in this vaccine). To determine whether the vaccine would have any adverse effects on reproduction, a preliminary DART (direct antigen rapid test) was carried out. This GLP-compliant test, which evaluates developmental and reproductive toxicology, did not reveal any adverse effects on female reproduction or the survival of fetuses or pups, nor were there any fetal visceral or skeletal findings. The results of the test did show that a sufficient transfer of anti-S glycoprotein antibody occurred across the placenta and through lactation. At present, a large definitive DART study in mice is ongoing, the results of which will be provided to the EMA. Congenital anomalies have not been found in association with the various wild-type adenoviral infections that regularly infect human populations worldwide [63].

Adverse events occurred more frequently in adults between the ages of 18 and 65 years than in the elderly (adults aged ≥ 65 years). Most of these were of mild-to-moderate severity, observed within the first week after injection (≤ 7 days) of either dose, and were observed more often after the first than the second dose [64]. The most frequently reported adverse events were local reactions, primarily pain at the injection side, followed much less frequently by redness and swelling, and very rarely, lymphadenopathy. These reactions, which are common following all kinds of vaccine injections, generally appear within 1–3 days of injection, and last for less than 48 h. The most commonly reported systemic reactions were fatigue and headache, myalgia and chills, and arthralgia and fever ($< 15\%$) [64]. Fewer than 0.1% participants reported serious adverse events related to the vaccine: three events were reported in the vaccine group (fever, increased C-reactive protein, and myelitis transverse) and two events in the control group (autoimmune hemolytic anemia and myelitis) [63]. Among those vaccinated with VaxZevria, fewer reported thrombosis following vaccination compared to reports that occur in the general population, demonstrating that the vaccine is not associated with an increased risk of thrombotic events. It is important to note that there have been reports of rare cases of thrombosis combined with thrombocytopenia and occasionally bleeding [65]. These events have been referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT), which includes cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis (SVT) [66]. Serious adverse events were also reported for the central nervous system; these included three cerebrovascular accidents, two embolic strokes, and one transient ischemic attack reported in the vaccine group. The respective numbers for the placebo group were 1/0/0. In addition, while there were no reports of deep vein thrombosis in the placebo group, two were reported in the vaccine group. Review of the medical histories of those for whom the stroke and transient ischemic

attack were reported revealed that these individuals had significant prior medical history and/or increased risk [67].

It has been shown that administration of the VaxZevria vaccine is not associated with an increased risk of thrombotic events. However, the reports of cerebral venous sinus thrombosis and splanchnic vein thrombosis accompanied by low platelet levels are being closely scrutinized and are the subject of ongoing investigation [64].

mRNA vaccines

In late 1987, graduate student Robert Malone performed an experiment that would eventually contribute to the development of mRNA vaccines. After mixing strands of mRNA into droplets of fat, he bathed human cells in the mixture. When the cells were found to produce proteins coded by the mRNA, it was shown that they were able to absorb mRNA delivered in this manner [68, 69]. A few years later, in 1990, the first successful use of in vitro transcribed (IVT) mRNA in animals was reported. In experiments carried out in mice, injection of reporter gene mRNA resulted in the production of detectable proteins [70]. However, overcoming the inefficiencies of in vivo delivery to get mRNA into an organism was only part of the battle; mRNA is also unstable and highly immunogenic. The promising results of the late 80 s and early 90 s failed to lead to the use of mRNA in developing therapeutic agents; DNA-based and protein-based therapeutic approaches were chosen instead [71].

mRNA vaccines start out with a basic structure comprising 5' and 3' untranslated regions (UTR) that flank the sequence for the vaccine antigen, with a 5' cap at one end and a 3' poly(A) tail at the other. Conventional mRNA-based vaccines encode the antigen of interest; vaccines based on self-amplifying RNAs encode both the antigen of interest and other nonstructural viral proteins that aid in amplifying the translation of mRNA and thus increasing the levels of protein expression [23]. Self-amplifying mRNAs are often derived from the genomes of positive-sense single-stranded RNA viruses. Regardless of origin, all mRNA are recognized as 'other' by the receptors of the innate immune system. Whether this is viewed as beneficial or detrimental depends on the therapeutic use to which it is put. It is potentially advantageous when developing a vaccine, because it may provide the spark that drives dendritic cell (DC) maturation that elicits robust T- and B-cell immune responses.

The in vitro transcribed (IVT) processes used to produce mRNA for use in vaccines can result in contaminants, such as double-stranded DNA (dsDNA). Pattern recognition receptors throughout the cellular compartments sense the presence of dsDNA, a strong PAMP (Pathogen-associated molecular pattern) that mimics both viral genomes and replication intermediates [72]. mRNA bound to lipid nanoparticles (LNP) drains passively through lymphatic

vessels. In this way, mRNA is delivered directly to the lymph nodes. Subsequently, antigen-presenting cells migrate to these nearby draining lymph nodes where T-cell priming occurs [73]. Self-replicating RNA vaccines have displayed increased immunogenicity and effectiveness after formulating the RNA in a cationic nanoemulsion based on the licensed MF59 (Novartis) adjuvant [74]. In 1990, the first report of successful use of IVT mRNA in animals was published documenting the production of proteins encoded by reporter gene mRNAs injected into mice [75].

On January 6, 2021, the EMA CHMP issued a positive opinion granting a conditional marketing authorization for the Spikevax (Moderna) COVID-19 vaccine [43]. Spikevax (mRNA-1273), an LNP-encapsulated mRNA vaccine, expresses the prefusion-stabilized full-length spike glycoprotein of SARS-CoV-2, the virus that causes Covid-19. It was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH) [76]. The vaccine efficacy estimate, based on a total of 95 adjudicated cases (63% of the target total), demonstrated an efficacy of 94.5% in the reduction and/or prevention of Covid-19 infection, including severe disease [77].

Glomerulonephritis was one of the more serious side effects noted following injection of this the vaccine [78]. As with other vaccinations, the most common side effect reported was pain at the injection site. The severity of the solicited systemic events increased after the second dose in the mRNA-1273 group, with an increase in the number of grade 2 events from 16.5% after the first dose to 38.1% after the second dose [48].

In those who received the Moderna mRNA-1273 vaccine, antibodies declined slightly but remained at appreciably high levels on days 90 and 180 after the second dose, with antibody detected among all participants. For the Pfizer/BioNTech T162b2 and AstraZeneca ChAdOx1 320 nCoV-19 vaccines, antibody levels declined by 55% and 84%, respectively, between 21 and 41 days and 70 days or more after the second dose was delivered. However, the heterogeneity of neutralization assays makes it difficult to directly compare these estimates with those of the other vaccines, including CoronaVac. Despite its global impact, the fact that SARS-Cov-2 is such a recent arrival on the world stage means that laboratories have not yet developed standardized methods for assessing it. Even when a lab uses the same live virus in its neutralization assays, the methods used for everything else—virus-serum neutralization, virus titration, serum dilution, readout, and reporting methods (e.g., NT50, NT100)—will vary in ways that make comparison difficult if not impossible [79]. For vaccines developed using innovative platforms, one of the most important factors has been the ability to transfer understanding gained from work with similar pathogens: AZD1222 was developed from a Middle

East respiratory syndrome coronavirus program, and the protein engineering approach used to stabilize the S protein was derived from an understanding of the respiratory syncytial virus fusion glycoprotein and the difference between prefusion and postfusion states, which was made possible only through long-term study.

