

REVIEW ARTICLE

Overview of approved and upcoming vaccines for SARS-CoV-2: a living review

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ABSTRACT

The rapid design and implementation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is testament to a successfully coordinated global research effort. While employing a variety of different technologies, some of which have been used for the first time, all approved vaccines demonstrate high levels of efficacy with excellent safety profiles. Despite this, there remains an urgent global demand for coronavirus disease 2019 vaccines that require further candidates to pass phase 3 clinical trials. In the expectation of SARS-CoV-2 becoming endemic, researchers are looking to adjust the vaccine constructs to tackle emerging variants. In this review, we outline different platforms used for approved vaccines and summarize latest research data with regards to immunogenicity, dosing regimens and efficiency against emerging variants.

Key words: SARS-CoV-2; vaccine; variant; efficacy; effectiveness.

INTRODUCTION

The betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to the most challenging global health crisis in the last hundred years. Infection can manifest itself in a range of clinical symptoms, which together are defined as coronavirus disease 2019 (COVID-19). COVID-19 has so far claimed over 2.6 million lives worldwide (17 March 2021) and led to long-term health impacts in many more. Compounding the medical implications of the pandemic, the associated

economic, social and mental health burden will likely take years to resolve. As a member of the Coronaviridae family, SARS-CoV-2 contains a positive-sense, single-stranded RNA genome which, along with other structural and non-structural proteins (extensively reviewed elsewhere [1]), encodes a spike glycoprotein composed of a trimer of S1 and S2 heterodimers. The S1 component contains a receptor binding domain (RBD) that allows infection of mammalian cells via the angiotensin-converting enzyme 2 receptor [2]. Binding to angiotensin-converting enzyme 2 induces a conformational change in the S

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Box 1: What is the consensus on COVID-19 vaccine development?

Despite significant advances in SARS-CoV-2 treatments, mass vaccination remains the most critical tool in countering the COVID-19 pandemic. There are 12 vaccine candidates approved for full or limited use worldwide, with many more currently being assessed in clinical and pre-clinical trials. These candidates are based on a variety of vaccine platforms including RNA, protein subunit, inactivated virus and viral vectors. All these platforms are based on a strong foundation of years of research efforts in these technologies.

In April 2020, the World Health Organization set out criteria for a viable vaccine candidate which included a minimum 50% efficacy against severe disease and a favourable safety profile. Candidates across a variety of platforms have met these criteria, including several vaccines which are estimated to have over 90% efficacy against severe disease, comparable to the most effective licenced vaccines to date. Candidates have proved to be safe, with mostly mild, time-limited side effects.

Box 2: Remaining unknowns in COVID-19 vaccine development

While all vaccines have been shown to be safe and effective, there are variations in reported efficacies due to the lack of standardization of the trial protocols and defined end-points. A critical research question to be answered centres around the longevity of vaccine-induced protection. Waning immune response following vaccination may necessitate regular booster shots. It is currently proposed that booster shots may be required on a biennial basis, as seen for patients previously infected with SARS-CoV-1 and MERS, where immunity lasted 2–3 years [3].

In addition, clinical trials thus far have only assessed protection against symptomatic disease and more information on prevention of asymptomatic transmission will be required.

As SARS-CoV-2 remains in circulation, mutations leading to increased transmissibility or virulence represent a growing challenge. Therefore, current research efforts focus on the efficacy against these emerging variants and modification of existing vaccine platforms to ensure appropriate protection.

glycoprotein, allowing the S2 component to mediate fusion with the host cell membrane [2,4]. Upon entry into the cell proteins encoded by virus are directly translated using host ribosomes while the viral genome is replicated by the viral replicase. Viral progeny exits the host cell on assembly, with nascent virus particles expelled from the respiratory tract by coughing or breathing, within droplets or as aerosols.

Because of its immunodominance and critical role in cell entry, the spike protein encoded either by DNA within a viral vector or mRNA, or produced as a recombinant adjuvanted protein, has been the focus for most vaccine efforts. In the majority of vaccine candidates, the spike protein sequence has been modified through the incorporation of paired proline residues. This modification has been found to stabilize the S protein in its prefusion conformation, which simultaneously increases its levels of expression and antigenicity [5].

