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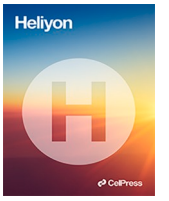

Review article

Viral vector- and virus-like particle-based vaccines against infectious diseases: A minireview

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A B S T R A C T

To overcome the limitations of conventional vaccines, new platforms for vaccine design have emerged such as those based on viral vectors and virus-like particles (VLPs). Viral vector vaccines are highly efficient and the onset of protection is quick. Many recombinant vaccine candidates for humans are based on viruses belonging to different families such as *Adenoviridae*, *Retroviridae*, *Paramyxoviridae*, *Rhabdoviridae*, and *Parvoviridae*. Also, the first viral vector vaccine licensed for human vaccination was the Japanese encephalitis virus vaccine. Since then, several viral vectors have been approved for vaccination against the viruses of Lassa fever, Ebola, hepatitis B, hepatitis E, SARS-CoV-2, and malaria. VLPs are nanoparticles that mimic viral particles formed from the self-assembly of structural proteins and VLP-based vaccines against hepatitis B and E viruses, human papillomavirus, and malaria have been commercialized. As evidenced by the accelerated production of vaccines against COVID-19, these new approaches are important tools for vaccinology and for generating rapid responses against pathogens and emerging pandemic threats.

1. Introduction

The era of vaccinology began in 1789 when Edward Jenner developed the first vaccination against smallpox. Since then, vaccines have prevented millions of deaths and, in 1978, even led to the eradication of this disease [1–3]. In the 19th century, Pasteur pioneered the development of vaccines based on the inactivation or attenuation of pathogens [2]. In the second half of the 20th century, the use of cell cultures to grow viruses facilitated the development of several inactivated and attenuated vaccines [1]. For a review of the history of vaccination, see Refs. [4,5].

Conventional vaccines developed before the advent of molecular biology toward the end of the 20th century consisted of inactivated or attenuated pathogens, toxoids, protein-based vaccines, or bacterial polysaccharides. Consequently, their use has reduced the impact of diseases such as polio, measles, tetanus, and diphtheria.

Nevertheless, despite decades of intensive research, effective vaccines have yet to be developed against certain human pathogens that, for example, exhibit high degrees of genetic variability (e.g., human immunodeficiency virus [HIV] and hepatitis C virus), lead to persistent or latent infection (e.g., HIV, hepatitis C virus, herpes simplex virus, Epstein-Barr virus), or fail to induce sterilizing immunity [6–10]. Moreover, traditional vaccines present several drawbacks such as safety concerns, which include the risk of reversion to virulence of live attenuated viruses, the possibility of contamination with live organisms, and risks to people with a weakened immune system. Also, vaccine production is expensive and time-consuming and requires a higher level of biosafety and specialized

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laboratories.

In recent decades, new promising vaccine platforms have emerged that are supported by advances in genetic engineering, molecular and cellular immunology, structural biology, bioinformatics, computational biology, nanotechnology, and synthetic biology, which is the case of recombinant viral vectors, virus-like particles (VLPs), mRNA, synthetic DNA, and bacterial vector vaccines. Moreover, new technologies for vaccine design are important tools in vaccinology for overcoming the limitations of traditional technology and facilitating rapid and efficient responses against new threats such as emerging pathogens and pandemic outbreaks. In this review, we aim to summarize the latest advances in virus engineering that have led to the development of safe and effective vaccines against pathogens causing current epidemics, such as influenza, Ebola, AIDS, and COVID-19, with a particular focus on viral vector- and VLP-based vaccine platforms.

2. Viral vector-based vaccines

Recombinant viruses are genetically modified and designed to be used as vaccines against infectious agents and in anti-cancer and gene therapies. Specifically, the use of viral vectors for gene therapy began in the 1990s [11]. From this point on, progress in genetic engineering, recombinant DNA technology, and the development of reverse genetic techniques to rescue recombinant viruses has facilitated the development of vector-based vaccine platforms. Viral vectors are built by inserting foreign antigens or transgenes, such as immunogens of interest, through recombinant DNA engineering into viral genetic material. Additionally, viral vectors are specifically modified to eradicate their intrinsic pathogenic properties. The newly constructed viral vector is then employed to deliver the antigen gene to the host, where it is transiently expressed at high levels to elicit robust immunity. Additionally, multivalent or multipathogen vaccines are constructed to express various transgenes simultaneously from the same or different pathogens [12]. Moreover, in passive immunization, the recombinant virus carries an antibody transgene [6,13–15].