Faster responses came from smaller biotechnology companies and academic institutions (with support from larger companies to scale up); whether this reflects a nimbler response or a different risk profile is unclear. All in all, it seems that having a broad range of research to call upon works best when preparing for unknown future pathogens.

Given the overwhelmingly global impact of SARS-CoV-2, it is worth noting that most of the COVID-19 vaccine doses have been administered in high-income or middle-income countries; as of June 2021, only 0.9% of people in low-income countries had received at least one dose. In parallel with ongoing investment in research, investment in manufacturing capacity, training, and the ability to deliver vaccines globally is crucial to build on the incredible successes of the past 18 months [80].

At the same time, the question of their safety in the long term remains unanswered. There is a great desire among world leaders and the pharmaceutical manufacturers to create and produce new anti-coronavirus vaccines. However, as of yet, humanity has no way to truly assess the results of worldwide vaccination; choosing the most optimal vaccine, depending on the biological characteristics of each individual, is extremely difficult because sufficient experience has not yet been accumulated. There has not been enough time to carry out long-term studies, and little or no data exist concerning the interaction of these vaccines with other vaccines, their use in women during pregnancy/breast feeding, or their use in immunocompromised subjects, subjects with comorbidities, or subjects with autoimmune or inflammatory disorders [64]. Thus, to date, vaccines created on the three main platforms (Fig. 1) show significant efficacy in the formation of an immune response.

At this moment, it is difficult to fully assess all the risks associated with a vaccine. Even in the future, perhaps in a few years, we will still only be able to determine whether they do not exceed the potential benefits. Will anti-coronavirus vaccines begin to demonstrate the negative effects on human health associated with the use of thiomersal [81], aluminum [82], and other components [83] in their composition, for which other vaccines are often criticized? Only time will answer this question. We, in turn, hope that a balance will be struck between the efficacy and the safety of anti-coronavirus vaccines, which will help maximize efficiency while minimizing the danger.

Obviously, anti-coronavirus vaccines will face the same problems as influenza vaccines. In the case of the influenza virus, it is also challenging that the virus is constantly

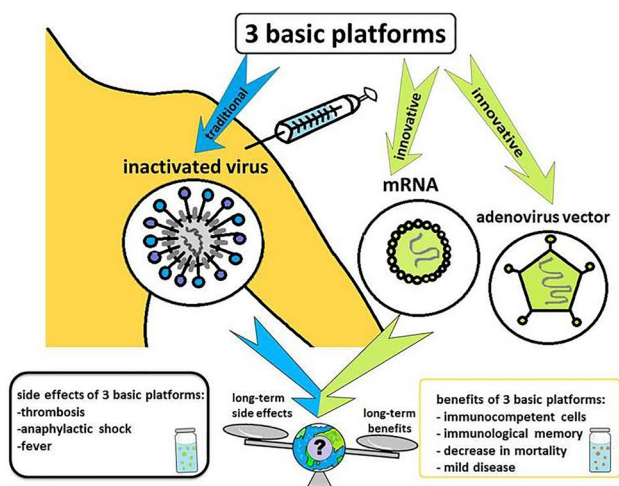


Fig. 1 Characterization of the three main vaccine platforms

changing. Human influenza viruses undergo changes in the genome, which leads to evolutionary changes in its antigens, in particular the glycoproteins of the outer membrane of the virus. As a result, the formulas of influenza vaccines have to be revised every year, taking into account the prevailing subtypes of viruses. Very few platforms are capable of responding very quickly and efficiently to the changing antigenic properties of the influenza virus.

«Solvency» of immunity following recovery from COVID-19

With the success of vaccine development, the strategies used to respond to the COVID-19 pandemic have shifted gradually from border controls, quarantine, and lockdowns to vaccinations and specific therapeutic agents.

The vaccination rate worldwide has reached enormous proportions, and it is likely that at least 75% of the world's population will be vaccinated. With the race to vaccinate the world against SARS-CoV-2 well on its way, many countries have already achieved impressive vaccination rates and are quickly reaping the benefits. However, not all highly vaccinated populations are seeing the same results [84].

Innovative vaccines compete with traditional vaccines

There is a significant difference in the immune responses elicited by the different vaccines. The mechanism in the CoronaVac vaccine is based on an inactivated SARS-CoV-2 virus with an alum adjuvant. While this vaccine has been shown to efficiently induce the production of neutralizing antibodies, no studies have been done that specifically compare its efficacy with that of other vaccines. One study used

modeling to predict how well different vaccines prevented symptomatic SARS-CoV-2 infection based on neutralizing antibody titers. The CoronaVac vaccine was not directly addressed in this study; however, modeling showed that, compared to adenoviral vector and mRNA vaccines, alum-adjuvanted inactivated virus vaccines had less protective efficacy against the virus, which had a strong correlation with lower titers of neutralizing antibodies. Based on their results, Khoury et al. also stated that vaccines that started with low efficacy against the virus were predicted to have a greater loss of efficacy over time for both the original virus and eventual variants [85]. The danger of deploying vaccines that may not provide sufficient long-lasting protection against a virus and its variants is that new waves of infection may occur, during which more variants emerge. Additionally, the deployment of sub-optimal vaccines may threaten trust in vaccination campaigns overall.

Another difference between the Sinovac vaccine (traditional approach) and the mRNA (innovative approach) and adenovirus-vector vaccines is cellular immune responses. Data on the cellular immune responses to the CoronaVac vaccine are lacking. Historically, it has been observed that alum adjuvant inactivated virus vaccines induce either no cellular response, or weak cellular responses, specifically cytotoxic CD8⁺ T-cell responses [85]. On the other hand, both mRNA and adenovirus-vector vaccines have shown robust, Th1 predominant cellular adaptive immune responses, with the production of antigen-specific CD4⁺ and CD8⁺ T cells [86]. As discussed above, the modeling study predicted that vaccines developed using adenoviral vectors and mRNA would have higher titers of neutralizing antibodies. This, coupled with the evidence of their stronger cellular immune responses, is predicated to lead to better outcomes for acute infections. In addition, it should result in stronger immunity that lasts longer [87]. The emerging variants to SARS-CoV-2 have shown themselves to be quite capable of evading neutralizing antibody activity; fortunately, the cellular immune responses are still both present and active against the variants [84]. This could explain the highly divergent epidemiologic outcomes observed in Qatar (innovative approach) and Bahrain (traditional approach), since the CoronaVac vaccine used heavily in Bahrain appears to induce weaker humoral responses, cellular responses, or both. Although the divergent outcomes observed in Qatar and Bahrain are potentially the most striking, the trend seems to hold true in other countries as well. A study carried out in Chile found that overall, IgG seropositivity for CoronaVac recipients reached 77% after two doses, while inoculation with a single dose led to low IgG seropositivity levels (28%). Seropositivity in Comirnaty (Pfizer/BioNTech) vaccine recipients surpassed 95% after two doses and 80% after one vaccine dose. A comparison of the results 4 weeks after completion of the full course of vaccination showed

that in those who received the CoronaVac vaccine, a steady decline in IgG seropositivity occurred that was not seen in those who received the Comirnaty (Pfizer/BioNTech) vaccine [88].