In this living review, we describe different strategies employed in SARS-CoV-2 vaccine development, ranging from the use of established technologies, such as inactivated or subunit vaccines, to novel platforms, such as lipid-encapsulated mRNA. Taking together all approved vaccines and current phase 3 clinical trial vaccine candidates, we will summarize the most recent published data on their efficacy and immunogenicity and discuss future research directions.

INACTIVATED VACCINES

This technology, previously used in the Salk Polio and rabies vaccines (HDBc and CCEEV), uses susceptible cell lines to propagate live virus, which can subsequently be harvested, purified and finally inactivated. Inactivated vaccines differ from attenuated virus vaccines as, despite retaining all viral structural antigens, the virus itself is unable to replicate. As such, inactivated

vaccines have improved safety profiles and demonstrate excellent stability without the requirement for -80°C storage, thus facilitating vaccine distribution. However, they are often weakly immunogenic and require adjuvants and boosting. While historically formalin was used to inactivate pathogens, it has been known to damage or alter the antigenic properties of proteins potentially leading to aberrant immune responses [6]. This risk has been mitigated by the introduction of β -propiolactone as an inactivating agent.

At present, two inactivated vaccine candidates for SARS-CoV-2 are in development (Table 1): CoronaVac (Sinovac, ClinicalTrials.gov NCT04352608) and BBIB-CorV (Sinopharm, ClinicalTrials.gov NCT04352608). Both use plaque-purified isolates propagated in Vero cells [7,8], BBIB-CorV is subsequently inactivated by β -propiolactone, while CoronaVac is inactivated using a combination of β -propiolactone and formaldehyde. Both vaccines are administered intramuscularly (IM) with an aluminium hydroxide adjuvant [9].

Table 1: inactivated vaccines

Name	Manufacturer	Booster	Efficacy ^a (%)
BBIBP-CorV	Sinopharm and the Wuhan Institute of Biological Products	Day 21	79.34
CoronaVac	Sinovac Biotech	Day 28	50.4 ^b

^aBMJ 2021; 372: n597, <http://dx.doi.org/10.1136/bmj.n597>

^bVarying efficacy data have been provided by trials in Turkey, Indonesia, Brazil [10]. (Trial numbers: BBIBP-CorV NCT04352608 phase 1/2, NCT04560881 phase 3. CoronaVac NCT04383574 phase 1/2, NCT04582344 phase 3 Turkey, NCT04508075 PHASE 3 Indonesia.)

So far, Sinopharm's BBIB-CorV, derived from the HB02 strain, is the only inactivated vaccine in human clinical trials that has been tested on participants above 60 years of age. Phase 1 dose-escalation studies assessing prime and boosting at 28 days with 2, 4 and 8 µg doses, showed all doses to be well-tolerated, with fever, pain at the vaccination site and fatigue being the most common side-effects. While inducing seroconversion in 100% of individuals at lowest dose (2 µg), seroconversion was delayed until Day 42 in the >60 age group, compared with Day 28 in the younger 18–59 group. Although neutralizing antibodies (nAbs) were detected in all vaccines across dose groups by Day 42 post-boost, titres were also found to be lower in the >60 group. In the follow-up phase 2 study, while inducing lower antibody titres than two dose 2 and 4 µg regimens, a single 8-µg dose was found to induce seroconversion in 75% of individuals in the 18–59 age group [7]. This vaccine, described as having 79% efficacy by Sinopharm, without publication of phase 3 trial data, was initially approved in China, UAE, Bahrain prior to more recent approval in other countries. Phase 3 data are likely to include more detailed information on immunogenicity, which had not previously been reported in phases 1 and 2. The CoronaVac vaccine, derived from the CN02 isolate, has already been licenced for use in China. Phase 1 and 2 trials assessed the vaccine in 144 and 600 individuals, respectively (aged 18–59 years). The vaccine was well-tolerated, with common side effects including pain at the injection site and fatigue. T cells measured by ELISpot reported in phase 1 had a maximum high average of 7.4 SFC/100 000 cells, 14 days post boost, across all groups ([https://doi.org/10.1016/S1473-3099\(20\)30831-8](https://doi.org/10.1016/S1473-3099(20)30831-8)).