To date, two main types of viral vectors have been designed: replicating and replication-deficient vectors [16–18]. Replicating vectors amplify the transgene and produce infectious progeny, whereas non-replicating vectors deliver a single copy of the transgene without replication which increases its safety profile. Replicating vectors generate a strong immunological response by mimicking natural infection. Replication-deficient vectors, expressing the immunogen under the control of an exogenous promoter, generate a weaker vaccine response and may require the use of an adjuvant [17]. Replicating vectors include adenovirus, retrovirus, rhabdovirus, and paramyxovirus vectors while replication-deficient vectors include adenovirus, retrovirus, and adeno-associated virus vectors (Table 2). Single-cycle viral vectors are also available which, with a single round of replication, increase antigen expression and avoid the formation of viral progeny. Single-cycle vectors have been developed from adenovirus and rhabdovirus [19–21]. Viral vector vaccines are usually extremely effective and offer rapid protection by inducing a strong humoral and cellular immune response, including the production of interferons and inflammatory cytokines [22–24]. The use of additional adjuvants is usually not necessary, which simplifies the vaccine composition and formulation process. Table 1 summarizes the main advantages and drawbacks of viral vector-based vaccines. For a review of immune response to vectored vaccines see Ref. [25].

Many viral vector-based vaccines have been approved for veterinary use such as canine distemper virus, feline leukemia virus, rabies virus, Newcastle disease virus (NDV), infectious bursal disease virus, and Marek disease [18,49]. For example, NDV-based influenza vaccines protect chickens from highly pathogenic avian influenza and are used as veterinary vaccines in Mexico and China [50,51]. The vaccinia virus was the first to be developed as a vaccine vector against hepatitis B [52]. In 2010, the first viral vector vaccine ChimeriVax-JE (Imojev) against the flavivirus Japanese encephalitis virus was licensed for use in humans [23].

Table 1
Advantages and disadvantages of viral vector vaccines.

Advantages	Disadvantages
Viral genomes are easy to manipulate	Possible preexisting immunity against the vector
	Potential risks derived from the integration into the host genome
	Potential recombination or reversion events that may generate virulent phenotypes
High yield of production of virus stocks	
High expression of transgenes	
Specific delivery of the immunogene to target cells	
Rapid humoral and cellular immune response	
No need for exogenous adjuvants.	
Less time- consuming/Accelerate production	
Less cost- consuming	
Facilitates a rapid response to newly emerging pathogens	
Facilitates re-engineering of new viral vectors	
Versatility	

Table 2
Main types of viral and VLP vectors for vaccine development reviewed in this paper.

Vector	Examples	Development	Vector genome form	Insert capacity (kb)	Immune response	Advantages	Disadvantages	References
Adenovirus	Human adenoviruses: Ad5, Ad2, Ad6, Ad36, Ad35 Chimpanzee adenoviruses: ChadOx1, AdC7, AdC68 Bovine adenoviruses: BAdV-3 Porcine adenoviruses: PAV-3	Replication-competent Replication-defective Single cycle	Episomal	8–37	Humoral and cellular	Great immunogenicity High levels of transgene transduction Broad cell tropism Several serotypes available Infection of dividing and non-dividing cells Lack of integration into the host genome Easy to manipulate Easy to produce Mucosal vaccination	High seroprevalence (especially against Ad5) Immunogenicity of the vector	[20,24, 26–29,30]
Retrovirus	HIV-1	Replication-defective Integrase- defective	Chromosomal integration	~8 (3–4 optimal)	Humoral and cellular	Optimal transduction of dendritic cells Efficient stimulation of T and B lymphocytes Large size of the transgene High and durable transgene expression Infection of dividing and non-dividing cells Low genotoxicity Low anti-vector immunity Candidates for mucosal vaccination	Oncogenesis ability (by integration in the host genome) Relatively high production cots	[31,32,33, 34]
AAV	AAV 2, 3, 5, 6, 8, 9	Replication-defective	Episomal (predominat) Integration into chromosome 9	~5	Humoral and cellular	Infection of dividing and non-dividing cells Lack of pathogenicity Broad tropism Low immunogenicity Long-term transgene expression Several serotypes available Easy to produce	Small size of the transgene Preexisting immunity Low transduction efficiency Immune response against the vector	[35–38]
Rhabdovirus	Rabies VSV	Replication-competent Replication-defective Single cycle	Cytosomal	~6	Humoral and cellular	Large size of the transgene (up to 6 kb) Easy manipulation by reverse genetics Possible design of multivalent vaccines Replication strictly in the cytoplasm Lack of integration into the genome Low preexisting immunity High titers of replication	Biosafety concerns	[21,39,40]