Looking at vaccination data updated as of June 2, 2021 in countries with a population exceeding 500,000, among the 10 countries with the highest doses of COVID-19 vaccines administered per capita, five relied in part on alum-adjuvanted inactivated virus vaccines: Bahrain, Chile, Hungary, the Maldives, and Mongolia [89]. The other five countries among the top 10—Israel, Malta, Qatar, the United Kingdom, and the United States—relied on only mRNA and/or adenovirus-vector vaccines. While all 10 countries have achieved high vaccination rates, as of June 4, 2021, the five countries that relied on inactivated virus vaccines had higher daily COVID-19 deaths per million people. In contrast, the trend for the average daily COVID-19 deaths per million across the five nations that did not rely on inactivated virus vaccines showed a steady decline after January 31, 2021. This decline in deaths was not seen in the five nations that relied on inactivated virus vaccines. Thus, across highly vaccinated countries, the reliance on inactivated virus vaccines seems to be associated with worse outcomes [84].

As we discussed earlier in this article, the SARS-CoV-2 coronavirus does not change rapidly, accumulating genetic mutations very slowly. In such a situation, the immunity formed in response to the use of a whole viral particle will be more complex, since an immune response will be formed to the entire palette of viral antigens. In the innovative approach used in the development of vaccines based on mRNA and adenoviral vectors, only the S-protein of the coronavirus is used as an antigen. Via microevolution, the coronavirus has demonstrated its ability to bypass the protective immune response based solely on one S-protein rather quickly, as demonstrated by the decreased efficacy of vaccines based on innovative approaches [90]. For example, in some regions of the United States, a 100-fold increase in the incidence of the delta variant of the virus was recorded within 2 months of its appearance, which occurred in tandem with a sixfold decrease in the incidence of the alpha variant. Obviously, in such a situation, inactivated vaccines that comprise a more complete set of coronavirus antigens are likely to be more effective, all other things being equal [91].

Twelve COVID-19 vaccine manufacturers have announced their plans for vaccine production, with an estimated capacity of approximately 10 billion doses by the end of 2021. However, even if this highly optimistic scenario is realized, and 10 billion doses are effectively manufactured, the production capacity currently in place cannot produce enough vaccine to provide for the two dose regimen planned for most COVID-19 vaccination schedules [92]. If we cannot get these vaccines to the people who need them, we are unlikely to achieve global herd immunity (60–80% of the

world population). Therefore, it is necessary to define the priorities for vaccination. The COVID-19 pandemic is not yet 2 years old, but it has already become clear that there has not been equitable or efficient distribution of COVID-19 vaccines. While citizens in affluent countries, large and small, have been given the choice to be vaccinated, those in poorer countries frequently have not. Countries with incomes in the low to middle ranges lack both the cash and in the infrastructure to carry out research, develop, and then manufacture COVID-19 vaccines [93]. To ensure equitable access to COVID-19 vaccines, COVAX (the vaccine pillar of the Access to COVID-19 Tools Accelerator) has been established to facilitate global cooperation in ensuring vaccine availability to lower income countries. But if the vaccine becomes available in sufficient quantities, where do we start?

There is no country for old men

Older people had borne the brunt of the pandemic, with the highest number of deaths occurring in the oldest age groups. However, little is known about the efficacy and safety of mRNA vaccines in older people, especially at the extremes of old age and in those who are frail. Despite the existence of annual influenza shots for quite some time, there are few data concerning their efficacy in the elderly, which is the subject of many disputes. It is likely that this will happen with COVID-19 vaccination programs as well [94]. At the beginning of the COVID-19 outbreak, some of the highest mortality occurred among elderly patients in long-term care facilities, as well as in older adults in general [95]. The case fatality rate, calculated using the official reports of infections and deaths due to COVID-19, was 7.2% overall. The highest numbers were reported for the elderly and for men [96]. This trend was seen across the world, as in most countries the severity of the consequences of COVID-19 infection depended upon age [97, 98]. Italy was hit particularly hard by this; during the first few months of the pandemic, older adults were the most likely to suffer severe COVID-19 infection. By the end of April 2020, 25.3% of total infections and 55.3% of deaths in Italy involved people > 80 years of age [99]. This has led to the general consensus that people aged 65 years or older and higher risk people below the age of 65 represent high-risk groups that should be given priority when it comes to vaccination. The official COVID-19 vaccination recommendations in Germany (https://www.rki.de/DE/Content/Infekt/Impfen/ImpfungenAZ/COVID19/Impfempfehlung_Zusfassung.html, accessed 21 January 2021) suggest beginning vaccinations in the oldest and most vulnerable population groups, as well as their medical and nursing care givers, and then gradually providing vaccinations to younger and less vulnerable or exposed groups [100].

Based on the above facts, it seems quite logical to strive to first vaccinate elderly people (65 years of age and older),

since mortality is higher in this group. In this regard, the quality of the vaccines used and their effectiveness is of primary importance. The highest efficacy and safety for the elderly have been reported for vaccines as such Comirnaty (Pfizer/BioNTech) and Oxford-AstraZeneca. In a large prospective cohort study based on over 10,000 care home residents, the BNT162b2 and Oxford-AstraZeneca COVID-19 vaccines were shown to protect against COVID-19 infections and reduce SARS-CoV-2 transmission; however, they were not able to eliminate the risk of infection [101]. Additional cohort studies have shown that patients with a score higher than 5 on the Clinical Frailty Scale required mechanical ventilation after infection with COVID-19 and are at greater risk of mortality [102]. But not everything is so simple.

Reports suggest that although COVID-19 is usually milder in vaccinated (i.e., when contracted after vaccination) than in unvaccinated individuals, mortality remains high among those who are hospitalized. Data from the International Severe Acute Respiratory and Emerging Infection Consortium show a mortality of 27% (400 of 1482 died) [103, 104]. For example, after providing BNT162b2 mRNA vaccines for approximately 35,000 nursing home residents (mean age: > 87 years), the Norwegian government received 100 reports of suspected fatal adverse events. Following expert investigation of these reports, 10 probable and 26 possible vaccine-related fatal events were found, or approximately 1 potential vaccine-related fatality for every 1,000 residents. Compared to healthy older adults receiving COVID-19 vaccines, nursing home residents showed higher vaccine-related fatality rate [105].

Following infection with COVID-19, almost all symptoms were reported less frequently in vaccinated compared with unvaccinated individuals. Vaccinated individuals were more likely to be completely asymptomatic, especially if they were 60 years or older. For those who had one dose of a vaccine and then contracted COVID-19, frailty was observed in older adults (≥ 60 years). Obese people, the elderly (especially those who are frail), and those living in poorer/deprived areas were found to be more likely to become infected with COVID-19 after receiving a single dose of vaccine than those in better circumstances. It remains unknown whether vaccination reduces the risk of post-acute sequelae of SARS-CoV-2 (PASC; also known as long COVID) [103]. Nevertheless, there is a good objective reason why it is necessary to vaccinate the elderly first—the weakness of the immune response.