Phase 2 studies measured responses to two doses, with boosting at either Day 14 or 28. The highest rates of seroconversion were found at 28 days post-boost. Although noting that titres of nAbs were lower than those found in convalescent patients, the authors suggest that memory B-cells may play a more important role in preventing infection than nAb titres, citing SARS and Middle East Respiratory Syndrome coronavirus (MERS) as examples of viruses where reinfections are rare despite waning nAb titres [8]. Estimates of efficacy in phase 3 clinical trials in Brazil, Indonesia and Turkey were 50.4%, 65.3% and 91.25%, respectively. This wide range is likely due to both the differences in trial methodology and the number of participants included in efficacy analysis.

Phase 3 trial of CoronaVac (NCT04651790) which should have efficacy data for people above 60s expected to be completed by January 2022.

RNA VACCINES

To date, two mRNA vaccines have been approved for use following the successful completion of phase 3 efficacy trials (Table 2). Both vaccines encode the stabilized prefusion form of the SARS-

Table 2: RNA vaccines

Name	Manufacturer	Booster	Efficacy ^a (%)
mRNA-1273	Moderna in partnership with the National Institute of Allergies and Infectious Diseases (NIAID)	Day 28	94.5
BNT162b2	BioNTech and Pfizer	Day 21	95

^aBMJ 2021; 372: n597, <http://dx.doi.org/10.1136/bmj.n597>. Trial numbers: mRNA-1273 NCT04470427, BNT162b2 NCT04368728.

CoV-2 spike glycoprotein trimer derived from the MN908947.3 sequence. This sequence is flanked by a 5'-CAP and an untranslated region, with a further untranslated region and poly-A-tail at the 3'-end. In both, the RNA has been modified to contain pseudouridine in place of uracil; this allows the evasion of host innate immune responses, which increases the efficiency of translation of the vaccine transgene [11, 12]. The mRNA is subsequently encapsulated in a PEGylated lipid nanoparticle, which facilitates cell entry of the administered vaccine.

RNA vaccines have several advantages over other vaccine strategies: they are non-infectious, cannot integrate into the host genome and do not induce vector-specific responses [12]. Also, as synthetic molecules, they can be quickly adapted to new emerging variants which are of particular interest with SARS-CoV-2. Furthermore, single- and double-stranded RNA moieties can prime various facets of innate immune responses through recognition by endosomal proteins, such as Toll-like receptors (TLR3 and TLR7), and components of the inflammasome in the cytosol [13].

The Pfizer/BioNTech vaccine was the first SARS-CoV-2 vaccine to be approved by the UK's Medicines and Healthcare Products Agency (MHRA) in December 2020. Initial phase 1 dose-escalation studies [14] were performed to compare the safety and immunogenicity of secreted (BNT162b1) and membrane-bound (BNT162b2) forms of the glycoprotein. A two-dose regimen assessing 10, 20 and 30 µg doses was performed in parallel with a single dose regimen of 100 µg. Although both vaccine candidates induced similar dose-dependent immunogenicity profiles, boosting significantly improved immunogenicity, while BNT162b2 was found to be associated with lower incidence and severity of systemic reactions.

In a randomized, placebo-controlled phase 3 trial (NCT04368728) [15], two 30 µg doses were given IM to 21 720 individuals 21 days apart, with a matched saline control given to the 21 728 volunteers in the placebo group. The primary outcome was COVID-19 disease measured 7 days following the second dose. Data showed disease in 8 of 18 198 vaccinated individuals with no prior evidence of infection, compared with 162 of 18 325 in the placebo group. Geometric mean titres (GMT) of vaccine-induced nAbs were compared with sera isolated from convalescent donors. At 7–14 days post-boost, GMTs were between 1.7 and 4.6× greater than the GMT of convalescent sera in young adults (aged 18–55), and 1.6× greater in older adults (aged 65–85 years) [16] assessed levels of nAbs induced in a cohort of individuals aged <60 and >80 that had received two doses of BNT162b2 and found a reduction in nAb levels in the older cohort. Furthermore, 31.3% of the >80-year-olds had no detectable antibodies compared with only 2.2% in the <60-year-olds group, a possible consequence of age-related immune senescence. This may be related to the decreased potential of older individuals to mount an effective immune memory response to vaccines. While T-cell responses were not directly measured to BNT162b2, the BNT162b1 candidate was shown capable of inducing both Th1-polarized CD4 and cytotoxic CD8 responses [17].

