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Vaccine efficacy—the biggest challenge today

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Abstract

The efficacy of viral vector-based vaccines is essential to provide long-term protection and prevention of emerging epidemics and pandemics in parallel to other vaccine platforms. The key challenges of achieving high vaccine efficacy relate to the engineering of highly potent antigens and the generation of long-lasting immunogenicity. Appropriate vaccine development also includes the ability to quickly react to emerging variants and their effects on vaccine efficacy. It can be achieved by booster vaccinations, rapid re-engineering of existing vaccines, but also by targeting conserved regions less prone to mutations, limiting the decrease in efficacy against new variants. Additional aspects involve alternative administration routes, for example, for respiratory infections, the application of intranasal delivery, which can enhance antigenicity and prolong vaccine action. Application of self-amplifying RNA can further potentially improve vaccine efficacy. Vaccine hesitancy has raised concerns about successful coverage of vaccine campaigns. The anti-vaccine campaigns based on misinformation and disinformation have caused serious damage to vaccinations during the Coronavirus disease 2019 (COVID-19) pandemic and to the spread of other infectious diseases.

Keywords

viral vector, nucleic acid-based vaccines, vaccine re-engineering, administration routes, emerging variants, vaccine hesitancy

Introduction

Successful vaccinations were achieved already in 1796 [1], but more recently, accelerated vaccine development has been established, especially during the Coronavirus disease 2019 (COVID-19) pandemic [2]. Although various vaccine platforms were available years ago, the variety of approaches, including whole virus vaccines, protein and peptide subunit vaccines, viral vector vaccines, and nucleic acid vaccines [3], saw accelerated development both for preclinical animal studies and clinical trials [4]. The engineering of COVID-19 vaccines provided the breakthrough for mRNA-based vaccines, showing good vaccine efficacy in clinical trials [5], emergency use authorization (EUA) in several countries [6], and additionally market approval [7]. Moreover, COVID-19 vaccines based on viral vectors [8, 9], DNA plasmids [10, 11], and whole

viruses have also proven successful [12, 13]. It is important to point out that vaccine efficacy refers to the protection against disease under controlled preclinical studies and clinical trials comparing the vaccine candidate to standard of care or placebo. In contrast, in real-world settings, such as mass vaccinations against COVID-19, vaccine effectiveness is used. The goal is to clearly make a distinction between vaccine efficacy and effectiveness in this review.

Despite recent success, vaccine development against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and other infectious agents remains a real challenge. The vaccine efficacy is reduced with time [14], and the emerging novel viral variants have further decreased vaccine efficacy in clinical trials and effectiveness in mass vaccinations [15]. Another issue of concern is vaccine hesitancy, which has been additionally enhanced by widespread unfounded misinformation and disinformation [16]. The data collected for the review covers literature search using PubMed, Scopus, and Google Scholar containing peer-reviewed publications but also some preprinted materials mainly published in English language starting from the onset of COVID-19 until the middle of April 2026. In addition to including publications on "COVID-19 vaccines in general" and "vaccine platforms", keywords such as "COVID-19 vaccine efficacy", "emerging SARS-CoV-2 variants", etc., have been used in the search.

Infectious agents and vaccine re-engineering

In contrast to bacterial infections, which have been successfully treated with antibiotics, the nature of viral infectious agents has proven more complicated and less efficient when it comes to antiviral therapy. Much of this difference is associated with the integral use of host cell components in the life cycle of viruses. For this reason, vaccine development represents an essential aspect of prophylactic and therapeutic interventions to restrict and preferentially eliminate viral infections. Although undoubtedly the strongest attention has been given to the recent COVID-19 pandemic, a large number of vaccines have been engineered for various viral pathogens such as human immunodeficiency virus (HIV), human papillomavirus (HPV), Ebola virus (EBOV), and influenza virus. Therefore, a short summary of essential viral vaccines is presented with the emphasis on COVID-19 vaccines. Although the main theme of this review is viral vector-based vaccine development, a description of other platforms for COVID-19 vaccines here is necessary to generate a better understanding of vaccine development, vaccine efficacy and effectiveness, and the challenges encountered today.

HIV vaccines

In the case of HIV, much has been achieved during the past ten years in the area of antiviral drugs to provide therapeutic efficacy resulting in non-detectable levels of the virus load in AIDS patients [17]. However, the treatment requires a cocktail of several drugs, whereas vaccines might be more straightforward and can be applied for both prophylactic and therapeutic activities.

The design of first-generation HIV-1 vaccines focused on neutralizing antibodies, whereas more recent development has involved T-cell responses and non-neutralizing antibodies against HIV structural proteins [18–20]. In a review, 21 clinical trials based on seven viral vectors, three DNA plasmids, four envelope proteins, five adjuvants, and three monoclonal antibodies (mAbs) conducted in South Africa were described [21]. In another review, HIV vaccines based on protein subunits, viral vectors, nucleic acids, and germline targeting have been described [22]. For example, a modified vaccinia Ankara (MVA) vector expressing the HIV gag p24 and p17 antigens showed no serious adverse events but some severe local reactions in a phase I trial [23] (Table 1). Due to the low and short immune responses achieved, the trial was terminated early. In another phase I trial conducted in HIV-uninfected adults, the Venezuelan equine encephalitis virus (VEE) vector expressing the HIV-1 subtype C gag (AVX101) was terminated due to vaccine stability issues and limited immune responses in humans [24]. Moreover, the canarypox vector-based vaccine canarypox virus (ALVAC)-HIV (vCP1521) was generally safe and well-tolerated in phase I [25]. In comparison to the RV144 phase III trial in Thailand with the ALVAC/AIDSVAX vaccine [26], the higher peak cellular and antibody responses were obtained for ALVAC-HIV (vCP1521). However, the Env-specific IgG and CD4+ Env responses declined significantly over time. In another approach, an adeno-associated virus (AAV) vector

was engineered to express broadly neutralizing antibodies (bnAbs) [27], designed to bind two different antigens or epitopes simultaneously. Application of bnAbs should provide superior potency, broader coverage, and reduce risk of viral escape. Based on this approach, a tri-specific antibody binding to CD4 binding sites, membrane proximal external regions, and V1V2 glycan sites showed an extraordinarily broad activity in vitro [28]. However, these findings need to be confirmed in clinical trials. A phase I study has been conducted with AAV delivery of bnAbPG9 for prevention of HIV in healthy adults [29]. Although the study was safe, the elicited antibody levels were low.

Table 1. Examples of vaccines developed against certain viruses.

Virus	Vaccine vector	Findings
HIV	MVA gag p24/p17	Phase I terminated: low immune responses [23]
HIV	VEE gag	Phase 1 terminated: stability issues, low immunity [24]
HIV	ALVAC-HIV	Safe, cellular & Ab responses in phase I [25]
HIV	AAV-bnAbs	Low Ab responses in phase I [29]
HIV	mRNA-LNPs	nAbs in 80% of vaccinees in phase I [30]
HIV	GT HIV gp120 NPs	Strong immune responses in phase I [31]
HPV	HPV-VLPs	Cervarix approved for cervical cancer [35]
HPV	HPV-VLPs	Gardasil, Gardasil 9 approved for cervical cancer [36, 37]
HPV	SFV-HPV E6/E7	Strong immune responses in all patients in phase I [40]
HPV	SFV-HPV E6/E7	Reduction in lesions in 94% of patients in phase II [41]
EBOV	VEE-GP/NP	Protection against EBOV in mice and guinea pigs [43]
EBOV	rVSV-ZEBOV	Excellent vaccine efficacy in phase III [44, 45]
EBOV	rVSV-ZEBOV	Approval by the FDA in 2019 [46]
EBOV	Ad26.ZEBOV/MVA	Robust humoral responses in phase II [47]
EBOV	Ad26.ZEBOV-GP	Approval by the EMA in 2020 [48]
IVA	LAIV	Approval by the FDA [52, 53]
IVA	Inactivated IVA	Approval of several vaccines [57]
IVA	Split-virion vaccine	Strong immune responses in phase IV [58, 59]
IVA	Split-virion vaccine	Approval of IIV3 and IIV4 vaccines [59]
IVA	Inflexal V virosomes	Good immunogenicity in clinical trials [63]
IVA	AdV-HA/M2e/NP	Strong immunogenicity, protection against IVA [65, 66]
IVA	PICV rP18tri	Strong immune responses, protection in mice [67, 68]
IVA	NDV-HA	Robust immune responses, protection in mice [69]
IVA	BEVS Flublok	Approval for vaccination against IVA and IVB [71]
IVA	MV-HA	Protection against IVA in cotton rats [72]
IVA	VSV-H5N1	Protection in mice against H5 clades 1 and 2 [73]
IVA	SFV-HA saRNA	90% protection in mice after 10 μg saRNA dose [74]
IVA	VEE-HA	80-86% Ab responses in phase I/II [75]
IVA	IVA-VLPs COBRA	Protection against multiple IVA subtypes [76]
IVA	HA mRNA	Strong immune responses in mice and macaques [77]
IVA	HA mRNA	Comparable Ab responses to control vaccine in phase I [78]
IVA	HA mRNA	Statistically superior to control vaccine in phase III [79]
COVID-19	CoronaVac (WV)	50.7% efficacy against symptomatic COVID-19 and 100% against hospitalization [12]
COVID-19	CoronaVac (WV)	EUA in 54 countries in 2021 [13]
COVID-19	BBIBP-CoV (WV)	78.1% vaccine efficacy in phase III [80]
COVID-19	BBIBP-CoV (WV)	EUA in China 2020, by the WHO in 2021 [81, 82]
COVID-19	COVAX-19 + Adj	Protection in hamster against SARS-CoV-2 [83]
COVID-19	COVAX-19 + Adj	Robust immune responses in phase II [84]
COVID-19	COVAX-19 + Adj	Reduced severity of COVID in phase III [85]
COVID-19	NVX-Cov2373 + Adj	Protection against SARS-CoV-2 in rats, baboons [86]
COVID-19	NVX-Cov2373 + Adj	Superior Ab responses to COVID-19 patient sera [87]

Table 1. Examples of vaccines developed against certain viruses. (*continued*)