When investigating immune responses following vaccination, ~50% of those > 80 years old had suboptimal neutralizing antibody responses after receiving the first dose of Comirnaty (Pfizer/BioNTech). Their T-cell responses were also lower compared to those of younger individuals. Individuals over 80 years of age differed from members of the younger group in four distinct ways that could explain

their poorer neutralization of SARS-CoV-2. They had (1) lower serum IgG levels coupled with (2) a smaller number of peripheral spike-specific $\text{IgG}^+\text{IgM}^-\text{CD19}^+$ memory B cells. They were found to have (3) lower somatic hypermutation in the BCR gene. Finally, individuals in this older group displayed (4) a marked reduction in IL-2-producing spike-reactive CD4^+ T cells. The poorer neutralizing responses in this group can thus be explained as follows: they had lower concentrations of antibodies (quantity) and/or lower affinity antibodies (quality) as the result of B cell selection, reduced support from CD4^+ T cells, or a combination [100].

Should we leave the recovered and children unvaccinated?

Recent studies suggest that current COVID-19 vaccines, many of which are based on the immunogenic regions of the S glycoprotein, may not be effective against newly emerging resistant SARS-CoV-2 variants. Fortunately, the response to these vaccines is not limited to producing neutralizing antibodies; it also includes CD4^+ and CD8^+ T-cell responses specific to the SARS-CoV-2 virus. These virus-specific T cell responses have been found following vaccination with vaccines developed from the various platforms (alum-adjuvanted inactivated virus, mRNA, and viral vectors). This is promising, because T cells are harder to dodge, since their epitopes are found all over viral proteins. Neutralizing antibodies are only effective across a small, specific region of the protein, which may have been altered beyond recognition in recent variants [106].

COVID-19 is a serious illness, although some who contract it remain asymptomatic. Common symptoms include a dry cough, sore throat, fever or chills, muscle or body aches, accompanied by shortness of breath/difficulty breathing. While many COVID-19 patients experience only mild symptoms, their magnitude varies depending upon age, the severity of disease, and whether there is any comorbidity. In the elderly and those with comorbidities, complications occur that can coalesce into a cytokine storm. These include pneumonia, acute respiratory distress syndrome (ARDS), sepsis/septic shock, and acute kidney injury. The complications associated with prolonged hospital stays, including confusion/mental decline, urinary tract infections, undernutrition, and sleep disturbances have been reported, along with cardiac (cardiomyopathy, arrhythmia) and neurologic complications. As of 10 April 2021, worldwide deaths attributable to severe COVID infection has reached 3 million [64].

Although the pandemic has not yet lasted 2 years, people have reported being reinfected after an initial infection with the virus. This has been observed with other coronaviruses that affect humans, but we do not know whether an initial COVID-19 infection can, or will, provide protective immunity against subsequent infections [107]. Since reinfection

with COVID-19 is a distinct possibility, the data collected so far indicate that in at least 20% of those infected, symptoms may be worse, particularly for the elderly and those who are immunocompromised. The latter two groups are likely to encounter serious complications [108]. Data also suggest that reinfection is not specific to any particular strain, and multiple strains with a different genetic sequence have been shown to cause reinfection.

The perceptions concerning what constitutes immunity and how to handle it differs from country to country. For instance, in Israel a waiting period of 3 months is recommended for people who have had COVID-19 before they receive one mRNA vaccine dose. Those with a positive serological result, regardless of vaccination status, are offered a 'green pass' (vaccine passport) [109]. Several studies (in Qatar, England, Israel, and the US) have found equally low infection rates among people who are fully vaccinated and those who have previously had COVID-19 [110–113]. A large study carried out in the UK and another that surveyed people internationally found that people with a history of SARS-CoV-2 infection experienced greater rates of side effects after vaccination. Among 2000 people who completed an online survey after vaccination, those with a history of COVID-19 were 56% more likely to experience a severe side effect that required hospital care [114]. SinoVac advises that vaccination be postponed for 6 months after an illness. They also note that neither the optimal nor the minimum interval between natural infection and vaccination has yet been established (product information). Moderna and AstraZeneca also recommend postponing vaccinations for a month in cases of documented positive PCR tests. Also suggests postponing vaccination by 6 months (product information).

The data suggest that antiviral specific immunity is long lasting, especially the memory B-cells found in COVID-19 convalescent patients. No statistically significant differences were observed between the number of memory B cells found in mild/moderate and severe/critical COVID-19 patients over a period ranging from 6 to 15 months, which suggests that the intensity and duration of the B cell response is not dependent on the severity of the disease. The data also suggest that SARS-CoV-2-specific T-cells remain viable long after recovery from COVID-19, which supports the development and use of effective vaccination programs as one way to help control COVID-19 [115]. Recent studies in unexposed individuals have shown that ~ 40–60% of them harbor SARS-CoV-2-reactive CD4⁺ T cells, which points to cross-reactive T-cell recognition between the circulating 'common cold' coronaviruses, to which many people have already been exposed, and the newcomer, SARS-CoV-2 [116]. Of particular interest is the recently discovered super immunity of the coronavirus. In essence, if people who have been ill with COVID-19 are then vaccinated against it, these

people develop resistance to various types of coronavirus, including those that have been modified.

There is some evidence that B cells in people who received both inoculations without ever having been infected are gaining the ability to recognize a variety of coronaviruses. Analysis of memory B cells in lymph-node samples collected from mRNA-vaccinated individuals showed that some had begun to mutate in response to vaccination. This continued for some time after these individuals had received their second dose of vaccine (up to 12 weeks). The mutations made it possible for the B cells to recognize the coronaviruses responsible for common colds, among others [117]. A study published in September 2021 in *Nature* reported that a spike protein with 20 mutations was "fully resistant to neutralizing antibodies made by most of the people tested who had been either infected or vaccinated—but not to everyone's." This mutated spike appears to be more resistant to the defenses usually sent to attack and intercept intruders. In people who had been infected with COVID-19, recovered, and months later received COVID-19 vaccinations, antibodies were discovered that were able to neutralize this spike. In fact, their antibodies were able to recognize and neutralize other coronaviruses as well [118]. Is such a hybrid super immunity tempting? Perhaps. But the possible danger associated with the mutation of B lymphocytes following the use of mRNA vaccines requires careful monitoring.

Children belong to a special group when it comes to health care in general and vaccines in particular. Statistics show that COVID-19 related mortality among children is very low, accounting for only 0.2% of total deaths. Since children are becoming infected, it is possible that the virus is unable to replicate as well in them as in adults. It has been proposed that children may have fewer of the ACE2 receptors used by the virus to gain entry to cells. While evidence concerning age-related differences in ACE2 expression in the nose and lungs is inconsistent, measurements of the viral load in human upper airways has failed to demonstrate any significant difference between children and adults. Children infected with COVID-19 tend to have milder symptoms than adults, but still produce antibodies at similar levels.

However, because their immune systems were less mature, the levels of T cells and neutralizing antibodies that function within the immune system were lower than those of adults. A study of adults and children infected with SARS-CoV-2 carried out in Hong Kong demonstrated that the adaptive immune response in children, particularly the response of the T cells, was weaker than that of the adults. This leads to speculation that some earlier event or experience is responsible for the difference [119].