The mRNA-1273 vaccine, co-developed by Moderna Inc. and the NIAID, was first given emergency use authorization by the FDA on 18 December 2020. Phase I dose-escalation and safety studies showed the vaccine to be well-tolerated with GMT of nAbs in volunteers receiving 100 or 200 µg dose having a similar distribution to those from convalescent patients. Th1-polarized T-cell responses, which are important for the control of intracellular pathogens, such as viruses, were also induced with some low frequency CD8 responses. However, increases in the

frequency of adverse events were seen at the highest dose, particularly following boost [18].

In a double-blinded, placebo-controlled efficacy phase 3 COVE trial (NCT04470427), 14 134 individuals were given 100 µg of the mRNA-1273 vaccine as IM homologous prime boost (1-month interval), while 14 073 received a placebo [19]. The primary endpoint was the prevention of COVID-19 illness onset at least 14 days post-boost. Following unblinding, symptomatic COVID-19 illness was found in 185 and 11 participants in the placebo and vaccine arms, respectively. When stratified by age, the efficacy was 95.6% in those aged 18–65 years and 86.4% in individuals above 65 years.

A further nanoparticle-enveloped, mRNA vaccine has been developed by CureVac; initial phase 1 prime-boost, dose-escalation studies assessed the safety and immunogenicity of a 2–12 µg dose range in two age groups, 18–40 and 41–60 [20] following a 28-day interval. Results showed seroconversion in all vaccines 12 days post-boost with nAb titres comparable with those found in the serum of convalescent patients.

PROTEIN VACCINES

Subunit vaccines are produced as recombinant antigens using bacterial, yeast or insect expression systems. They can be subdivided into two groups: protein subunit and self-assembling virus-like particle vaccines; production is readily scalable, and subunit vaccines exhibit both excellent stability and safety profiles. While antigens are selected based on their capacity to elicit humoral responses, protein vaccines seldom induce strong immune responses and often require adjuvanted booster vaccinations [21]. Poor immunogenicity may result from an inability to induce an immune response through stimulation of pattern recognition receptors, the short half-life of exogenous proteins in the body and finally whether the expression system enables post-translational modification (e.g. glycosylation) of the antigen. This vaccine platform has previously been successfully employed for the hepatitis B virus surface antigen and human papillomavirus vaccines [22]. Preliminary results are only available from one protein vaccine candidate in phase 3 trials so far, this section will briefly discuss the ongoing research for promising protein subunit vaccines currently in development.

NVX-CoV2373 (Table 3) is a recombinant baculovirus-expressed nanoparticle vaccine adjuvanted with Matrix-M1-adjuvant. A randomized, placebo-controlled phase 1 and 2 clinical trials using a two-dose regimen, given IM following a 21-day interval, showed a positive correlation between nAb concentrations and anti-spike IgG [23,24]. The vaccine demonstrated a good safety profile with only mild adverse events reported and no serious adverse events. The Matrix-M1 adjuvant combined with 5 µg of nanoparticles induced anti-S IgG levels equivalent to 25 µg nanoparticles alone. Furthermore, vaccines given the

adjuvant with both 5 and 25 µg nanoparticles induced nAbs 100-fold higher than those given 25 µg nanoparticles alone. Recently, Novavax [25] announced that efficacy for the NVX-CoV2373/Matrix-M1 vaccine a phase 3 trial (NCT04611802) was 96.4% in preventing mild, moderate and severe disease in the UK, this reduced to 55.4% in South Africa, where the majority of cases were due to B.1.351 variant. Most importantly, the vaccine attained 100% efficacy against severe disease, including all hospitalization and death [26].

ZF2001 is the second recombinant protein vaccine to have started phase 3 clinical trials. This vaccine encodes the RBD antigen and is adjuvanted with aluminium hydroxide. Although there is a lack of pre-clinical data on the vaccine, the results of both phase 1 and 2 trials, consisting of 50 and 900 healthy adults respectively, are published as a preprint [26]. There were no severe adverse reactions to the vaccine, with only mild side-effects being reported, all of which resolved within 4 days of inoculation. However, in the phase 2 trial seven participants reported serious adverse events which the investigators inferred to be unrelated to the vaccine. Individuals in the phase 1 clinical trial received three IM doses of the adjuvanted RBD-dimer vaccine, 30 days apart, with the placebo group receiving adjuvant alone. The phase 2 clinical trial included groups receiving either two or three doses of 25 or 50 µg. Two weeks after the final dose, the two-dose group demonstrated seroconversion rates of 76% (at 25 µg) and 72% (at 50 µg). In comparison, groups receiving three doses showed an increase to 97% (at 25 µg) and 93% (at 50 µg) seroconversion at the same time point. As there was no evidence for a dose-dependent enhancement in immunogenicity, the phase 3 clinical trial is proceeding with three doses of 25 µg. The trial is expected to conclude by April 2022 [27].