Virus	Vaccine vector	Findings
COVID-19	NVX-Cov2373 + Adj	76.1% efficacy against symptomatic COVID-19 and 100% against severe disease in phase III [88]
COVID-19	NVX-Cov2373 + Adj	CMA in the EU in 2020 and in the UK in 2021 [89]
COVID-19	ChAdOx1 nCoV-19	Protection against SARS-CoV-2 in macaques [90]
COVID-19	ChAdOx1 nCoV-19	62-90% vaccine efficacy in phase III [8]
COVID-19	ChAdOx1 nCoV-19	EUA in the UK in 2020 [9]
COVID-19	Ad5-nCoV	EUA in China in 2021 [91]
COVID-19	Ad26.COV2.S	52.9% vaccine efficacy in phase III [92]
COVID-19	Ad26.COV2.S	EUA by the FDA in 2021 [93]
COVID-19	Ad26-S/Ad5-S	91% vaccine efficacy in phase III [95]
COVID-19	Ad26-S/Ad5-S	EUA in Russia in 2020 [96]
COVID-19	VSV-SARS-CoV-2 S	Protection of mice against SARS-CoV-2 [97]
COVID-19	VSV-SARS-CoV-2 S	Low immunogenicity, termination of phase I trial [98]
COVID-19	VSV-ΔG	Potent nAbs in golden Syrian Hamsters [99]
COVID-19	VSV-ΔG	Robust nAb responses in phase II [100]
COVID-19	INO-4800 DNA	Robust Ab responses in mice and guinea pigs [101]
COVID-19	INO-4800 DNA	Superior Ab response after high dose booster in phase II [102]
COVID-19	ZyCoV-D DNA	nAbs in mice, guinea pigs and rabbits [103]
COVID-19	ZyCoV-D DNA	nAbs in phase I/II [104]
COVID-19	ZyCoV-D DNA	66.6% vaccine efficacy in phase III [10]
COVID-19	ZyCoV-D DNA	EUA granted in India in 2021 [11]
COVID-19	BNT162b2 RNA	Protection against SARS-CoV-2 in macaques [105]
COVID-19	BNT162b2 RNA	95% vaccine efficacy in phase III [5]
COVID-19	BNT162b2 RNA	EUA granted in the EU and Switzerland in 2020 [6]
COVID-19	mRNA-1273 RNA	Protection against SARS-CoV-2 in mice and primates [106]
COVID-19	mRNA-1273 RNA	94.1% vaccine efficacy in phase III [107]
COVID-19	mRNA-1273 RNA	EUA granted by the FDA in 2020 [108]
COVID-19	LNP-nCoVsaRNA	Ab responses in mice [109]
COVID-19	LNP-nCoVsaRNA	< 100% seroconversion in phase I [110]
COVID-19	LNP-nCoVsaRNA	Superior seroconversion after booster dose in phase II [111]
COVID-19	LUNAR-CoV RNA	Phase II: 95% protection against severe COVI-19 and 55% protection against symptomatic COVID-19 [112]
COVID-19	LION-VEECoV RNA	Safety and immunogenicity in phase II/III [113]
COVID-19	LION-VEECoV RNA	EUA granted in India in 2025 [114]

AAV: adeno-associated virus; Ab: antibody; Ad26: adenovirus serotype 26; Adj: adjuvant; ALVAC: canarypox virus; BEVS: baculovirus expression vector system; bnAbs: broadly neutralizing antibodies; CMA: conditional marketing authorization; COBRA: computationally optimized broadly reactive antigen; COVID-19: Coronavirus disease 2019; EBOV: Ebola virus; EMA: European Medicines Agency; EUA: emergency use authorization; FDA: Food and Drug Administration; GP: glycoprotein; GT: germline targeting; HA: hemagglutinin; HIV: human immunodeficiency virus; HPV: human papillomavirus; IVA: influenza virus A; IVB: influenza virus B; LAIV: live attenuated influenza virus; LION: lipid inorganic nanoparticle; LNP: lipid nanoparticle; MV: measles virus; MVA: modified vaccinia Ankara; nAbs: neutralizing antibodies; NDV: Newcastle disease virus; NP: nucleoprotein; NPs: nanoparticles; PICV: Pichinde virus; S: spike; saRNA: self-amplifying RNA; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SFV: Semliki Forest virus; VEE: Venezuelan equine encephalitis virus; VLPs: virus-like particles; VSV: vesicular stomatitis virus; WV: whole virus; ZEBOV: Zaire Ebola virus.

Vaccines based on lipid nanoparticle (LNP) encapsulated mRNA have also been developed for HIV. The HVTN302 phase I trial was conducted with three different stabilized HIV envelope trimer antigens [30]. The vaccination was generally well tolerated, although a higher proportion (6.5%) of urticaria compared to other mRNA vaccines was detected. Neutralizing antibodies were elicited in 80% of vaccinees after three immunizations.

An interesting promising new approach relates to germline targeting [31]. It can be achieved by the design of a series of immunogens for the stimulation of rare naïve B cells for the induction of broadly neutralizing activity. The germline-targeting immunogen eOD-GT8 60mer, an outer domain of HIV gp120,

was presented on nanoparticles in the G001 phase I trial [32]. Detectable B-cell expression of VRC01-class precursors was found in 97% of individuals receiving eOD-GT8 and the immunogen effectively primed the immune system [32]. Another phase I trial (G002) is in progress to study the safety and immunogenicity after booster vaccinations with the gp120 core-based nanoparticle immunogen (Core-g28v2 60mer) [33].

HPV vaccines

Effective prophylactic vaccines against HPV have been developed based on virus-like particles (VLPs), self-assembled spontaneously from the HPV L1 major capsid protein to target cervical cancer [34]. VLPs are non-infectious supramolecular structures, which resemble original viruses in shape and structure, but do not contain a functional genome. The Cervarix vaccine (GlaxoSmithKline), based on L1 VLPs from HPV-16 and HPV-18, is produced in baculovirus-infected insect cells [35], whereas the Gardasil vaccine (Merck & Co) VLPs from HPV-16, HPV-18, HPV-6 and HPV-11 are produced in *Saccharomyces cerevisiae* yeast cells [36]. Furthermore, Gardasil 9 was developed to contain VLPs from five additional oncogenic types of HPV (HPV-31, 33, 45, 52 and 58), which provided type-specific protection against 90% of cervical cancers worldwide [37]. In a systematic review and network meta-analysis based on 11 randomized clinical studies, vaccine efficacy was determined for bivalent (2vHPV), quadrivalent (4vHPV), and nine-valent HPV (9vHPV) vaccines [38]. The 2vHPV vaccine was most effective at 98% (95% CI 0.00 to 0.29) against HPV-18, whereas 4vHPV was superior at 99% (95% CI 0.00 to 0.10) and 97% (95% CI 0.00 to 0.45), respectively, for cervical intraepithelial neoplasia grade 2+ (CIN2+) associated with HPV-16 and HPV-18. In the case of persistent infection with HPV-31, 33, 45, 52, and 58, 9vHPV showed more than 95% vaccine effectiveness. Additionally, the 2vHPV vaccine demonstrated cross-effectiveness against HPV-31, 33, and 45, and the 4vHPV vaccine against HPV-31.

The successful development of these prophylactic HPV vaccines has, however, not addressed the need for the treatment of existing HPV lesions in cancer patients. For this reason, self-amplifying RNA (saRNA) viruses have been utilized for immunotherapeutic applications. Typically, saRNA viruses carry replicase genes responsible for efficient RNA replication in host cells, requiring reduced doses, leading to enhanced durability and potentially causing fewer adverse events. They can be applied as recombinant viral particles, RNA replicons, or DNA plasmids. Replication-deficient Semliki Forest virus (SFV) particles have been engineered for the expression of the HPV E6/E7 fusion proteins, resulting in regression and complete elimination of established tumors in tumor-bearing mice [39]. The SFV-HPV E6/E7 vaccine was safe and well tolerated in patients with HPV-induced cancers in phase I [40]. Moreover, strong immune responses against HPV-16 were detected in all 12 patients. Furthermore, in phase II, 18 patients with CIN3 were vaccinated with SFV-HPV E6/E7, resulting in a reduction in lesions in 94% of the patients three weeks post-vaccination [41]. Based on histopathologic evaluation, complete responses were obtained in 50% of the patients, and HPV-16 clearance was seen in 63% of patients.

EBOV vaccines

EBOV disease (EVD) is characterized by its rapid onset and high mortality rates after EBOV infections, which has encouraged vaccine development [42]. The administration of VEE particles expressing the EBOV glycoprotein (GP) and nucleoprotein (NP) protected both mice and guinea pigs against challenges with lethal doses of EBOV [43]. Moreover, expression of the EBOV GP from the Zaire strain from vesicular stomatitis virus (VSV) particles [rVSV-ZEBOV (Zaire EBOV)] showed excellent efficacy in phase III trials in Guinea and Sierra Leone [44, 45]. Although by definition, vaccine efficacy should be addressed in clinical trials, the authors mention that the rVSV-ZEBOV vaccine showed 75.1% (95% CI 7.1 to 94.2%; $p = 0.1791$) vaccine effectiveness for eligible adults and 76.3% (95% CI 15.5 to 95.1%; $p = 0.3351$) for individuals eligible and not eligible for vaccination [44]. In the other phase III trial [45], the vaccination effectiveness of protection was 100% (95% CI 68.9 to 100.0%; $p = 0.0045$). The rVSV-ZEBOV vaccine was approved by the Food and Drug Administration (FDA) in 2019 [46].

In another approach, the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen was assessed for safety and immune memory responses after booster vaccination with Ad26.ZEBOV in healthcare and front-line

workers in the Democratic Republic of Congo in a phase II trial [47]. The vaccinations were well tolerated, and similar robust humoral immune responses were detected in individuals receiving the booster vaccination one or two years after the first dose, indicating the advantage of booster vaccinations in at-risk individuals. The Ad26.ZEBOV-GP vaccine (Zabdeno) was approved by the European Medicines Agency (EMA) in 2020 [48].

Influenza virus vaccines

The development of vaccines against influenza viruses has become familiar to everybody due to the annual flu epidemics and the engineering of novel vaccines each year to challenge emerging new influenza virus variants [49, 50].

Numerous approaches have been applied for influenza vaccine development, including vaccines based on whole viruses, protein subunits, virosomes, viral vectors and mRNA [51]. For example, live attenuated influenza viruses have been engineered by the introduction of mutations or by passaging parental influenza virus multiple times in virus-susceptible cells of embryonic chicken eggs. Low virulence strains containing for example, influenza A (H1N1) and A (H3N2) subtypes, are tested in human volunteers before being approved by the FDA as vaccines [52]. For example, both live attenuated influenza virus vaccines and inactivated influenza virus vaccines showed effectiveness of 50% (95% CI 2 to 75%) and 71% (95% CI 51 to 82%), respectively, in children of 2 to 17 years when compared to unvaccinated children [53]. The approach of developing inactivated whole influenza virus vaccines can provide high safety, robust and long duration of immunogenicity, and no risk of reversion of virulence [54, 55]. Several inactivated whole influenza virus vaccines have been approved [56]. In another approach, split-virion vaccines have been engineered by disrupting the viral envelope and splitting open the viral particles, providing additional safety compared to inactivated whole virus vaccines [57]. Good safety and strong immunogenicity were achieved in a phase IV trial in China with the split-virion influenza virus vaccine Aleph [58]. The trivalent IIV3 and quadrivalent IIV4 inactivated influenza vaccines have been approved for marketing in China [59].

Vaccines have also been developed based on virosomes, which comprise reconstituted influenza virus envelopes containing hemagglutinin (HA), neuraminidase (NA) and viral phospholipids [60, 61]. Two virosome-based vaccines reached the market in the 1990s: Epaxal® against hepatitis A [62] and Inflexal® V against influenza virus [63]. Moreover, the adjuvanted influenza virosome-based Inflexal V vaccine demonstrated good immunogenicity in healthy adults aged 18–60 years [64].