It has been proposed that early previous exposure to other human coronaviruses causes adult immune systems to partially recognize SARS-CoV-2 and respond to the parts of it for which they already have antibodies. This phenomenon,

known now as original antigenic sin, was described in 1960 when Thomas Francis noted that people produced the most antibodies against the first strain of influenza to which they were exposed; for most people, this is during childhood. Following on from this, it would make sense that the immune systems of children are recognizing and responding to the newest coronavirus differently than those of adults. Therefore, it is not surprising that when measured, antibodies in adults targeted the conserved portions of SARS-CoV-2 most similar to those of other coronaviruses, whereas antibodies in children covered a broader range that included all sections of the virus [119]. The mortality rate from coronavirus among children is still very low and this is encouraging (Fig. 2).

Thus, in our opinion, over the next 4–5 years, about 5–6 billion people will become infected with SARS-CoV-2, which will lead to the coveted but elusive herd immunity. Collective immunity will be formed in two main ways: at the expense of unvaccinated people who have recovered from infection (fast vector) and vaccinated people who have recovered from infections that occurred after vaccination (slow vector). By far the greatest death toll will be observed in the fast vector.

In the current state of the pandemic, in our opinion, it is necessary to first vaccinate the elderly (aged 65+) [120]. However, before vaccination, it is imperative to determine which medication(s), based on sex, concomitant diseases, allergic reactions, and the age of the elderly person, are needed to provide support both during the vaccine delivery schedule and afterwards [121]. By extrapolation, today's statistics tell us that about 2% of people die from

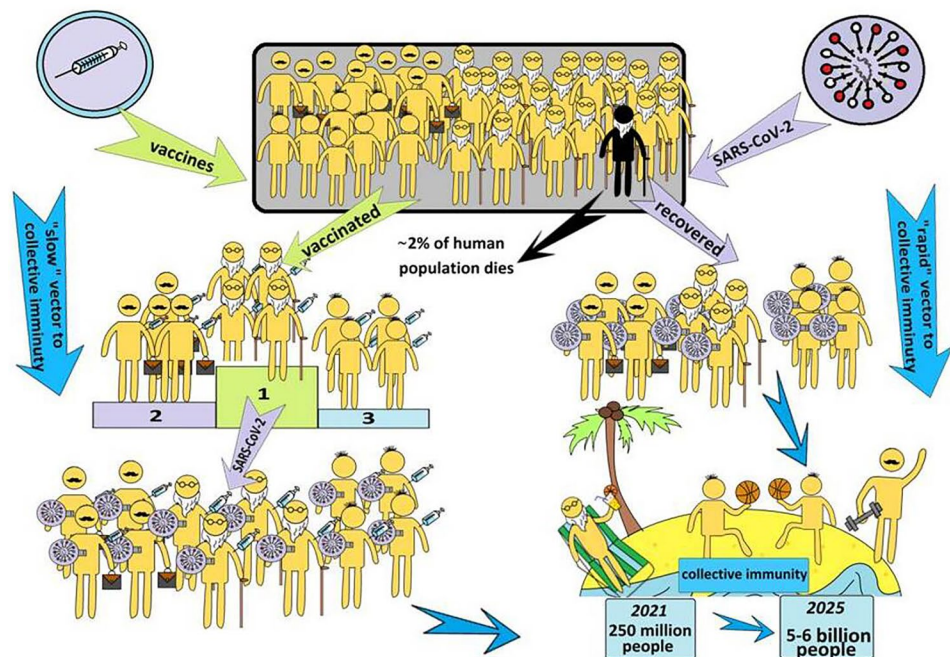
the coronavirus. Until all 8 billion people on the planet become infected, at least 160 million people may die. The use of vaccines should significantly reduce this threat. Obviously, while vaccines cannot speed up this transition to a pandemic-free period, they can certainly reduce the number of people who fall victim to the coronavirus.

Conclusion

Based on the current situation, there are only two possible outcomes during a pandemic: get sick or get vaccinated. It is absolutely necessary that the elderly, those 65 years of age and older, receive vaccinations, since worldwide this segment of the population has suffered the highest mortality. Vaccinated people will still get sick with the new subtypes of coronavirus that emerge over time, but they will not become as ill as unvaccinated, and they will survive.

In our opinion, only the immunity engendered by infection with a real viral particle can provide the powerful long-term immunological memory to the coronavirus that will protect against SARS-CoV-2 for at least the next 5–6 years. This is true because changes to the genome of the coronavirus are not so radical that the immune response formed is completely powerless against new subtypes. In contrast to naturally developed immunity, most vaccines present the body with only certain coronavirus antigens, increasing the microorganism's chances of evading the defenses formed in response to vaccination. However, the obvious benefit of vaccines is the ability to get better in the short term, due in part to a less severe infection and shorter disease course,

Fig. 2 Predictive scheme for the outcome of the SARS-CoV-2 coronavirus pandemic



which reduces mortality and the likelihood of long-term side effects associated with the disease. Over time, both vaccinated and unvaccinated people will contract the coronavirus, which will lead to the formation of herd immunity. Perhaps the main conclusion that can be drawn from today's pandemic is that if pandemic has already begun, safe and effective vaccines must be made that will prevent a large number of victims. Stay strong.

Funding The research results are obtained within the framework of as state assignment V.I. Vernadsky Crimean Federal University for 2021 and the planning period of 2022–2023 No. FZEG-2021-0009 (“Development of oligonucleotide constructs for making selective and highly effective preparations for medicine and agriculture”, registration number 121102900145-0).

Declarations

Conflict of interest The authors declare no conflict of interest.