VIRAL VECTORED VACCINES

Viral vectored vaccines employ recombinant viruses modified to encode antigens derived from the target pathogen to directly infect host cells. Upon infection, the host cell produces and displays the antigen of interest, triggering an immune response. Viral vectored platforms have previously been used against several infectious disease, the most notable being a recombinant vesicular stomatitis virus vaccine against Ebola (rVSV-ZEBOV), which was developed in response to the 2013 outbreak [28]. Prior to the COVID-19 pandemic, no adenovirus-based vaccine had been licenced for use in humans, with pre-existing immunity to circulating adenoviruses suggested as a potential barrier for their use.

Four viral-vectored SARS-CoV-2 vaccine candidates have reached phase 3 clinical trials (Table 4). All are replication-deficient adenoviruses expressing the SARS-CoV-2 spike

Table 3: protein vaccines

Name	Manufacturer	Booster	Efficacy 8 ^a
NVX-CoV2373	Novavax	Day 21	96.4% ^b
ZF2001	Anhui Zhifei Longcom in partnership with the Chinese Academy of Medical Sciences	Day 14	Not calculated

^a BMJ 2021; 372: n597 (<http://dx.doi.org/10.1136/bmj.n597>).

^b Novavax, 11 March 2021. (Trial numbers: NVX-CoV2373 NCT04368988 phase 1/2, NCT04611802 phase 3. ZF2001, NCT04646590 nphase 3.)

Table 4: viral vector vaccines

Name	Manufacturer	Booster	Efficacy ^a (%)
ChAdOx1 nCoV-19	AstraZeneca in partnership with the University of Oxford	Days 28–84 ^b	82.4 ^c
Gam-COVID-Vac (aka Sputnik V)	The Gamaleya Research Institute (Russian Ministry of Health)	Day 21	91.60
Ad26.COV2.S	Johnson & Johnson	None	72
Ad5-nCoV	CanSino Biologics in partnership with the Academy of Military Medical Sciences	None	65.7

^a BMJ 2021; 372: n597, <http://dx.doi.org/10.1136/bmj.n597>.

^b In clinical trials, booster doses were administered any time within 4–12 weeks of the initial dose. See below for further discussion of dosing intervals.

^c The average efficacy across both SD/SD and LD/SD dosing regimens was originally calculated at 70.4% [36].

On the inclusion of a further 5541 participants in the efficacy analysis, this was revised down [37]. Data using 12 weeks boost showed 82.4%. (ChAdOx1 nCoV-19 NTC04444674—South Africa, NTC04324606—UK phase 1/2, NTC04400838—UK phase 2/3, ADZ12222—Phase 3 AstraZeneca. Gam-COVID-Vac NCT04437875 phase 1/2, NCT04656613 phase 3. AD26.COV2.S NCT04436276 phase 1/2, NCT04505722 phase 3. Ad5-nCoV NCT04552366 phase 1, NTC04341389 phase 2, NCT04526990 phase 3.)