Different viral vectors have been utilized for influenza virus vaccine development. For example, adenoviruses expressing the conserved antigenic regions of the stem region of HA2, chimeric HA, M2e, NP, and T/B cell epitopes elicited robust immunogenicity and protection against different subtypes of influenza viruses [65, 66]. Furthermore, a three-plasmid reverse genetics system was applied to engineer a Pichinde virus (PICV) vector expressing HA and/or NP antigens [67]. The rP18tri vaccine elicited specific humoral and adaptive immune responses against HA and NP in mice and provided long-term protection against the PR8 lethal mouse-adapted influenza strain [68]. Newcastle disease virus (NDV) vectors have also been used for influenza virus vaccine development. Expression of the *HA* gene from the human influenza A/WSN/33 virus in a vector based on the NDV Hitchner B1 strain elicited potent humoral immune responses in immunized mice and protected mice from challenges with the influenza A/WSN/33 virus [69].

The baculovirus expression vector system (BEVS) has been applied for the production of the recombinant Influenza-Flublok Quadrivalent vaccine [70]. The vaccine contains the HA gene of four influenza virus strains: A/Hawaii/70/2019 (H1N1), A/Minnesota/41/2019 (an A/Hong Kong/45/2019-like virus) (H3N2), B/Washington/02/2019 and B/Phuket/3073/2013. It has been approved for vaccination against influenza A and B subtype viruses [71].

Among other viral vectors, measles virus (MV) particles expressing the HA gene from the influenza virus A Sapporo/107/2013 strain protected cotton rats against influenza virus challenges [72]. Moreover, VSV-H5N1 particles rendered mice 100% resistant to challenges with homologous H5 clade 1 but also with various H5 clade 2 strains [73]. In the case of saRNA vectors, 90% protection was achieved in mice after

administration of only 10 μg of SFV-HA RNA [74]. In a phase I/II trial, strong antibody responses were obtained in 80% and 86% of individuals vaccinated with VEE-HA particles (AVX502) after one and two doses, respectively [75].

The design of next generation immunogens against a broad range of influenza virus strains has been supported by the application of the computationally optimized broadly reactive antigen (COBRA) methodology [76]. Alignment of HA and NA multilayered consensus sequences from multiple subtypes of influenza viruses allowed evaluation of protective immune responses in mice. Targeting H1, H2, H3, H5, H7, N1, and N2 proteins, vaccinated mice were protected against multiple influenza virus subtypes.

Finally, based on the success of applying mRNA-LNPs for COVID-19 vaccine development, mRNA-LNPs were engineered to express monovalent, trivalent, or quadrivalent (qIRV) formulations of the influenza virus A and B HA gene [77]. Durable functional antibody responses were achieved in mice and macaques. In phase I, the qIRV was well tolerated, and reactogenicity, HA inhibition and seroconversion were higher compared to the control vaccine QIV (Fluzone High-Dose Quadrivalent, Sanofi Pasteur) [78]. In phase III, the quadrivalent mRNA-HA vaccine showed a relative efficacy of 34.5% (95% CI 7.4 to 53.9%) and was statistically superior compared to a control vaccine [79].

COVID-19 vaccines

Obviously, the greatest attention of vaccine development has recently been dedicated to COVID-19 vaccines due to the onset of the pandemic. All possible approaches, including vaccines based on whole viruses, protein subunits, viral vectors, and nucleic acids, have been verified as previously described [2]. Therefore, only a brief summary is included below and in Table 1. Among whole virus-based approaches, the CoronaVac (Sinovac) vaccine showed 67.7% (95% CI, 35.9 to 83.7%) efficacy against symptomatic COVID-19 and 100% efficacy against hospitalization in phase III [12]. It was granted EUA in 54 countries in 2021 [13]. The inactivated BBIBP-CorV (Sinopharm) whole virus vaccine showed 78.1% (95% CI, 64.8 to 86.3%) vaccine efficacy in phase III [80] and was granted EUA in China in 2020 [81] and by the WHO in 2021 [82].

The COVAX-19 protein subunit vaccine comprising the extracellular domain (ECD) of the SARS-CoV-2 spike (S) protein and an adjuvant elicited strong humoral and cellular immune responses in mice and provided protection against challenges with SARS-CoV-2 in hamsters [83]. The robust immune responses of COVAX-19 were confirmed in phase II [84]. COVAX-19 showed reduced severity and disease rates in phase III [85]. The NVX-CoV2373 vaccine, consisting of the nanoparticle-encapsulated full-length SARS-CoV-2 S protein and the Matrix M1 adjuvant, protected rats and baboons from SARS-CoV-2 challenges [86]. NVX-CoV2373 demonstrated superior antibody and CD4+ T-cell responses compared to serum samples from COVID-19 patients in phase I/II [87]. In phase III, NVX-CoV2373 provided 76.3% (95% CI, 57.4 to 86.8%) efficacy against symptomatic COVID-19 and 100% (95% CI, 17.9 to 100.0%) efficacy against severe COVID-19 [88]. NVX-CoV2373 was granted conditional marketing authorization (CMA) in the EU in 2021 and in the UK in 2022 [89].

Although a variety of viral vectors have been utilized for COVID-19 vaccine development, the focus here is solely on adenoviruses and rhabdoviruses. The chimpanzee virus vector ChAdOx1 has been engineered to express the full-length SARS-CoV-2 S protein, leading to robust antibody responses and protection of macaques challenged with SARS-CoV-2 [90]. Furthermore, 62.1% (95% CI 41.0 to 75.7%) vaccine efficacy was obtained after two standard doses and 90.0% (95% CI 67.4 to 97.0%) after a low dose and a standard dose in phase III [8]. The ChAdOx1 nCoV-19 vaccine was granted EUA in the UK in 2020 [9]. Likewise, the Ad5-based Ad5-nCoV vaccine received EUA in China in 2021 [91]. Furthermore, the single dose Ad26.COV2.S vaccine demonstrated a 52.9% (95% CI, 47.1 to 58.1%) vaccine efficacy in phase III [92], and the FDA granted EUA in 2021 [93]. Alternatively, Ad vectors have been used for the expression of the SARS-CoV-2 S protein according to a prime-booster strategy, where the first vaccination with Ad26-S is followed by Ad5-S [94]. The Ad26-S/Ad5-S regimen (Sputnik V) showed a 91.6% (95% CI 85.6 to 95.2%) vaccine efficacy in phase III [95], and EUA was granted in Russia in 2020 [96].

VSV vectors expressing the SARS-CoV-2 S protein resulted in protection of BALB/c mice against SARS-CoV-2 challenges [97]. The VSV-SARS-CoV-2 S (V590) vaccine showed good safety and tolerability in phase I, but the inferior immune responses compared to sera from convalescent COVID-19 patients led to the termination of the trial [98]. Moreover, the SARS-CoV-2 S gene was introduced into the VSV vector replacing the VSV G protein, which elicited potent neutralizing antibodies in golden Syrian hamsters vaccinated with the chimeric VSV-ΔG vector [99]. The VSV-ΔG vaccine induced robust neutralizing antibody responses against SARS-CoV-2 in phase II [100].

Among DNA-based COVID-19 vaccines, the synthetic INO-4800 vaccine induced robust immune responses and neutralized SARS-CoV-2 in mice and guinea pigs [101]. In phase II, individuals who had at least 12 months earlier received two doses of INO-4800 were vaccinated with an INO-4800 booster dose of 1 or 2 mg [102]. Superior immunogenicity was obtained in vaccinees who received the higher dose. The ZyCoV-D DNA vaccine containing the SARS-CoV-2 S receptor binding domain (RBD) elicited neutralizing antibodies and T-helper1 (Th1)-biased responses in mice, guinea pigs, and rabbits [103]. Good safety and robust immune responses were obtained in phase I/II [104], and a 66.6% (95% CI 47.6 to 80.7%) vaccine efficacy was achieved in phase III [10]. ZyCoV-D was granted EUA in India in 2021 [11].

In the case of mRNA-based COVID-19 vaccines, the LNP encapsulated prefusion-stabilized full-length SARS-CoV-2 S RNA (BNT162b2) vaccine provided protection against SARS-CoV-2 challenges in immunized macaques [105]. A vaccine efficacy of 95% (95% CI, 90.3 to 97.6%) was obtained for the BNT162b2 vaccine in phase III [5]. EUA was granted for BNT162b2 in the EU and Switzerland in 2020 [6]. Another RNA-LNP vaccine, mRNA-1273, protected mice and primates against SARS-CoV-2 challenges [106]. In phase III, the mRNA-1273 vaccine showed a 94.1% (95% CI, 89.3 to 96.8%; $p < 0.001$) vaccine efficacy [107]. The FDA granted EUA for mRNA-1273 in 2020 [108].

The approach of developing saRNA-based COVID-19 vaccines resulted in superior mRNA quantities and the potential of using lower doses for immunization [109]. The VEE replicon-based LNP-nCoVsaRNA vaccine elicited strong antibody responses in mice [109]. The LNP-nCoVsaRNA vaccine showed good safety and tolerability in phase I, and although 100% seroconversion was not achieved, specific immune responses were elicited [110]. Superior seroconversion rates were seen in phase II by the prolongation of dosing intervals or by the administration of a 0.1 μg booster dose after two 1.0 μg doses [111]. The LUNAR-COV19 RNA LNP formulation showed 95% protection against severe COVID-19 and 55% overall protection against symptomatic disease in phase II [112]. The lipid inorganic nanoparticle (LION) formulation of VEE-SARS CoV-2 S RNA showed good safety and immunogenicity in a phase II/III trial [113]. EUA was granted to LION VEE-SARS CoV-2 S in India in 2025 [114].

Vaccine waning and emerging variants

Vaccinations against various infectious diseases have been characterized by a decrease of protection efficacy with time. There are two contributing reasons for the reduced vaccine efficacy and effectiveness: waning with time and emerging new variants of virus strains. Studies on influenza virus vaccines [115, 116] and mumps vaccines [117] have demonstrated waning. Simulation studies have also been conducted on vaccine efficacy, vaccine effectiveness, and waning [118]. Waning of humoral immunity was investigated for different types of COVID-19 vaccines three months post-vaccination in healthcare workers [119]. The study revealed that a two-dose homologous vaccination with the ChAdOx1 nCoV-19 vaccine or homologous mRNA-1273 booster vaccinations induced more durable immune responses than two-dose homologous mRNA vaccinations, homologous BNT162b2 booster vaccinations, or two-dose ChAdOx1 nCoV-19 vaccinations followed by a BNT162b2 booster vaccination. In a systematic review and meta-analysis, a decrease in protection against SARS-CoV-2 infection decreased by 21.0% over a six-month period in individuals of all ages receiving full vaccination [120]. There was no difference between vaccinations with the BNT162b2, mRNA-1273, Ad26.COV2.S and ChAdOx1 nCoV-19 vaccines. Vaccine effectiveness was reduced by only 10% for severe disease and remained higher than 70% for six months.