References

- Tan W, Zhao X, Ma X, et al. A novel coronavirus genome identified in a cluster of pneumonia cases—Wuhan, China 2019–2020.
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565–74.
- Rambaut A, Holmes EC, O’Toole Á, Hill V, McCrone JT, Ruis C, du Plessis L, Pybus OG. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nat Microbiol*. 2020;5:1403–7.
- Zhu X, Mannar D, Srivastava SS, Berezuk AM, Demers JP, Saville JW, Leopold K, Li W, Dimitrov DS, Tuttle KS, et al. Cryo-electron microscopy structures of the N501Y SARS-CoV-2 spike protein in complex with ACE2 and 2 potent neutralizing antibodies. *PLoS Biol*. 2021;19:e3001237.
- Deng S, Xing K, He X. Mutation signatures inform the natural host of SARS-CoV-2. *bioRxiv*. 2021. <https://doi.org/10.1101/2021.07.05.451089>.
- Dobson AP, Carper ER. Infectious diseases and human population history. *Bioscience*. 1996;46:115–26.
- Zhao J, Zhao S, Ou J, et al. COVID-19: coronavirus vaccine development updates. *Front Immunol*. 2020;11: 602256. <https://doi.org/10.3389/fimmu.2020.602256>.
- Klein S, Cortese M, Winter SL, et al. SARS-CoV-2 structure and replication characterized by in situ cryo-electron tomography. *Nat Commun*. 2020;11:5885.
- Liu K, Tan S, Niu S, et al. Cross-species recognition of SARS-CoV-2 to bat ACE2. *Proc Natl Acad Sci USA*. 2021;118(1):9–9. <https://doi.org/10.1073/PNAS.2020216118>.
- Moeller NH, Shia K, Demir O, et al. Structure and dynamics of SARS-CoV-2 proofreading exoribonuclease ExoN. Version 1. *bioRxiv*. Preprint. 2021. <https://doi.org/10.1101/2021.04.02.438274>.
- Worobey M, et al. The emergence of SARS-CoV-2 in Europe and North America. *Science*. 2020;370:564–70.
- Telwate S, Martin HA, Marczak R, Fozouni P, Vallejo-Gracia A, Kumar GR, Murray V, Lee S, Ott M, Wong JK, Yukl SA. Novel RT-ddPCR assays for measuring the levels of subgenomic and genomic SARS-CoV-2 transcripts. *Methods*. 2021. <https://doi.org/10.1016/j.ymeth.2021.04.011> (Epub ahead of print).
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- <https://coronavirus.jhu.edu/map.html>.
- Oberemok VV, Laikova KV, Yurchenko KA, et al. SARS-CoV-2 will constantly sweep its tracks: a vaccine containing CpG motifs in ‘lasso’ for the multi-faced virus. *Inflamm Res*. 2020;69:801–12.
- Song Y, Zhang M, Yin L, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). *Int J Antimicrob Agents*. 2020;56(2): 106080. <https://doi.org/10.1016/j.ijantimicag.2020.106080>.
- Stöhr K. Vaccinate before the next pandemic? *Nature*. 2010;465:161.
- McCracken MK, Kuklis CH, Kannadka CB, et al. Enhanced dengue vaccine virus replication and neutralizing antibody responses in immune primed rhesus macaques. *NPJ Vaccines*. 2021;6:77. <https://doi.org/10.1038/s41541-021-00339-y>.
- Ponnuraj EM, Springer J, Hayward AR, Wilson H, Simoes EAF. Antibody-dependent enhancement, a possible mechanism in augmented pulmonary disease of respiratory syncytial virus in the Bonnet Monkey model. *J Infect Dis*. 2003;187(8):1257–63. <https://doi.org/10.1086/374604>.
- Lee WS, Wheatley AK, Kent SJ, et al. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol*. 2020;5:1185–91.
- Ricke DO. Two different antibody-dependent enhancement (ADE) risks for SARS-CoV-2 antibodies. *Front Immunol*. 2021. <https://doi.org/10.3389/fimmu.2021.640093>.
- Pan H, Wu Q, Zeng G, et al. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18–59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial. *MedRxiv preprint*. 2021. <https://doi.org/10.1101/2021.07.23.21261026>.
- Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines—a new era in vaccinology. *Nat Rev Drug Discov*. 2018;17:261–79.
- Ivins BE, Welkos SL. Recent advances in the development of an improved, human anthrax vaccine. *Eur J Epidemiol*. 1988;4(1):12–9.
- Mallapaty S. Kids and COVID: why young immune systems are still on top. *Nature*. 2021;597:166–8. <https://doi.org/10.1038/d41586-021-02423-8>.
- Wiktor TJ, Plotkin SA, Grella DW. Human cell culture rabies vaccine: antibody response in man. *JAMA*. 1973;224(8):1170–1.
- Izda V, Jeffries MA, Sawalha AH. COVID-19: a review of therapeutic strategies and vaccine candidates. *Clin Immunol*. 2021;222:108634.
- Tseng C-T, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS ONE*. 2012;7(4): e35421. <https://doi.org/10.1371/journal.pone.0035421>.
- Corbett KS, Edwards D, Leist SR, et al. SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. 2020. <https://doi.org/10.1101/2020.06.11.145920>.
- Agrawal AS, Tao X, Algaissi A, Garron T, Narayanan K, Peng B-H, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. *Hum Vaccines Immunother*. 2016;12(9):2351–6. <https://doi.org/10.1080/21645515.2016.1177688>.
- <https://www.who.int/news/item/01-06-2021-who-validates-sinov-ac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations>.

32. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21:181–92.
33. Kremsner P, Mann P, Bosch J, et al. Phase 1 assessment of the safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2 in human volunteers. medRxiv. 2020:2020.11.09.20228551.
34. Mallapaty S. China COVID vaccine reports mixed results—what does that mean for the pandemic? *Nature*. 2021.
35. Riad A, Sağıröglü D, Üstün B, et al. Prevalence and risk factors of coronavac side effects: an independent cross-sectional study among healthcare workers in Turkey. *J Clin Med*. 2021;10:2629. <https://doi.org/10.3390/jcm10122629>.
36. Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 Vaccine in Chile. *New Engl J Med*. 2021;385:875–84.
37. Quast I, Tarlinton D. B cell memory: understanding COVID-19. *Immunity*. 2021;54:205–10.
38. Pan H, Wu Q, Zeng G, Yang J. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18–59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial. 2021. <https://doi.org/10.1101/2021.07.23.21261026>.
39. Kremer EJ. Pros and cons of adenovirus-based SARS-CoV-2 vaccines. *Mol Therapy*. 2020. <https://doi.org/10.1016/j.ymthe.2020.10.002>.
40. Schlimgen R, et al. Risks associated with lentiviral vector exposures and prevention strategies. *J Occup Environ Med*. 2016;58:1159–66.
41. Scheiermann J, Klinman DM. Clinical evaluation of CpG oligonucleotides as adjuvants for vaccines targeting infectious diseases and cancer. *Vaccine*. 2014;32:6377–89.
42. Food and Health Bureau (FHB). Report on evaluation of safety, efficacy and quality of CoronaVac COVID-19 vaccine (Vero Cell) inactivated. 2021. Available online: https://www.fhb.gov.hk/download/our_work/health/201200/e_evaluation_report_CoronaVac.pdf. Accessed on 1 Apr 2021.
43. Voysey M, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99–111. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32661-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext).
44. Jones I, Roy P. Sputnik V COVID-19 vaccine candidate appears safe and effective. *Lancet*. 2021. [https://doi.org/10.1016/S0140-6736\(21\)00191-4](https://doi.org/10.1016/S0140-6736(21)00191-4).
45. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 spike immunogen induces potent humoral and cellular immune responses. *NPJ Vaccines*. 2020;5:91–91.
46. WHO. Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19: background document to the WHO interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing, 14 January 2021. Geneva: World Health Organization; 2021. [https://www.who.int/publications/i/item/background-document-on-mrna-vaccin-bnt162b2-\(pfizer-biontech\)-against-covid-19](https://www.who.int/publications/i/item/background-document-on-mrna-vaccin-bnt162b2-(pfizer-biontech)-against-covid-19).
47. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMoa2034577>.
48. Hillus D, Schwarz T, Tober-Lau P, Hastor H, Thibeault C, Kasper S, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv. 2021. <https://doi.org/10.1101/2021.05.19.21257334>.
49. Lindsey R, Baden MD, Hana M, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403–16. <https://doi.org/10.1056/NEJMoa2035389>.
50. Mendonça SA, Lorincz R, Boucher P, et al. Adenoviral vector vaccine platforms in the SARS-CoV-2 pandemic. *NPJ Vaccines*. 2021;6:97.
51. Chang J. Adenovirus vectors: excellent tools for vaccine development. *Immune Netw*. 2021;21(1): e6. <https://doi.org/10.4110/in.2021.21.e6>.
52. Tatsis N, Ert HCJ. Adenoviruses as vaccine vectors. Philadelphia: The Wistar Institute, University of Pennsylvania; 2004. <https://doi.org/10.1016/j.ymthe.2004.07>.
53. Tamanini A, Nicolis E, Bonizzato A, Bezzerri V, Melotti P, Assael BM, Cabrini G. Interaction of adenovirus type 5 fiber with the coxsackievirus and adenovirus receptor activates inflammatory response in human respiratory cells. *J Virol*. 2006;80:11241–54.
54. Medzhitov R, Janeway C Jr. Innate immune recognition: mechanism and pathways. *Immunol Rev*. 2000;173:89–97.
55. Afkhami S, Yao Y, Xing Z, et al. Methods and clinical development of adenovirus-vectored vaccines against mucosal pathogens. *Mol Therapy Methods Clin Dev*. 2016. <https://doi.org/10.1038/mtm.2016.30>.
56. Hoelscher MA, Garg S, Bangari DS, Belser JA, Lu X, Stephenson I, et al. Development of adenoviral-vector-based pandemic influenza vaccine against antigenically distinct human H5N1 strains in mice. *Lancet*. 2006;367:475–81.
57. Lemiale F, et al. Enhanced mucosal immunoglobulin A response of intranasal adenoviral vector human immunodeficiency virus vaccine and localization in the central nervous system. *J Virol*. 2003;77:10078–87.
58. Vogels R, et al. Replication-deficient human adenovirus type 35 vectors for gene transfer and vaccination: efficient human cell infection and bypass of preexisting adenovirus immunity. *J Virol*. 2003;77:8263–71.
59. Saito I, Oya Y, Yamamoto K, Yuasa T, Shimojo H. Construction of nondefective adenovirus type 5 bearing a 2.8-kilobase hepatitis B virus DNA near the right end of its genome. *J Virol*. 1985;54:711–9.
60. Xiang ZQ, Yang Y, Wilson JM, Ertl HC. A replication-defective human adenovirus recombinant serves as a highly efficacious vaccine carrier. *Virology*. 1996;219:220–7.
61. Zhang Y, et al. Acute cytokine response to systemic adenoviral vectors in mice is mediated by dendritic cells and macrophages. *Mol Ther*. 2001;3:697–707.
62. Xiang ZQ, Yang Y, Wilson JM, Ertl HC. A replication-defective human adenovirus recombinant serves as a highly efficacious vaccine carrier. *Virology*. 1996;219:220–7.
63. Gras-Champel V, Liabeuf S, Baud M, et al. Atypical thrombosis associated with Vaxzevria® (AstraZeneca) vaccine: data from the French Network of Regional Pharmacovigilance Centres. *Therapies*. 2021. <https://doi.org/10.1016/j.therap.2021.05.007>.
64. EMA, European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Assessment Report—COVID-19 Vaccine AstraZeneca. 29 January 2021 EMA/94907/2021, 2021. https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf.
65. Hernándezab AF, Calinac D, Poulas K, et al. Safety of COVID-19 vaccines administered in the EU: Should we be concerned? *Toxicol Rep*. 2021;8:871–9. <https://doi.org/10.1016/j.toxrep.2021.04.003>.