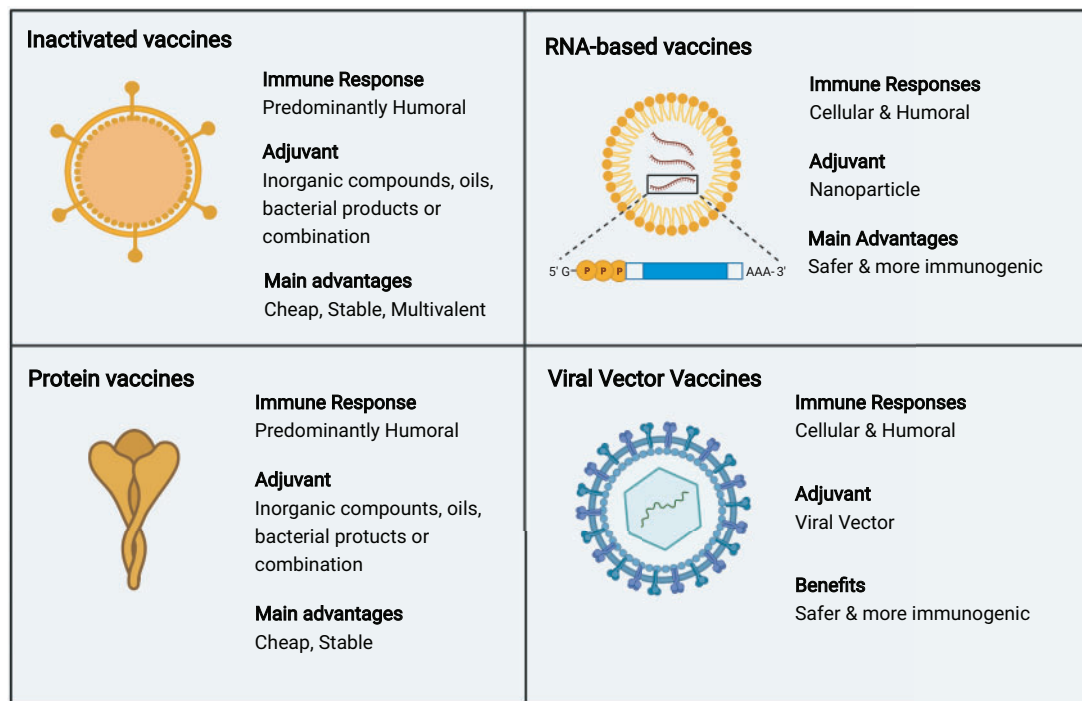


Figure 1: the four dominant SARS-CoV-2 vaccine platforms. Inactivated and protein vaccines elicit a strong humoral response. In contrast, mRNA and viral vector vaccines elicit a stronger cellular immune response due to the production of vaccine antigens by host cells and cross-presentation on human leukocyte antigen class 1. Based on this endogenous production of viral antigens, mRNA and viral vector vaccines typically do not require addition of adjuvants. However, protein and inactivated vaccines still outcompete RNA and viral vector vaccines in terms of costs and stability

protein [30–33] and have previously been extensively characterized as viral vectors.

Phase 1 and 2 trials, testing dose ranges between 5×10^9 and 1.5×10^{11} viral particles (vp), showed minor side-effects common to all adenoviral vector candidates: primarily pain at site of injection, headache and fever [30–33]. Although Ad5-nCoV demonstrated similar immunogenicity across doses, side-effects occurred at increased frequencies at the highest dose [34]. While AstraZeneca found all three doses to be well-tolerated, increased doses were concomitant with nAb levels [30]. Both Ad26.COV2.S and Ad5-nCoV tested a single-dose regimen in phase 3 trials.

Despite methodological variation between studies, all candidates were found to induce both humoral and cellular responses. Levels of anti-RBD or anti-spike IgG peaked at Day 28, while T-cell responses, measured by IFN- γ ELISpot, peaked at Day 14 post-boost. All studies found a positive correlation between antibody titres against the RBD or S and the nAb titres. Furthermore, authors noted that CD4⁺ T-cell responses induced by Ad26.COV2.S and ChAdOx1 nCoV-19 were Th1-biased [32, 35].

Initial analysis of the vaccine efficacy for ChAdOx1 nCoV-19 was based on a meta-analysis of two smaller single-blind clinical trials [36]. Initially, both aimed to assess the

efficacy of a two-dose regimen of the standard dose (SD/SD). However, a subgroup of participants received a lower priming dose of 2.2×10^{10} vp, followed by a SD of 5×10^{10} vp (LD/SD). While vaccine efficacy was calculated as 62% for SD/SD participants, it increased to 90% for LD/SD participants with a 4-week prime-boost interval. However, SD/SD with a longer interval (12 weeks or more) had a similarly high efficacy [37]; this was the regimen approved by MHRA in December 2020. Reduced anti-vector immunity to the lower first dose along with waning anti-vector response over the 12-week interval have been suggested as potential explanations for the different efficacies of the tested regimens.

AstraZeneca received MHRA approval for this vaccine in December 2020, implementing a SD/SD regimen with a 12-week interval. The Joint Committee on Vaccination and Immunization (JCVI) then recommended prioritizing first doses of any vaccine, giving the second dose at up to 12 weeks [38]. Researchers have since updated the efficacy results, including data from all four clinical trials and some *post hoc* exploratory analysis of the effect of extending the prime-boost interval [37]. Efficacy and IgG and nAb titres were higher among those who received the booster at 12 weeks or later compared with those who received it within 6 weeks. Protection did not appear to significantly wane during the 12-week interval. This provides compelling evidence that the JCVI's recommendation was the correct response in a pandemic setting.