Emerging and re-emerging viral strains and variants play an important role in the decrease in the efficacy and the effectiveness seen for a number of viral vaccines. The classic example of reduced vaccine effectiveness relates to the ever-changing surface structure of influenza viruses due to emerging variations in epitopes of the HA and NA proteins, the main targets for antigen development against influenza viruses [121]. Likewise, the SARS-CoV-2 S protein epitopes comprise the antigens of choice for COVID-19 vaccines [122]. To limit the length of this section, the focus here is solely on emerging variants of SARS-CoV-2 and their impact on the efficacy and the effectiveness of COVID-19 vaccines. Detailed studies on emerging variants have classified them as variants of concern (VoC), variants of interest (VoI), and variants under monitoring (VuM) [123]. Today, a long list of SARS-CoV-2 variants, including alpha, beta, delta, gamma, omicron, and recent subvariants of omicron, has been discovered [124]. However, due to the large number of published studies on SARS-CoV-2 variants and their impact on vaccine efficacy and effectiveness already reviewed [2, 125], a brief summary is presented below, and examples are listed in Table 2. In the case of whole virus-based vaccines, homologous and heterologous booster vaccinations with the ChAdOx1 nCoV-19 vaccine improved vaccine efficacy against delta and omicron variants [126]. In another study, individuals previously vaccinated with Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccines received booster vaccinations with the NVX-CoV2373 protein subunit vaccine, which showed high pseudovirus-neutralizing antibody (PsVNA) responses against the D614G variant and low responses against the omicron BQ.1.1 and XBB.1 variants [127].

Table 2. Examples of SARS-CoV-2 variants and COVID-19 vaccine efficacy.

Vaccine	Variants	Findings
WV		
VLA2001	Delta, omicron	Improved VE for homologous/ChAdOx1 nCoV-19 boosters [126]
Protein subunit		
NVX-CoV2373	D614G, BQ1.1, XBB.1	High PsVNA for D614G, low for BQ.1 and XBB.1 after booster in persons previously vaccinated with Ad and mRNA vaccines [127]
Viral		
ChAdOx1	Beta	No protection against mild-to-moderate COVID-19 [128]
nCoV-19	Alpha, delta	Lower transmission reduction for delta than alpha, better VE for BNT162b2 than for ChAdOx1 nCoV-19 [129]
Ad26.COV2.S	Beta, gamma	Reduced nAb responses compared to original strain [130]
Ad26.COV2.S	Delta	Durability of VE for at least 6 months [131]
DNA		
INO-4800	Delta, alpha, beta, gamma	Comparable nAb responses for gamma and original strain, 2.1-fold (alpha) and 6.9-fold (beta) reduction [132]
INO-4802	Alpha, beta, gamma	Enhanced nAb responses for variants and original strain [133]
RNA		
BNT162b2	Delta	67% VE in Spain [134], 90% in the UK [135]
BNT162b2	BA.1, BA.2	VE 25% in US [136], 30% in Israel [137], 51% in Qatar [138]
mRNA-1273	Alpha, beta, gamma, delta	1.2-fold (alpha), 2.1- to 8.4-fold (beta, gamma, delta) reduction in nAb titers compared to D614G [139]
mRNA-1273.214	BA.1, alpha, beta, gamma, delta	Enhanced nAb titers against omicron, higher binding activity against alpha, beta, gamma, and delta [140]
XBB.1.5	XBB.1.5, EG5	27-fold enhanced nAbs levels against XBB.1.5 and EG5 [141]
LNP-nCoVsaRNA	D614G, alpha	Protection against D614G and alpha in hamsters [142]

Ad26: adenovirus serotype 26; COVID-19: Coronavirus disease 2019; LNP: lipid nanoparticle; nAbs: neutralizing antibodies; PsVNA: pseudovirus-neutralizing antibody; saRNA: self-amplifying RNA; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; VE: vaccine effectiveness; WV: whole virus. Adapted from [2].

Among viral vector-based vaccines, the ChAdOx1 nCoV-19 vaccine did not manage to provide protection against the beta variant measured by pseudovirus and live-virus neutralization assays [128]. In another study, the ChAdOx1 nCoV-19 vaccine or the BNT162b2 mRNA vaccine was evaluated for SARS-CoV-2 transmission of the alpha and delta variants [129]. The transmission was inferior for the delta variant

compared to the alpha variant. Moreover, higher reduction in transmission was obtained for the mRNA-based vaccine. A reduction of neutralizing antibody responses after a single administration of the Ad26.COV2.S vaccine was observed for the beta and gamma variants compared to the original SARS-CoV-2 strain [130]. Moreover, the durability of the vaccine efficacy of Ad26.COV2.S against the delta variant was at least six months [131].

The DNA-based INO-4800 vaccine elicited comparable levels of neutralizing antibodies for the gamma variant and the original SARS-CoV-2 strain [132]. Moreover, 2.1- and 6.9-fold reductions of neutralizing antibodies were obtained for the alpha and beta variants, respectively. To address SARS-CoV-2 variants, the next-generation INO-4802 was designed to target RBD and 2P mutations, resulting in potent neutralizing antibody and T-cell responses against the original SARS-CoV-2 strain and the alpha, beta, and gamma variants [133]. Immunization experiments in macaques showed improved neutralizing and ACE2 blocking activity for both the variants and the original strain.

In the case of mRNA-based vaccines, the BNT162b2 vaccine effectiveness against the delta variant was 68% (95% CI, 48 to 80%) in Spain [134] and 90% (95% CI, 84 to 94%) in the UK [135]. The vaccine effectiveness against the omicron BA.1 and BA.2 variants was 63% (95% CI, 58 to 67%) in the US [136], 30% (95% CI, 9 to 55%) in Israel [137], and 49.4% (95% CI, 47.1 to 51.6%) in Qatar [138]. In the context of the mRNA-1273 vaccine, the alpha variant showed a 1.2-fold decrease in neutralizing antibody titers compared to the D614G strain and a 2.1- to 8.4-fold reduction in titers for the beta, gamma, and delta variants [139]. Certain mRNA-based vaccines have also been subjected to re-engineering efforts to improve the immunogenicity against emerging variants. For example, the bivalent mRNA-1273.214 was designed to contain the original mRNA-1273 and the corresponding RNA for the omicron BA.1 variant [140]. The bivalent vaccine elicited higher neutralizing antibody titers against omicron and also induced higher binding activity against the alpha, beta, gamma, and delta variants than the mRNA-1273 vaccine in a phase II/III study [140]. Booster vaccination with the updated mRNA XBB.1.5 vaccine induced 27-fold enhanced neutralizing antibody titers against the omicron XBB.1.5 and EG5.1 variants and also against other emerging viruses such as HV.1, HK.3, JD.1.1, and JN.1 [141]. Among saRNA-based vaccines, strong immune responses and protection of hamsters against D614G and alpha variant challenges were obtained for the LNP-nCoVsaRNA vaccine [142].

Vaccine hesitancy

Successful vaccination does not only rely on efficacy or effectiveness but also depends on how broad population coverage is reached by vaccination programs. Despite the success seen for elimination and restriction of widespread infectious diseases such as smallpox, polio, and measles, recent decline in vaccination rates has enhanced the risk of their re-emergence. For example, outbreaks of measles, rubella, poliomyelitis, and diphtheria are likely to return due to reduced vaccination of children in the US [143]. Moreover, recent attacks against polio vaccine campaigns and healthcare workers in Pakistan and Afghanistan have presented an increased risk of spread of disease in the local population [144]. Vaccine development has always been subjected to skepticism and hesitancy, which has reached new levels with the COVID-19 pandemic [145], at least partly due to the introduction of mRNA-based vaccines. The main concerns have been related to unfounded claims that mRNA technology is novel and has never been tested in animal models and human trials. However, publications from the 1990s clearly demonstrated appropriate and safe successful administration of mRNA in mouse muscle in vivo [146]. Unfortunately, the massive spread of misinformation, disinformation, and conspiracy theories, particularly through social media, has contributed to the negative attitude towards vaccines and has strengthened vaccine hesitancy.

In general, vaccine efficacy, effectiveness, and safety in eliminating adverse events are the key components to provide confidence and limit hesitancy among the general population. However, in the case of the COVID-19 pandemic, with an estimated 13.6 billion doses administered [147], it comes as no surprise that adverse events, even serious ones, have been registered. In any case, the adverse events and death rates in vaccinated individuals have been significantly lower compared to unvaccinated persons, therefore showing that the benefits outweigh the risks by a large margin.

In the context of hesitancy and COVID-19 vaccines, several surveys and systematic reviews have been conducted. In one study, vaccine acceptance ranged from 12% to 91.4% [148]. Unwillingness toward vaccinations and ethnicity could be established in Black/African American origin. Additionally, sex, age, race, education level, and income status strongly influence the approval level of COVID-19 vaccinations. Black/African Americans and pregnant and breastfeeding women were more hesitant to receive vaccines than males in general [148]. Based on a national online survey in China, vaccines were considered more favorable in individuals with a higher educational level, married people, people in good health, non-smokers, and persons responsive to precautionary hygiene such as hand washing, mask wearing, and social distancing [149]. Persons with a higher level of trust in medical doctors and a reduced confidence in conspiracy theories were more in favor of vaccinations. In a study on children aged 12–15 years, 42% showed no hesitancy at all to COVID-19 vaccines, 22% "a little hesitancy", 21% "some hesitancy" and 15% "strong hesitancy" [150]. Although no statistically significant differences were seen for age, gender, race, and parental education, a correlation between TV watching and hesitancy was established. In a meta-analysis of 35 studies, healthcare workers showed vaccine hesitancy from 4.3% to 72% [151]. Only 4.3% hesitancy was reported in China, in the US it was 8–18%, and in Europe from 7% to 32.5%, and in Africa, it was as high as 72% in Congo. Lower hesitancy levels were seen in male healthcare workers, elderly people, and doctoral degree holders. Those individuals who had been infected by SARS-CoV-2, directly cared for patients, and had experience with influenza vaccinations were more favorably opinionated towards vaccinations.

In a Norwegian study, subgroups of COVID-19 vaccine hesitancy were identified, including males, residents in rural areas, and parents with children younger than 18 years of age [152]. Those individuals who preferred to receive information from peers, social media, online forums, and blogs showed a higher degree of hesitancy. In an online survey, a correlation between conspiracy theories and vaccine hesitancy was identified [153]. It was also revealed that those who did not consider the COVID-19 pandemic dangerous and even denied the existence of SARS-CoV-2/COVID-19 were hesitant about being vaccinated. Overall, it is of utmost importance to have access to accurate information on COVID-19, vaccines, and vaccinations to be able to counteract the large extent of misinformation today [153]. Furthermore, a national survey in the US concluded that persons who considered COVID-19 vaccines unsafe knew less about SARS-CoV-2/COVID-19 and therefore were more likely to believe in myths and conspiracy theories [16]. Typically, they had a lower level of education, earned less, and lived in rural areas. A study in Ireland indicated that most of the general public underestimated vaccine effectiveness and had not absorbed the concept of vaccine waning [154].

Undoubtedly, vaccine hesitancy significantly contributes to public health risk. Therefore, it is necessary to understand the psychological factors behind the hesitancy to rectify the situation by addressing unclear issues through extensive sharing of accurate information. Open communication between scientists, clinicians, pharmaceutical companies, authorities, and the general public will convince everybody of the undisputed benefits of vaccinations compared to the risks of contracting COVID-19.