66. Blattman JN, et al. Impact of epitope escape on PD-1 expression and CD8 T-cell exhaustion during chronic infection. *J Virol*. 2009;83:4386–94. <https://doi.org/10.1128/JVI.02524-08>.
67. EMA, European Medicines Agency. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets statement issued on April 4th, 2021, 2021. <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>.
68. Johnson PLF, Kochin BF, McAfee MS, et al. Vaccination alters the balance between protective immunity, exhaustion, escape, and death in chronic infections. *J Virol*. 2011;85(11):5565–70. <https://doi.org/10.1128/JVI.00166-11>.
69. EMA, European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Assessment Report—Comirnaty (Pfizer/BioNTech). 19 February 2021 EMA/707383/2020, 2021. https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf.
70. Dolgin E. The tangled history of mRNA vaccines. News feature 14 September 2021. *Nature*. 2021;597:318–24. <https://doi.org/10.1038/d41586-021-02483-w>.
71. Wolff JA, et al. Direct gene transfer into mouse muscle in vivo. *Science*. 1990;247:1465–8 (**This study demonstrates protein production from RNA administered in vivo**).
72. Suschak JJ, Williams JA, Schmaljohn CS. Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Hum Vaccin Immunother*. 2017;13:2837–48.
73. Kariko K, Muramatsu H, Ludwig J, Weissman D. Generating the optimal mRNA for therapy: HPLC purification eliminates immune activation and improves translation of nucleoside-modified, protein-encoding mRNA. *Nucleic Acids Res*. 2011;39:e142.
74. Lim HX, Lim J, Zajayeri SD, Poppema S, Poh CL. Development of multiepitope peptide-based vaccines against SARS-CoV-2. *Biomed J*. 2020. <https://doi.org/10.1016/j.bj.2020.09.005>.
75. Brito LA, et al. A cationic nanoemulsion for the delivery of next-generation RNA vaccines. *Mol Ther*. 2014;22:2118–29.
76. Graham BS. Rapid COVID-19 vaccine development. *Science*. 2020;368:945–6. <https://doi.org/10.1126/science.abb8923> *Medline*.
77. Sekar A, Campbell R, Tabbara J, et al. ANCA glomerulonephritis after the Moderna COVID-19 vaccination. *Kidney Int*. 2021;100:473–4.
78. Lee LA, Franzel L, Atwell J, Datta SD, Friberg IK, Goldie SJ, Reef SE, Schwalbe N, Simons E, Strelbel PM, Sweet S, Suraratdech C, Tam Y, Vynnycky E, Walker N, Walker DG, Hansen PM. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. *Vaccine*. 2013;31(Suppl 2):B61–72. <https://doi.org/10.1016/j.vaccine.2012.11.035> *Medline*.
79. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384:1412–23.
80. Chen X, Chen Z, Azman AS, et al. Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination. medRxiv: the preprint server for health sciences. 2021.
81. Tregoning JS, Flight KE, Higham SL, et al. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol*. 2021;21:626–36.
82. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. *Pediatrics*. 2001;107(5):1147–54. <https://doi.org/10.1542/peds.107.5.1147>.
83. Liang Z, Zhu H, Wang X, et al. Adjuvants for coronavirus vaccines. *Front Immunol*. 2020. <https://doi.org/10.3389/fimmu.2020.589833>.
84. Zhao K, Wang H, Wu C. The immune responses of HLA-A*0201 restricted SARS-CoV S peptide-specific CD8+ T cells are augmented in varying degrees by CpG ODN, PolyI: C and R848. *Vaccine*. 2011;29:6670–8. <https://doi.org/10.1016/j.vaccine.2011.06.100>.
85. Alhinaio ZA, Elsidig N. Countries with similar COVID-19 vaccination rates yet divergent outcomes: are all vaccines created equal? *Int J Infect Dis*. 2021;110:258–60. <https://doi.org/10.1016/j.ijid.2021.06.040>.
86. Wang Q, Yang L, Jin H, et al. Vaccination against COVID-19: a systematic review and meta-analysis of acceptability and its predictors. *Prev Med*. 2021;150: 106694. <https://doi.org/10.1016/j.ypmed.2021.106694>.
87. Anderson EJ, Roupheal NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383:2427–38. <https://doi.org/10.1056/nejmoa2028436>.
88. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;80:371. <https://doi.org/10.1126/science.abf4063>.
89. Sauré D, O’Ryan M, Torres JP, et al. Dynamic IgG seropositivity after rollout of CoronaVac and BNT162b2 COVID-19 vaccines in Chile: a sentinel surveillance study. *Lancet Infect Dis*. 2021. [https://doi.org/10.1016/S1473-3099\(21\)00479-5](https://doi.org/10.1016/S1473-3099(21)00479-5).
90. Hannah R, Ortiz-Ospina E, Beltekian D, Mathieu E, Hasell J, Macdonald B, et al. Coronavirus (COVID-19) vaccinations—statistics and research—our world in data. *Ourworldindata* 2021 <https://ourworldindata.org/covid-vaccinations>. Accessed 7 June 2021.
91. Andrews N, Tessier E, Stowe J, et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. *MedRxiv Preprint Server Health Scis*. 2021. <https://doi.org/10.1101/2021.09.15.21263583>.
92. Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. *MedRxiv Preprint Server for Health Sci*. 2021. <https://doi.org/10.1101/2021.08.06.21261707>.
93. Pagliusi S, Jarrett S, Hayman B, et al. Emerging manufacturers engagements in the COVID-19 vaccine research, development and supply. *Vaccine*. 2020;38:5418–23. <https://doi.org/10.1016/j.vaccine.2020.06.022>.
94. Emanuel EJ, Persad G, Kern A, et al. An ethical framework for global vaccine allocation. *Science*. 2020;369:1309–12. <https://doi.org/10.1126/science.abe2803>.
95. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. *Age Ageing*. 2021;50(2):279–83. <https://doi.org/10.1093/ageing/afaa274>.
96. Amore S, Puppo E, Melara J, et al. Impact of COVID-19 on older adults and role of long-term care facilities during early stages of epidemic in Italy. *Sci Rep*. 2021;11:12530.
97. Onder G, Rezza G, Brusaferro S. Case-Fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA J Am Med Assoc*. 2019;2019–2020:2020. <https://doi.org/10.1001/jama.2020.4683>.
98. D’Adamo H, Yoshikawa T, Ouslander JG. Coronavirus disease 2019 in geriatrics and long-term care: the ABCDs of COVID-19. *J Am Geriatr Soc*. 2020;68:912–7. <https://doi.org/10.1111/jgs.16445>.
99. Omori R, Matsuyama R, Nakata Y. The age distribution of mortality from novel coronavirus disease (COVID-19) suggests no