The efficacy of Gam-COVID-Vac in phase 3 was reported to be 91.6%, with 16 cases of COVID-19 among the 14 964 participants in the vaccine group compared with 62 cases among the 4902 in the placebo group [39]. Gam-COVID-Vac stands out among the viral vectored candidates as that with the highest efficacy reported thus far and the only candidate to use two human adenovirus serotypes (Ad26 and Ad5) in a heterologous prime-boost approach. AstraZeneca are now sponsoring a clinical trial to evaluate the immunogenicity of one dose of its vaccine in combination with one dose of Gam-COVID-Vac, with an estimated completion date of 12 October 2021 [40].

The phase 3 study of the Janssen/Johnson & Johnson Ad26.COVS vaccine showed a single dose to be 66% effective in preventing moderate to severe COVID-19 28 days after vaccination, based on 468 symptomatic cases among 43 783 participants [41], it was on this basis that the EMA and the FDA granted emergency use authorization for this candidate.

CanSino's vaccine candidate, based on Ad5, had 65.7% efficacy, as announced by press release [42]. It is unclear how many participants were included in efficacy analysis as data from phase 3 remain unpublished. Despite relatively lower efficacies of Ad5-nCoV and Ad26.COVS, their single-dose regimen may prove attractive to countries which face logistical problems in vaccine administration.

SARS-COV-2 VARIANTS AND VACCINE EFFICACY

The low fidelity of the RNA virus replicase enzymes normally results in the generation of diverse viral populations. However, coronaviruses possess a 3'-exonuclease that can proof-read replicated genomes and reduce the frequency of errors. Despite this, several notable variants have emerged and become dominant: B.1.1.7, B.1.351 and P.1 and P.2. While all vaccines

developed to date are derived from the Spike protein sequence containing the D614 residue, most circulating variants now contain the G614 residue. This substitution has been found to increase transmissibility with a little impact on neutralization. However, B.1.351 and P.1 and P.2 variants have been found to contain several additional mutations in their Spike sequences that confer reduced susceptibility to nAbs [43]. Three of these mutations (N501Y, K417N and E484K) commonly occur together and are located within the RBD.

Several recent publications have assessed the ability of vaccine-induced responses to neutralize these variants. Wang et al. [44] found a 1–3-fold decrease in the neutralization sensitivity of pseudoviruses carrying combinations of variant residues by plasma taken from individuals given either of the approved mRNA vaccines. In comparison, the ability of convalescent plasma, to neutralize variants was reduced by up to 29-fold, broadly in line with epidemiological reports of infections with the new strain in convalescent individuals. Madhi et al. [45] found ChAdOx1 nCoV-19 to be ineffective at preventing mild to moderate disease caused by the B.1.351 variant, with 48% of serum samples unable to mediate neutralization. Serum isolated from individuals vaccinated with Pfizer and ChAdOx was found have a reduction in their ability to neutralize the B.1.351 variant *in vitro* by 7.6- and 9-fold, respectively [46].

The increasing global prevalence of these variants poses urgent questions on the efficacy of existing vaccines and is likely to require the development of new iterations of booster vaccines to ensure maximal coverage and protection against current and future variants. The minor changes required to create these new boosters could allow regulators to expedite their approval through use of existing safety profile data.

Efficacy against variant of SARS-CoV-2, as recently highlighted by the Novavax news of its efficacy against the original strain 96.4% and the efficacy seen in South Africa 48.6% against variant strains ([25]; www.novavax.com/covid-19-coronavirus-vaccine-candidate-updates), suggests the same vaccine may be more effective in some areas that other, dependent on the circulating variants.