Conclusions

This review has provided examples of vaccine development against several infectious agents such as HIV, EBOV, HPV, influenza viruses, and SARS-CoV-2. Different types of vaccines have also been described. In the case of COVID-19, the urgent need for a vaccine against SARS-CoV-2 demanded a full-scale spectrum of alternative approaches. As it turned out, vaccines based on whole viruses, protein subunits, viral vectors, and nucleic acids provided protection against SARS-CoV-2 and substantially reduced hospitalization and severe cases of COVID-19. Moreover, several different types of viral vectors proved their efficacy and effectiveness, although adenovirus-based vectors seemed to be the preferred viral vectors used. On the other hand, vectors based on saRNA viruses have caught attention due to their potent expression and therefore the need of reduced doses and the possibility to choose between the administration of recombinant viral particles, RNA replicons or layered DNA replicons [155].

In comparison of the various vaccine platforms, clearly there is no universal superior system available. It is, however, useful to discuss how viral vectors fare to established vaccine platforms. For example, traditional whole-virus vaccines and adjuvanted quadrivalent influenza vaccines have proven highly successful although the vaccine production process is slow and possibilities to quickly adjust to new emerging strains are limited. In this context, viral vectors can be rapidly re-engineered and adjusted to novel needs. Moreover, adenovirus and saRNA virus vectors can be utilized for intranasal administration, which in the case of respiratory disease have proven advantageous [156, 157]. Another example is that although approved drugs against HPV using BEVS [35] and yeast cell [36] production are available, there are clinical trials in progress using vectors based on the SFV saRNA particles [40, 41]. The already approved HPV drugs are prophylactic, the current SFV-based approach also targets cancer patients with existing HPV lesions. In comparison to mRNA-based vaccines, the adenovirus-based vaccines have probably been slightly inferior, but the Ad26.COV2.S vaccine has proven highly efficient after a single immunization in contrast to the two doses required for mRNA-based vaccines. However, marketing authorization for the Ad26.COV2.S vaccine was withdrawn in the EU due to commercial reasons. Moreover, the FDA revoked the EUA for the Ad26.COV2.S vaccine because of its rare side effects such as thrombosis, but also due to the widespread availability of re-engineered mRNA-based vaccines. Likewise, the ChAdOx1 nCoV-19 has been withdrawn due to the development of updated vaccines targeting SARS-CoV-2 variants and due to some rare blood clotting events. However, for vaccines against Middle East Respiratory Syndrome (MERS), Nipah and Marburg viruses, the ChAdOx1 platform remains actively in use. The Sputnik V vaccine has not been formally withdrawn from the market, but production issues and low international demand has favored the use of Sputnik Light, a single dose of Ad26-S [158].

Obviously, with waning vaccine efficacy and effectiveness with time and the presence of emerging variants, booster vaccinations have become mandatory. In contrast to mRNA-based vaccines, no LNP formulations are required for the delivery of viral vectors. Moreover, viral vectors have proven efficient for intranasal administration, which is an attractive alternative delivery route, especially for respiratory viruses such as SARS-CoV-2. In the context of saRNA-based vaccines, although intranasal delivery of LNP-encapsulated saRNA expressing firefly luciferase (FLuc) was inferior to intramuscular administration to mice [159], the opposite was observed for SARS-CoV-2 vaccines in hamsters [160]. Therefore, it is important to explore different administration routes applying several vaccine platforms for achieving optimum delivery and immune responses.

Another aspect of importance is the type of immune and T-cell responses associated with vaccinations. Although some studies have indicated that mRNA-based vaccines show poor induction of mucosal immunity and T-cell responses, studies on saRNA-based vaccines have been proven efficient as described above [160]. Moreover, studies have demonstrated that saRNA vectors can efficiently elicit Th1 cell biased responses in rodents [109]. This is an important factor, which should be taken into consideration when next-generation vaccines are engineered.

Although it has been claimed that mRNA platforms allow a faster adaptation to emerging variants, re-engineering and large-scale GMP production of viral vectors is straightforward, and the safety levels are acceptable for second and third generation viral vectors. Related to the potential vaccine waning, a reduction in vaccine efficacy and effectiveness has been observed for emerging variants compared to the original SARS-CoV-2 strain. Booster vaccinations have to some extent enhanced the vaccine efficacy and effectiveness, but also re-engineering of existing vaccines to better address the mutational modifications in epitopes of the SARS-CoV-2 S protein has proven successful. However, other approaches such as the development of pan-vaccines targeting other areas of SARS-CoV-2 should further potentially improve vaccine efficacy and effectiveness.

Finally, regional and economical differences between industrial and developing countries should not be neglected in vaccine promotion and achievement of global success. Access to vaccines can be compromised by the lack of purchasing power but also because of logistic problems with vaccine transport, storage and administration. The first-generation mRNA-based vaccines were highly temperature sensitive and required

storage at –80°C, which triggered the development of lipid-free thermostable mRNA vaccines allowing storage for up to 6 months at 40°C [161]. Moreover, vaccine hesitancy has played a major role not only in developing countries but also among lower income populations in developed countries as described above.

Abbreviations

AAV: adeno-associated virus

Ab: antibody

Ad26: adenovirus serotype 26

Adj: adjuvant

ALVAC: canarypox virus

BEVS: baculovirus expression vector system

bnAbs: broadly neutralizing antibodies

CIN2+: cervical intraepithelial neoplasia grade 2+

CMA: conditional marketing authorization

COBRA: computationally optimized broadly reactive antigen

COVID-19: Coronavirus disease 2019

EBOV: Ebola virus

EMA: European Medicines Agency

EUA: emergency use authorization

FDA: Food and Drug Administration

GP: glycoprotein

GT: germline targeting

HA: hemagglutinin

HIV: human immunodeficiency virus

HPV: human papillomavirus

IVA: influenza virus A

IVB: influenza virus B

LAIV: live attenuated influenza virus

LION: lipid inorganic nanoparticle

LNP: lipid nanoparticle

mAbs: monoclonal antibodies

MV: measles virus

MVA: modified vaccinia Ankara

NA: neuraminidase

nAbs: neutralizing antibodies

NDV: Newcastle disease virus

NP: nucleoprotein

NPs: nanoparticles

PICV: Pichinde virus

PsVNA: pseudovirus-neutralizing antibody

RBD: receptor binding domain

S: spike

saRNA: self-amplifying RNA

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SFV: Semliki Forest virus

Th1: T-helper1

VE: vaccine effectiveness

VEE: Venezuelan equine encephalitis virus

VLPs: virus-like particles

VSV: vesicular stomatitis virus

WV: whole virus

ZEBOV: Zaire Ebola virus

Declarations

Author contributions

KL: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. The author read and approved the submitted version.

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The author declares that he has no conflicts of interest.

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References

1. Jenner's Breakthrough [Internet]. Philadelphia: College of Physicians of Philadelphia; c2026 [cited 2026 Apr 20]. Available from: https://historyofvaccines.org/history/edward-jenner-frs-frcpe/timeline/
2. Lundstrom K. COVID-19 Vaccines: Where Did We Stand at the End of 2023? Viruses. 2024;16:203. [DOI] [PubMed] [PMC]
3. Amanna IJ, Slifka MK. Successful Vaccines. Curr Top Microbiol Immunol. 2020;428:1–30. [DOI] [PubMed] [PMC]
4. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586:516–27. [DOI] [PubMed]
5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al.; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383:2603–15. [DOI] [PubMed] [PMC]
6. Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First Approval. Drugs. 2021;81:495–501. [DOI] [PubMed] [PMC]
7. FDA Approves First COVID-19 Vaccine [Internet]. [cited 2026 Apr 20]. Available from: http://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine
8. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al.; Oxford COVID Vaccine Trial Group. 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. [DOI] [PubMed] [PMC]
9. GOV.UK. Regulatory Approval of COVID-19 Vaccine AstraZeneca [Internet]. [cited 2026 Apr 20]. Available from: http://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca
10. Khobragade A, Bhate S, Ramaiah V, Deshpande S, Giri K, Phophle H, et al.; ZyCoV-D phase 3 Study Investigator Group. Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): the interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India. Lancet. 2022;399:1313–21. [DOI] [PubMed] [PMC]
11. Mallapaty S. India's DNA COVID vaccine is a world first - more are coming. Nature. 2021;597:161–2. [DOI] [PubMed]
12. Palacios R, Patiño EG, de Oliveira Piorelli R, Conde MTRP, Batista AP, Zeng G, et al. Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac - PROFISCOV: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21:853. [DOI] [PubMed] [PMC]
13. WHO validates Sinovac COVID-19 vaccine for emergency use and issues interim policy recommendations [Internet]. [cited 2026 Jan 9]. Available from: https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
14. Suah JL, Husin M, Tok PSK, Tng BH, Thevananthan T, Low EV, et al. Waning COVID-19 Vaccine Effectiveness for BNT162b2 and CoronaVac in Malaysia: An Observational Study. Int J Infect Dis. 2022;119:69–76. [DOI] [PubMed] [PMC]
15. Gupta RK. Will SARS-CoV-2 variants of concern affect the promise of vaccines? Nat Rev Immunol. 2021;21:340–1. [DOI] [PubMed] [PMC]
16. Kricorian K, Civen R, Equils O. COVID-19 vaccine hesitancy: misinformation and perceptions of vaccine safety. Hum Vaccin Immunother. 2022;18:1950504. [DOI] [PubMed] [PMC]
17. UNAIDS. Fast track: Ending the AIDS epidemic by 2030 [Internet]. c2026 [cited 2026 Apr 20]. Available from: https://www.unaids.org/en/resources/documents/2014/fast_track