- large difference of susceptibility by age. *Sci Rep.* 2020;10:1–9. <https://doi.org/10.1038/s41598-020-73777-8>.
100. Istituto superiore di sanità. Epidemia COVID-19 aggiornamento nazioanle 28 aprile 2020. Available Online: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integ-ata-COVID-19_28-aprile-2020.pdf/.
 101. Brenner H. Focusing COVID-19 vaccinations on elderly and high-risk people. *Lancet Region Health Europe.* 2021. <https://doi.org/10.1016/j.lanepe.2021.100044>.
 102. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, Fuller C, Irwin-Singer A, Davies D, Tut G, Lopez BJ, Moss P, Hayward A, Copas A, Shallercross L. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. *Lancet Infect Dis.* 2021. [https://doi.org/10.1016/S1473-3099\(21\)00289-9](https://doi.org/10.1016/S1473-3099(21)00289-9).
 103. Pizano-Escalante MG, Anaya-Esparza LM, Nuño K, et al. Direct and indirect effects of COVID-19 in frail elderly: interventions and recommendations. *J Pers Med.* 2021;11(10):999. <https://doi.org/10.3390/jpm11100999>.
 104. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis.* 2021. [https://doi.org/10.1016/S1473-3099\(21\)00460-6](https://doi.org/10.1016/S1473-3099(21)00460-6).
 105. Egan C, Knight S, Baillie K, Harrison E, et al. Hospitalised vaccinated patients during the second wave, update April '21. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/982499/S1208_CO-CIN_report_on_impact_of_vaccination_Apr_21.pdf.
 106. Chen L-K. COVID-19 vaccination and frailty in older adults. *Arch Gerontol Geriatr.* 2021;96: 104487. <https://doi.org/10.1016/j.archger.2021.104487>.
 107. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* 2020;20:533–4. [https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1) PMID:32087114.
 108. Galanti M, Shaman J. Direct observation of repeated infections with endemic coronaviruses. *J Infect Dis.* 2021;223:409–15. <https://doi.org/10.1093/infdis/jiaa392>.
 109. Wang J, Kaperak C, Sato T, et al. COVID-19 reinfection: a rapid systematic review of case reports and case series. *J Investig Med.* 2021;69:1253–5.
 110. Block J. Vaccinating people who have had covid-19: why doesn't natural immunity count in the US? *BMJ.* 2021;374: n2101. <https://doi.org/10.1136/bmj.n2101>.
 111. Murchu EO, Byrne P, Carty PG, et al. Quantifying the risk of SARS-CoV-2 reinfection over time. *Rev Med Virol.* 2021:e2260.
 112. Bertollini R, Chemaitelly H, Yassine HM, Al-Thani MH, Al-Khal A, Abu-Raddad LJ. Associations of vaccination and of prior infection with positive PCR test results for SARS-CoV-2 in airline passengers arriving in Qatar. *JAMA.* 2021;326:185–8. <https://doi.org/10.1001/jama.2021.9970>.
 113. Hall VJ, Foulkes S, Charlett A, SIREN Study Group, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet.* 2021;397:1459–69. [https://doi.org/10.1016/S0140-6736\(21\)00675-9](https://doi.org/10.1016/S0140-6736(21)00675-9).
 114. Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: a three-month nationwide experience from Israel. [Preprint.] *medRxiv.* 2021. <https://doi.org/10.1101/2021.04.20.21255670>.
 115. Mathioudakis AG, Ghrew M, Ustianowski A, et al. Self-reported real-world safety and reactogenicity of covid-19 vaccines: a vaccine recipient survey. *Life (Basel).* 2021;11:249. <https://doi.org/10.3390/life11030249> PMID:33803014.
 116. Jung JH, Rha M-S, Sa M, et al. SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells. *Nat Commun.* 2021;2:4043.
 117. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell.* 2020;181(7):1489–1501.e15. <https://doi.org/10.1016/j.cell.2020.05.015>.
 118. Turner JS, et al. *Nature.* 2021;596:109–13.
 119. Callaway E. COVID super-immunity: one of the pandemic's great puzzles. *Nature.* 2021;598:393–4.
 120. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, Li M, Jin H, Cui G, Chen P, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis.* 2021. Available online: <http://www.thelancet.com/infection> PubMed online. Accessed on 27 Mar 2021.
 121. Li M, Yang J, Wang L, et al. A booster dose is immunogenic and will be needed for older adults who have completed two doses vaccination with CoronaVac: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. <https://doi.org/10.1101/2021.08.03.21261544>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.