EFFECTIVENESS OF THE VACCINE

Data from mass population vaccination efforts will provide valuable insights into the effectiveness of different vaccine candidates in different population groups. In a study of over 1 million Israeli citizens, BNT162b2 had an efficacy of 92% 7 days post-boost [47], including individuals over 70 years of age. Real-world data are particularly helpful to assess the vaccines' ability to prevent disease, hospitalizations and transmission. In the UK, Public Health England calculated that those aged 70 years or over who had been vaccinated with a single dose of BNT162b2 or ChAdOx1 nCoV-19 had their risk of emergency hospitalization decreased by 43% and 37%, respectively [48]. This was observed despite a reported decrease of immunogenicity demonstrated with BNT162b2 mRNA vaccine after the first dose in elderly populations [49]. Overall, a recent study including 5.4 million adults in the UK showed an 85% and 94% reduction of COVID-19-related hospitalizations 28–34 days after a single dose of BNT162b2 and ChAdOx1, respectively [50].

Early simulation experiments predicted that a vaccine efficacy of at least 60% was necessary across the whole population

in order to stop the epidemic [51]. However, several factors may effectively lower vaccination coverage including groups with co-morbidities and vaccine-hesitancy. Preliminary results from a safety and immune efficacy study showed that haematological cancer patients have a markedly decreased antibody response (<15%) to BNT162b2 compared with healthy individuals after the first dose [52]. In line with this, only 17% (76/436) of solid organ transplant recipients, who were vaccinated, developed antibodies at a median of 20 days after the first dose. Among the recipients who developed antibodies, 69% received mRNA-1273 and 32% received BNT162b2 [53]. This indicates that vaccination of individuals caring for vulnerable groups may be beneficial.

Furthermore, assessing effectiveness data worldwide allows researchers to monitor the effect of vaccines on emerging SARS-CoV-2 variants. For instance, the SIREN study demonstrated 72% effectiveness of BNT162b2 21 days after the first dose and 86% 7 days after the second dose in healthcare workers, despite the spread of B.1.1.7 variant in the UK [54]. However, the evidence on vaccines preventing the spread of new variants, viral shedding and asymptomatic infections is still too limited to justify removing preventative measures, such as social distancing.

RAPID RESPONSE AND REMAINING CHALLENGES

The successful development of multiple SARS-CoV-2 vaccines has largely resulted from global funding investments and hitherto unprecedented international collaboration, allowing decades of research and know-how in vaccine development to come to fruition.

Clinical trial timelines have been compressed significantly, with regulatory bodies prioritizing vaccine research and trials being carried out in parallel rather than sequentially. Furthermore, use of novel mRNA-based vaccines has accelerated vaccine development and delivery.

Data accumulated from the phase 3 clinical trials outlined above demonstrate high levels of efficacy at preventing COVID-19 across vaccine platforms. Disparities between dosage and booster intervals may account for moderate intra-platform variability in immunogenicity and reactivity. In addition, the lack of harmonization in some immunological assays employed potentially explains the discrepancies in the reporting of immunogenicity data. This highlights the value of international standardization in assessing SARS-CoV-2 immune markers, as is currently being advocated by the World Health Organization.

Longitudinal analysis of patient cohorts for infection, disease and retention of immune responses is ongoing and will provide insight into whether subsequent boosters are required for longer-term protection. Furthermore, the recent emergence of SARS-CoV-2 variants could necessitate the prospective re-evaluation of vaccine-induced protection and development of modified vaccine boosters.

SARS-CoV-2 is likely to remain a public health problem for the foreseeable future, particularly with the added complications of vaccine hesitancy and refusal, and poor vaccine access in low- and middle-income countries. An argument can be made for more equitable distribution of vaccines to prevent evolutionary hotspots that will drive the emergence of new SARS-CoV-2 variants. It remains to be seen how the vaccine rollout will affect virus mutation rates and alter viral evolution globally. In general, however, the research infrastructure and

collaborations established since the start of the pandemic will undoubtedly help reduce the burden of disease and accelerate the development of medical innovations more broadly.

DATA AVAILABILITY STATEMENT

There is no new data available.

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AUTHORS' CONTRIBUTIONS

J.A., V.B., L.C., J.K., M.O. and F.C.R.: conceptualization. F.C.R.: project administration. J.K.: supervision. J.A.: visualization. J.A., V.B., L.C., J.K. and M.O.: writing—original draft. J.K., J.A. and F.C.R.: writing—review and editing. All named authors have contributed by reviewing the current peer-reviewed and preprint literature and writing of the manuscript. The consortium has provided a platform for a wide-range literature assessment in the context of local and joint COVID-19 literature initiatives and organized cross-university review efforts. All authors have approved the final version.

CONFLICT OF INTEREST

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