18. Lee JH, Crotty S. HIV vaccinology: 2021 update. Semin Immunol. 2021;51:101470. [DOI] [PubMed] [PMC]
19. Haynes BF, Wiehe K, Borrow P, Saunders KO, Korber B, Wagh K, et al. Strategies for HIV-1 vaccines that induce broadly neutralizing antibodies. Nat Rev Immunol. 2023;23:142–58. [DOI] [PubMed] [PMC]
20. Stephenson KE, D'Couto HT, Barouch DH. New concepts in HIV-1 vaccine development. Curr Opin Immunol. 2016;41:39–46. [DOI] [PubMed] [PMC]
21. Laher F, Bekker L, Garrett N, Lazarus EM, Gray GE. Review of preventative HIV vaccine clinical trials in South Africa. Arch Virol. 2020;165:2439–52. [DOI] [PubMed] [PMC]
22. Shim I, Rogowski L, Venketaraman V. Progress and Recent Developments in HIV Vaccine Research. Vaccines (Basel). 2025;13:690. [DOI] [PubMed] [PMC]
23. Peters BS, Jaoko W, Vardas E, Panayotakopoulos G, Fast P, Schmidt C, et al. Studies of a prophylactic HIV-1 vaccine candidate based on modified vaccinia virus Ankara (MVA) with and without DNA priming: effects of dosage and route on safety and immunogenicity. Vaccine. 2007;25:2120–7. [DOI] [PubMed]
24. Wecker M, Gilbert P, Russell N, Hural J, Allen M, Pensiero M, et al. Phase I safety and immunogenicity evaluations of an alphavirus replicon HIV-1 subtype C gag vaccine in healthy HIV-1-uninfected adults. Clin Vaccine Immunol. 2012;19:1651–60. [DOI] [PubMed] [PMC]
25. Gray GE, Huang Y, Grunenberg N, Laher F, Roux S, Andersen-Nissen E, et al. Immune correlates of the Thai RV144 HIV vaccine regimen in South Africa. Sci Transl Med. 2019;11:eaax1880. [DOI] [PubMed] [PMC]
26. Mdluli T, Jian N, Slike B, Paquin-Proulx D, Donofrio G, Alrubayyi A, et al. RV144 HIV-1 vaccination impacts post-infection antibody responses. PLoS Pathog. 2020;16:e1009101. [DOI] [PubMed] [PMC]
27. Miller EP, Finkelstein MT, Erdman MC, Seth PC, Fera D. A Structural Update of Neutralizing Epitopes on the HIV Envelope, a Moving Target. Viruses. 2021;13:1774. [DOI] [PubMed] [PMC]
28. Steinhardt JJ, Guenaga J, Turner HL, McKee K, Louder MK, O'Dell S, et al. Rational design of a trispecific antibody targeting the HIV-1 Env with elevated anti-viral activity. Nat Commun. 2018;9:877. [DOI] [PubMed] [PMC]
29. Priddy FH, Lewis DJM, Gelderblom HC, Hassanin H, Streatfield C, LaBranche C, et al. Adeno-associated virus vectored immunoprophylaxis to prevent HIV in healthy adults: a phase 1 randomised controlled trial. Lancet HIV. 2019;6:e230–9. [DOI] [PubMed] [PMC]
30. Parks KR, Moodie Z, Allen MA, Yen C, Furch BD, MacPhee KJ, et al. Vaccination with mRNA-encoded membrane-anchored HIV envelope trimers elicited tier 2 neutralizing antibodies in a phase 1 clinical trial. Sci Transl Med. 2025;17:eady6831. [DOI] [PubMed] [PMC]
31. Jardine J, Julien J, Menis S, Ota T, Kalyuzhniy O, McGuire A, et al. Rational HIV immunogen design to target specific germline B cell receptors. Science. 2013;340:711–6. [DOI] [PubMed] [PMC]
32. Venkatesan P. Preliminary phase 1 results from an HIV vaccine candidate trial. Lancet Microbe. 2021;2:e95. [DOI] [PubMed]
33. International AIDS Vaccine Initiative. A Phase 1 Study to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core) [Internet]. [cited 2026 Apr 20]. Available from: http://www.clinicaltrials.gov/study/NCT05001373
34. Markowitz LE, Schiller JT. Human Papillomavirus Vaccines. J Infect Dis. 2021;224:S367–78. [DOI] [PubMed] [PMC]
35. Szarewski A. HPV vaccine: Cervarix. Expert Opin Biol Ther. 2010;10:477–87. [DOI] [PubMed]
36. McLemore MR. Gardasil: Introducing the new human papillomavirus vaccine. Clin J Oncol Nurs. 2006;10:559–60. [DOI] [PubMed]
37. Cuzick J. Gardasil 9 joins the fight against cervix cancer. Expert Rev Vaccines. 2015;14:1047–9. [DOI] [PubMed]

38. Lin R, Jin H, Fu X. Comparative efficacy of human papillomavirus vaccines: systematic review and network meta-analysis. Expert Rev Vaccines. 2023;22:1168–78. [DOI] [PubMed]
39. Daemen T, Riezebos-Brilman A, Bungener L, Regts J, Dontje B, Wilschut J. Eradication of established HPV16-transformed tumours after immunisation with recombinant Semliki Forest virus expressing a fusion protein of E6 and E7. Vaccine. 2003;21:1082–8. [DOI] [PubMed]
40. Komdeur FL, Singh A, van de Wall S, Meulenberg JJM, Boerma A, Hoogeboom BN, et al. First-in-Human Phase I Clinical Trial of an SFV-Based RNA Replicon Cancer Vaccine against HPV-Induced Cancers. Mol Ther. 2021;29:611–25. [DOI] [PubMed] [PMC]
41. Eerkens AL, Esajas MD, Brummel K, Vledder A, van Rooij N, Plat A, et al. Vvax001, a Therapeutic Vaccine, for Patients with HPV16-Positive High-grade Cervical Intraepithelial Neoplasia: A Phase II Trial. Clin Cancer Res. 2025;31:1016–26. [DOI] [PubMed]
42. Kuehn R, Ryan H, Okwaraeke KC, Gould S, Chaplin M, Riley M, et al. Vaccines for preventing Ebola virus disease. Cochrane Database Syst Rev. 2024;11:CD015828. [DOI] [PubMed] [PMC]
43. Pushko P, Bray M, Ludwig GV, Parker M, Schmaljohn A, Sanchez A, et al. Recombinant RNA replicons derived from attenuated Venezuelan equine encephalitis virus protect guinea pigs and mice from Ebola hemorrhagic fever virus. Vaccine. 2000;19:142–53. [DOI] [PubMed]
44. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015;386:857–66. [DOI] [PubMed]
45. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017;389:505–18. [DOI] [PubMed] [PMC]
46. Saphire EO. A Vaccine against Ebola Virus. Cell. 2020;181:6. [DOI] [PubMed]
47. Larivière Y, Matuvanga TZ, Osang'ir BI, Milolo S, Meta R, Kimbulu P, et al. Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccine regimen plus Ad26.ZEBOV booster at 1 year versus 2 years in health-care and front-line workers in the Democratic Republic of the Congo: secondary and exploratory outcomes of an open-label, randomised, phase 2 trial. Lancet Infect Dis. 2024;24:746–59. [DOI] [PubMed]
48. Zabdeno [Internet]. European Medicines Agency; c1995–2026 [cited 2026 Apr 20]. Available from: http://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno
49. Palese P. Making better influenza virus vaccines? Emerg Infect Dis. 2006;12:61–5. [DOI] [PubMed] [PMC]
50. Chen J, Wang J, Zhang J, Ly H. Advances in Development and Application of Influenza Vaccines. Front Immunol. 2021;12:711997. [DOI] [PubMed] [PMC]
51. Blanco-Lobo P, Nogales A, Rodríguez L, Martínez-Sobrido L. Novel Approaches for The Development of Live Attenuated Influenza Vaccines. Viruses. 2019;11:190. [DOI] [PubMed] [PMC]
52. Wang P, Zheng M, Lau S, Chen P, Mok BW, Liu S, et al. Generation of DelNS1 Influenza Viruses: a Strategy for Optimizing Live Attenuated Influenza Vaccines. mBio. 2019;10:e02180–19. [DOI] [PubMed] [PMC]
53. Poehling KA, Caspard H, Peters TR, Belongia EA, Congeni B, Gaglani M, et al. 2015-2016 Vaccine Effectiveness of Live Attenuated and Inactivated Influenza Vaccines in Children in the United States. Clin Infect Dis. 2018;66:665–72. [DOI] [PubMed] [PMC]
54. Ainai A, Suzuki T, Tamura S, Hasegawa H. Intranasal Administration of Whole Inactivated Influenza Virus Vaccine as a Promising Influenza Vaccine Candidate. Viral Immunol. 2017;30:451–62. [DOI] [PubMed]

55. Ainai A, van Riet E, Ito R, Ikeda K, Senchi K, Suzuki T, et al. Human immune responses elicited by an intranasal inactivated H5 influenza vaccine. Microbiol Immunol. 2020;64:313–25. [DOI] [PubMed] [PMC]
56. Taaffe J, Zhong S, Goldin S, Rawlings KS, Cowling BJ, Zhang W. An overview of influenza H5 vaccines. Lancet Respir Med. 2025;13:e20–1. [DOI] [PubMed]
57. Hu Y, Shao M, Hu Y, Liang Q, Jia N, Chu K, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine: a randomized, double-blind, controlled phase III clinical trial in children aged 6-35 months in China. Hum Vaccin Immunother. 2020;16:1691–8. [DOI] [PubMed] [PMC]
58. Li S, Li L, Ai X, Yang L, Bai Y, Wang Z, et al. A randomized, controlled, blinded study of the safety, immunogenicity and batch consistency of Aleph inactivated split influenza vaccine made in China in Chinese people. Hum Vaccin Immunother. 2014;10:557–65. [DOI] [PubMed] [PMC]
59. Influenza vaccine for 2020-2021. Med Lett Drugs Ther. 2020;62:145–50. [PubMed]
60. Soema PC, Kompier R, Amorij J, Kersten GFA. Current and next generation influenza vaccines: Formulation and production strategies. Eur J Pharm Biopharm. 2015;94:251–63. [DOI] [PubMed]
61. Glück R, Mischler R, Finkel B, Que JU, Scarpa B, Jr SJC. Immunogenicity of new virosome influenza vaccine in elderly people. Lancet. 1994;344:160–3. [DOI] [PubMed]
62. Bovier PA. Epaxal: a virosomal vaccine to prevent hepatitis A infection. Expert Rev Vaccines. 2008;7:1141–50. [DOI] [PubMed]
63. Herzog C, Hartmann K, Künzi V, Kürsteiner O, Mischler R, Lazar H, et al. Eleven years of Inflexal V-a virosomal adjuvanted influenza vaccine. Vaccine. 2009;27:4381–7. [DOI] [PubMed]
64. Künzi V, Klap JM, Seiberling MK, Herzog C, Hartmann K, Kürsteiner O, et al. Immunogenicity and safety of low dose virosomal adjuvanted influenza vaccine administered intradermally compared to intramuscular full dose administration. Vaccine. 2009;27:3561–7. [DOI] [PubMed]
65. Tutykhina I, Esmagambetov I, Bagaev A, Pichugin A, Lysenko A, Shcherbinin D, et al. Vaccination potential of B and T epitope-enriched NP and M2 against Influenza A viruses from different clades and hosts. PLoS One. 2018;13:e0191574. [DOI] [PubMed] [PMC]
66. Hassan AO, Amen O, Sayedahmed EE, Vemula SV, Amoah S, York I, et al. Adenovirus vector-based multi-epitope vaccine provides partial protection against H5, H7, and H9 avian influenza viruses. PLoS One. 2017;12:e0186244. [DOI] [PubMed] [PMC]
67. Dhanwani R, Ly H, Liang Y. Recombinant Tri-Segmented Pichinde Virus as a Novel Live Viral Vaccine Platform. Methods Mol Biol. 2017;1581:169–79. [DOI] [PubMed] [PMC]
68. Dhanwani R, Zhou Y, Huang Q, Verma V, Dileepan M, Ly H, et al. A Novel Live Pichinde Virus-Based Vaccine Vector Induces Enhanced Humoral and Cellular Immunity after a Booster Dose. J Virol. 2015;90:2551–60. [DOI] [PubMed] [PMC]
69. Nakaya T, Cros J, Park MS, Nakaya Y, Zheng H, Sagrera A, et al. Recombinant Newcastle disease virus as a vaccine vector. J Virol. 2001;75:11868–73. [DOI] [PubMed] [PMC]
70. Yang LPH. Recombinant trivalent influenza vaccine (flublok(®)): a review of its use in the prevention of seasonal influenza in adults. Drugs. 2013;73:1357–66. [DOI] [PubMed]
71. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. N Engl J Med. 2017;376:2427–36. [DOI] [PubMed]
72. Ito T, Kumagai T, Yamaji Y, Sawada A, Nakayama T. Recombinant Measles AIK-C Vaccine Strain Expressing Influenza HA Protein. Vaccines (Basel). 2020;8:149. [DOI] [PubMed] [PMC]
73. Furuyama W, Reynolds P, Haddock E, Meade-White K, Le MQ, Kawaoka Y, et al. A single dose of a vesicular stomatitis virus-based influenza vaccine confers rapid protection against H5 viruses from different clades. NPJ Vaccines. 2020;5:4. [DOI] [PubMed] [PMC]

74. Fleeton MN, Chen M, Berglund P, Rhodes G, Parker SE, Murphy M, et al. Self-replicative RNA vaccines elicit protection against influenza A virus, respiratory syncytial virus, and a tickborne encephalitis virus. J Infect Dis. 2001;183:1395–8. [DOI] [PubMed]
75. A Phase 1/2 Clinical Trial of an Alphavirus Replicon Vaccine for Influenza [Internet]. Blue Ash: Aprecia Pharmaceuticals, LLC.; c2018 [cited 2026 Apr 20]. Available from: http://www.clinicaltrials.gov/study/NCT00440362?tab=researcher
76. Uno N, Ross TM. Multivalent next generation influenza virus vaccines protect against seasonal and pre-pandemic viruses. Sci Rep. 2024;14:1440. [DOI] [PubMed] [PMC]
77. Hauguel T, Sharma A, Mastrocola E, Lowry S, Maddur MS, Hu CH, et al. Preclinical immunogenicity and safety of hemagglutinin-encoding modRNA influenza vaccines. NPJ Vaccines. 2024;9:183. [DOI] [PubMed] [PMC]
78. Branche A, Mulligan MJ, Maniar A, Puente O, Oladipupo I, Crowther G, et al. A Phase 1/2 Randomized Study to Evaluate the Safety, Tolerability, and Immunogenicity of Nucleoside-Modified Messenger RNA Influenza Vaccines in Healthy Adults. Vaccines (Basel). 2025;13:383. [DOI] [PubMed] [PMC]
79. Fitz-Patrick D, McVinnie DS, Jackson LA, Crowther G, Geevarughese A, Cannon KD, et al.; Pfizer C4781004 Trial Investigators. Efficacy, Immunogenicity, and Safety of Modified mRNA Influenza Vaccine. N Engl J Med. 2025;393:2001–11. [DOI] [PubMed]
80. Kaabi NA, Zhang Y, Xia S, Yang Y, Qahtani MMA, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021;326:35–45. [DOI] [PubMed] [PMC]
81. Sinovac's coronavirus vaccine candidate approved for emergency use in China-source [Internet]. Reuters; c2026 [cited 2026 Apr 20]. Available from: https://www.reuters.com/article/idUSKBN25O0Z0/
82. Taylor A. WHO grants emergency use authorization for Chinese-made Sinopharm coronavirus vaccine [Internet]. The Washington Post; c1996–2026 [cited 2026 Apr 20]. Available from: https://www.washingtonpost.com/world/2021/05/07/who-sinopharm-emergency-use/
83. Li L, Honda-Okubo Y, Baldwin J, Bowen R, Bielefeldt-Ohmann H, Petrovsky N. Covax-19/Spikogen® vaccine based on recombinant spike protein extracellular domain with Advax-CpG55.2 adjuvant provides single dose protection against SARS-CoV-2 infection in hamsters. Vaccine. 2022;40:3182–92. [DOI] [PubMed] [PMC]
84. Tabarsi P, Anjidani N, Shahpari R, Mardani M, Sabzvari A, Yazdani B, et al. Safety and immunogenicity of SpikoGen®, an Advax-CpG55.2-adjuvanted SARS-CoV-2 spike protein vaccine: a phase 2 randomized placebo-controlled trial in both seropositive and seronegative populations. Clin Microbiol Infect. 2022;28:1263–71. [DOI] [PubMed] [PMC]
85. Tabarsi P, Anjidani N, Shahpari R, Mardani M, Sabzvari A, Yazdani B, et al. Evaluating the efficacy and safety of SpikoGen®, an Advax-CpG55.2-adjuvanted severe acute respiratory syndrome coronavirus 2 spike protein vaccine: a phase 3 randomized placebo-controlled trial. Clin Microbiol Infect. 2023;29:215–20. [DOI] [PubMed] [PMC]
86. Tian J, Patel N, Haupt R, Zhou H, Weston S, Hammond H, et al. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice. Nat Commun. 2021;12:372. [DOI] [PubMed] [PMC]
87. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. N Engl J Med. 2020;383:2320–32. [DOI] [PubMed] [PMC]
88. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of the NVX-CoV2373 Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial. Clin Infect Dis. 2023;76:398–407. [DOI] [PubMed] [PMC]

89. Parums DV. Editorial: First Approval of the Protein-Based Adjuvanted Nuvaxovid (NVX-CoV2373) Novavax Vaccine for SARS-CoV-2 Could Increase Vaccine Uptake and Provide Immune Protection from Viral Variants. Med Sci Monit. 2022;28:e936523. [DOI] [PubMed] [PMC]
90. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020;586: 578–82. [DOI] [PubMed] [PMC]
91. China approves two more domestic COVID-19 vaccines for public use [Internet]. Reuters; c2026 [cited 2026 Apr 20]. Available from: https://www.reuters.com/article/idUSKBN2AP1V8/
92. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al.; ENSEMBLE Study Group. Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S. N Engl J Med. 2022;386:847–60. [DOI] [PubMed] [PMC]
93. Emergency use authorization (EUA) of the janssen covid-19 vaccine to prevent coronavirus disease 2019 (COVID-19) [Internet]. Janssen Pharmaceutical Companies; c2021 [cited 2026 Apr 20]. Available from: http://www.fda.gov/media/146304/download
94. Balakrishnan VS. The arrival of Sputnik V. Lancet Infect Dis. 2020;20:1128. [DOI] [PubMed] [PMC]
95. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al.; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021;397:671–81. [DOI] [PubMed] [PMC]
96. Callaway E. Russia's fast-track coronavirus vaccine draws outrage over safety. Nature. 2020;584: 334–5. [DOI] [PubMed]
97. Case JB, Rothlauf PW, Chen RE, Kafai NM, Fox JM, Smith BK, et al. Replication-Competent Vesicular Stomatitis Virus Vaccine Vector Protects against SARS-CoV-2-Mediated Pathogenesis in Mice. Cell Host Microbe. 2020;28:465–74.e4. [DOI] [PubMed] [PMC]
98. Robbins JA, Tait D, Huang Q, Dubey S, Crumley T, Cote J, et al. Safety and immunogenicity of intramuscular, single-dose V590 (rVSV-SARS-CoV-2 Vaccine) in healthy adults: Results from a phase 1 randomised, double-blind, placebo-controlled, dose-ranging trial. EBioMedicine. 2022;82:104138. [DOI] [PubMed] [PMC]
99. Yahalom-Ronen Y, Tamir H, Melamed S, Politi B, Shifman O, Achdout H, et al. A single dose of recombinant VSV-ΔG-spike vaccine provides protection against SARS-CoV-2 challenge. Nat Commun. 2020;11:6402. [DOI] [PubMed] [PMC]
100. Yahalom-Ronen Y, Erez N, Fisher M, Tamir H, Politi B, Achdout H, et al. Neutralization of SARS-CoV-2 Variants by rVSV-ΔG-Spike-Elicited Human Sera. Vaccines (Basel). 2022;10:291. [DOI] [PubMed] [PMC]
101. Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun. 2020;11:2601. [DOI] [PubMed] [PMC]
102. Yao A, Jia S, Cheng X, Pan H, Wang Z, Yang H, et al. Immunogenicity and safety of a booster dose of the COVID-19 DNA vaccine in healthy adults aged 18 years and above: a single-center, randomized, observer-blind, placebo-controlled phase 2 trial. BMC Infect Dis. 2025;25:750. [DOI] [PubMed] [PMC]
103. Dey A, Rajanathan TMC, Chandra H, Pericherla HPR, Kumar S, Choonia HS, et al. Immunogenic potential of DNA vaccine candidate, ZyCoV-D against SARS-CoV-2 in animal models. Vaccine. 2021; 39:4108–16. [DOI] [PubMed] [PMC]
104. Momin T, Kansagra K, Patel H, Sharma S, Sharma B, Patel J, et al. Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India. EClinicalMedicine. 2021;38:101020. [DOI] [PubMed] [PMC]
105. Vogel AB, Kanevsky I, Che Y, Swanson KA, Muik A, Vormehr M, et al. BNT162b vaccines protect rhesus macaques from SARS-CoV-2. Nature. 2021;592:283–9. [DOI] [PubMed]

106. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med. 2020;383:1544–55. [DOI] [PubMed] [PMC]
107. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al.; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403–16. [DOI] [PubMed] [PMC]
108. FDA Takes Additional Action in Fight against COVID-19 by Issuing Emergency Use Authorization for Second COVID-19 Vaccine [Internet]. Cision US Inc.; c2026 [cited 2026 Apr 20]. Available from: https://www.prnewswire.com/news-releases/fda-takes-additional-action-in-fight-against-covid-19-by-issuing-emergency-use-authorization-for-second-covid-19-vaccine-301196303.html
109. McKay PF, Hu K, Blakney AK, Samnuan K, Brown JC, Penn R, et al. Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. Nat Commun. 2020;11:3523. [DOI] [PubMed] [PMC]
110. Pollock KM, Cheeseman HM, Szubert AJ, Libri V, Boffito M, Owen D, et al.; COVAC1 study Group. Safety and immunogenicity of a self-amplifying RNA vaccine against COVID-19: COVAC1, a phase I, dose-ranging trial. EClinicalMedicine. 2022;44:101262. [DOI] [PubMed] [PMC]
111. Szubert AJ, Pollock KM, Cheeseman HM, Alagaratnam J, Bern H, Bird O, et al. COVAC1 phase 2a expanded safety and immunogenicity study of a self-amplifying RNA vaccine against SARS-CoV-2. EClinicalMedicine. 2023;56:101823. [DOI] [PubMed] [PMC]
112. Important Announcement [Internet]. William Reed Ltd.; c2025 [cited 2026 Apr 20]. Available from: http://www.biopharma-reporter.com
113. GEMCOVAC® mRNA Vaccines for COVID-19 [Internet]. Gennova Biopharmaceuticals Limited; c2006–2025 [cited 2026 Apr 20]. Available from: https://gennova.bio/gemcovac-19-2/
114. HDT bio receives emergency use approval for covid-19 vaccine in India [Internet]. GlobalData Plc.; c2026 [cited 2026 Apr 21]. Available from: https://www.pharmaceutical-technology.com/news/hdt-bio-vaccine-india-approval/
115. Ray GT, Lewis N, Klein NP, Daley MF, Wang SV, Kulldorff M, et al. Intraseason Waning of Influenza Vaccine Effectiveness. Clin Infect Dis. 2019;68:1623–30. [DOI] [PubMed] [PMC]
116. Tokars JI, Patel MM, Foppa IM, Reed C, Fry AM, Ferdinands JM. Waning of Measured Influenza Vaccine Effectiveness Over Time: The Potential Contribution of Leaky Vaccine Effect. Clin Infect Dis. 2020;71:e633–41. [DOI] [PubMed] [PMC]
117. Lewnard JA, Grad YH. Vaccine waning and mumps re-emergence in the United States. Sci Transl Med. 2018;10:eaao5945. [DOI] [PubMed] [PMC]
118. Nikas A, Ahmed H, Zarnitsyna VI. Estimating Waning of Vaccine Effectiveness: A Simulation Study. Clin Infect Dis. 2023;76:479–86. [DOI] [PubMed] [PMC]
119. Lim SY, Kim JY, Jung J, Yun S, Kim S. Waning of humoral immunity depending on the types of COVID-19 vaccine. Infect Dis (Lond). 2023;55:216–20. [DOI] [PubMed]
120. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet. 2022;399:924–44. [DOI] [PubMed] [PMC]
121. DeDiego ML, Chiem K, Topham DJ. Directed selection of amino acid changes in the influenza hemagglutinin and neuraminidase affecting protein antigenicity. Vaccine. 2018;36:6383–92. [DOI] [PubMed]
122. Papageorgiou AC, Mohsin I. The SARS-CoV-2 Spike Glycoprotein as a Drug and Vaccine Target: Structural Insights into Its Complexes with ACE2 and Antibodies. Cells. 2020;9:2343. [DOI] [PubMed] [PMC]
123. Choi JY, Smith DM. SARS-CoV-2 Variants of Concern. Yonsei Med J. 2021;62:961–8. [DOI] [PubMed] [PMC]

124. Taucher C, Lazarus R, Dellago H, Maurer G, Weisova P, Corbic-Ramljak I, et al.; Valneva Phase 3 Booster Trial Group. Safety and immunogenicity against ancestral, Delta and Omicron virus variants following a booster dose of an inactivated whole-virus COVID-19 vaccine (VLA2001): Interim analysis of an open-label extension of the randomized, controlled, phase 3 COV-COMPARE trial. J Infect. 2023;87:242–54. [DOI] [PubMed]
125. Nawaz S, Janiad S, Fatima A, Saleem M, Fatima U, Ali A. Rapidly Evolving SARS-CoV-2: A Brief Review Regarding the Variants and their Effects on Vaccine Efficacies. Infect Disord Drug Targets. 2024;24: 58–66. [DOI] [PubMed]
126. de Bruyn G, Wang J, Purvis A, Ruiz MS, Adhikarla H, Alvi S, et al. Safety and immunogenicity of a variant-adapted SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant as a booster in adults primed with authorized vaccines: a phase 3, parallel-group study. EClinicalMedicine. 2023;62: 102109. [DOI] [PubMed] [PMC]
127. Tran TNM, May BP, Ung TT, Nguyen MK, Nguyen TTT, Dinh VL, et al. Preclinical Immune Response and Safety Evaluation of the Protein Subunit Vaccine Nanocovax for COVID-19. Front Immunol. 2021;12:766112. [DOI] [PubMed] [PMC]
128. Lyke KE, Atmar RL, Islas CD, Posavad CM, Deming ME, Branche AR, et al.; DMID 21-0012 Study Group. Immunogenicity of NVX-CoV2373 heterologous boost against SARS-CoV-2 variants. NPJ Vaccines. 2023;8:98. [DOI] [PubMed] [PMC]
129. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al.; Wits-VIDA COVID Group. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384: 1885–98. [DOI] [PubMed] [PMC]
130. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, et al. Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. N Engl J Med. 2022;386:744–56. [DOI] [PubMed] [PMC]
131. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021;596:268–72. [DOI] [PubMed] [PMC]
132. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Durability of the Single-Dose Ad26.COV2.S Vaccine in the Prevention of COVID-19 Infections and Hospitalizations in the US Before and During the Delta Variant Surge. JAMA Netw Open. 2022;5:e222959. [DOI] [PubMed] [PMC]
133. Andrade VM, Christensen-Quick A, Agnes J, Tur J, Reed C, Kalia R, et al. INO-4800 DNA vaccine induces neutralizing antibodies and T cell activity against global SARS-CoV-2 variants. NPJ Vaccines. 2021;6:121. [DOI] [PubMed] [PMC]
134. Walters JN, Schouest B, Patel A, Reuschel EL, Schultheis K, Parzych E, et al. Prime-boost vaccination regimens with INO-4800 and INO-4802 augment and broaden immune responses against SARS-CoV-2 in nonhuman primates. Vaccine. 2022;40:2960–9. [DOI] [PubMed] [PMC]
135. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Guevara M, Fernández-Huerta M, Burgui C, et al.; Investigators; other members of the Working Group for the Study of COVID-19 in Navarre. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. Euro Surveill. 2021;26:2100894. [DOI] [PubMed] [PMC]
136. Sheikh A, Robertson C, Taylor B. BNT162b2 and ChAdOx1 nCoV-19 Vaccine Effectiveness against Death from the Delta Variant. N Engl J Med. 2021;385:2195–7. [PMID: 34670038 PMCID: PMC8552534 DOI: 10.1056/NEJMc2113864].
137. Regev-Yochay G, Gonen T, Gilboa M, Mandelboim M, Indenbaum V, Amit S, et al. Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron. N Engl J Med. 2022;386:1377–80. [DOI] [PubMed] [PMC]

138. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, AlMukdad S, Yassine HM, Al-Khatib HA, et al. Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. N Engl J Med. 2022;386: 1804–16. [DOI] [PubMed] [PMC]
139. Choi A, Koch M, Wu K, Dixon G, Oestreicher J, Legault H, et al. Serum Neutralizing Activity of mRNA-1273 against SARS-CoV-2 Variants. J Virol. 2021;95:e0131321. [DOI] [PubMed] [PMC]
140. Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, et al. A Bivalent Omicron-Containing Booster Vaccine against Covid-19. N Engl J Med. 2022;387:1279–91. [DOI] [PubMed] [PMC]
141. Wang Q, Guo Y, Bowen A, Mellis IA, Valdez R, Gherasim C, et al. XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against XBB subvariants and JN.1. Cell Host Microbe. 2024;32:315–21.e3. [DOI] [PubMed] [PMC]
142. Frise R, Baillon L, Zhou J, Kugathasan R, Peacock TP, Brown JC, et al. A self-amplifying RNA vaccine protects against SARS-CoV-2 (D614G) and Alpha variant of concern (B.1.1.7) in a transmission-challenge hamster model. Vaccine. 2022;40:2848–55. [DOI] [PubMed] [PMC]
143. Kiang MV, Bubar KM, Maldonado Y, Hotez PJ, Lo NC. Modeling Reemergence of Vaccine-Eliminated Infectious Diseases Under Declining Vaccination in the US. JAMA. 2025;333:2176–87. [DOI] [PubMed] [PMC]
144. Faizan A, Rehman T, Mughal S. Re-emergence of polio in Pakistan: Can the nation achieve the WPV1 eradication goal? Health Sci Rep. 2024;7:e1862. [DOI] [PubMed] [PMC]
145. Hromić-Jahjefendić A, Barh D, Uversky V, Aljabali AA, Tambuwala MM, Alzahrani KJ, et al. Can COVID-19 Vaccines Induce Premature Non-Communicable Diseases: Where Are We Heading to? Vaccines (Basel). 2023;11:208. [DOI] [PubMed] [PMC]
146. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. Science. 1990;247:1465–8. [DOI] [PubMed]
147. COVID-19 vaccination, World [Internet]. WHO; c2024 [cited 2026 Apr 20]. Available from: https://data.who.int/dashboards/covid19/vaccines
148. Yasmin F, Najeeb H, Moeed A, Naeem U, Asghar MS, Chughtai NU, et al. COVID-19 Vaccine Hesitancy in the United States: A Systematic Review. Front Public Health. 2021;9:770985. [DOI] [PubMed] [PMC]
149. Wu J, Li Q, Tarimo CS, Wang M, Gu J, Wei W, et al. COVID-19 Vaccine Hesitancy Among Chinese Population: A Large-Scale National Study. Front Immunol. 2021;12:781161. [DOI] [PubMed] [PMC]
150. Willis DE, Presley J, Williams M, Zaller N, McElfish PA. COVID-19 vaccine hesitancy among youth. Hum Vaccin Immunother. 2021;17:5013–5. [DOI] [PubMed] [PMC]
151. Biswas N, Mustapha T, Khubchandani J, Price JH. The Nature and Extent of COVID-19 Vaccination Hesitancy in Healthcare Workers. J Community Health. 2021;46:1244–51. [DOI] [PubMed] [PMC]
152. Ebrahimi OV, Johnson MS, Ebling S, Amundsen OM, Halsøy Ø, Hoffart A, et al. Risk, Trust, and Flawed Assumptions: Vaccine Hesitancy During the COVID-19 Pandemic. Front Public Health. 2021;9: 700213. [DOI] [PubMed] [PMC]
153. Storey D. COVID-19 Vaccine Hesitancy. Glob Health Sci Pract. 2022;10:e2200043. [DOI] [PubMed] [PMC]
154. Lunn PD, Timmons S. Public misperceptions of COVID-19 vaccine effectiveness and waning: experimental evidence from Ireland. Public Health. 2023;214:81–4. [DOI] [PubMed] [PMC]
155. Lundstrom K. Self-Replicating Alphaviruses: From Pathogens to Therapeutic Agents. Viruses. 2024; 16:1762. [DOI] [PubMed] [PMC]
156. Yan S, Luo Y, Zhan N, Xu H, Yao Y, Liu X, et al. Intranasal delivery of a recombinant adenovirus vaccine encoding the PEDV COE elicits potent mucosal and systemic antibody responses in mice. Microbiol Spectr. 2024;12:e0069224. [DOI] [PubMed] [PMC]
157. Jung HE, Ku KB, Kang BH, Park JH, Kim HC, Kim K, et al. Intranasal delivery of an adenovirus-vector vaccine co-expressing a modified spike protein and a genetic adjuvant confers lasting mucosal immunity against SARS-CoV-2. Antiviral Res. 2023;216:105656. [DOI] [PubMed] [PMC]

158. Komissarov AA, Dolzhikova IV, Efimov GA, Logunov DY, Mityaeva O, Molodtsov IA, et al. Boosting of the SARS-CoV-2-Specific Immune Response after Vaccination with Single-Dose Sputnik Light Vaccine. J Immunol. 2022;208:1139–45. [DOI] [PubMed] [PMC]
159. Bathula NV, Friesen JJ, Casmil IC, Wayne CJ, Liao S, Soriano SKV, et al. Delivery vehicle and route of administration influences self-amplifying RNA biodistribution, expression kinetics, and reactogenicity. J Control Release. 2024;374:28–38. [DOI] [PubMed]
160. Jennewein MF, Schultz MD, Beaver S, Battisti P, Bakken J, Hanson D, et al. Intranasal replicon SARS-CoV-2 vaccine produces protective respiratory and systemic immunity and prevents viral transmission. Mol Ther. 2025;33:3286–306. [DOI] [PubMed] [PMC]
161. Coleman HJ, Rauch A, Langsfeld E, Anderson K, Parlikar U, Funke HH, et al. Lipid-free, thermostable mRNA vaccines prepared using atomic layer deposit ion. J Pharm Sci. 2026;115:104066. [DOI] [PubMed] [PMC]