(*continued on next page*)

Table 2 (*continued*)

Vector	Examples	Development	Vector genome form	Insert capacity (kb)	Immune response	Advantages	Disadvantages	References
Paramyxovirus	MV NDV HPIV3	Replication competent Replication-defective	Cytosomal	3–6	Humoral, cellular, and mucosal	Easy manipulation by reverse genetics Replication strictly in the cytoplasm Lack of integration into the genome Stable expression Absence of preexisting immunity (NDV) Low-cost manufacturing Large-scale production (egg-based manufacturing, NDV)	Preexisting immunity (MV) Moderate size of the transgene (up to 6 kb)	[41,42,43]
VLPs	HPV VLPs HEV VLPs HBV VLPs IAV VLPs	Replication incompetent Ordered repetitive presentation of the epitopes	Absence of viral genome	–	Humoral and cellular response	Lower doses of antigen are needed Strong immunogenicity Versatility Safety		[44,45,46,47,48]

Abbreviations: Ad, adenovirus; ChAd, Chimpanzee adenovirus; HBV, hepatitis B virus; HEV, hepatitis E virus; HIV-1, Human immunodeficiency virus-1; HPIV3, Human parainfluenza virus-3; HPV, human papillomavirus; IAV, Influenza A virus; MV, Measles virus; NDV, Newcastle disease virus; VLPs, Virus-like-particles; VSV, Vesicular Stomatitis Virus.

ChimeriVax-JE is a live attenuated vaccine constructed using strain 17D of the yellow fever flavivirus by replacing the sequences encoding the pre-membrane and envelope proteins with the corresponding sequences from the Japanese encephalitis virus [53]. This vector is commercialized in Australia and Asia [54] and a single dose elicits a rapid immune response with a good safety profile [55,56].

Although at present only a few viral vector vaccines have been approved for their use in humans (Table 3), the widespread use of adenoviral vector vaccines against SARS-CoV-2 has proven to be safe. Consequently, numerous clinical trials using recombinant viral vector vaccines are currently being conducted. For a review of the viral-vectored vaccine clinical trials that have been conducted in Europe, see Ref. [57].

Many human recombinant vaccine candidates are based on viruses belonging to the families *Adenoviridae, Retroviridae, Poxviridae,*

Table 3
Examples of viral and VLP vectors approved or in advanced clinical trials for human vaccination.

Target pathogen or disease	Vaccine	Vector	Immunogen	Status	References
Ebola	rVSV-ZEBOV (Ervebo)	VSV	GP glycoprotein (Zaire strain)	Licensed	[58,59,60]
	GamEvac-Combi	VSV and Ad5	GP glycoprotein (Zaire strain)	Licensed for emergency use	[61,62]
	Ad5-EBOV	Ad5	GP glycoprotein (Zaire strain)	Licensed	[25,62]
	Zabdeno (Ad26.ZEBOV) + Mvabea (MVA-BN-Filo)	Ad26 + MVA	GP glycoprotein (different strains)	Licensed	[59,63]
	rVSVΔG-EBOV GP	VSV	GP glycoprotein (Zaire strain)	Phase 2/3	[64,65]
	ChAd3-EBO-Z	Chimpanzee Ad3	GP glyprotein (Zaire strain)	Phase 2	[64]
Hepatitis B	Recombivax HB	VLP	Hepatitis B Surface S antigen (HBsAg)	Licensed	[66,67,68]
	Engerix-B	VLP	Hepatitis B surface S antigen (HBsAg)	Licensed	[45,66,69]
	Heplisav-B	VLP	Hepatitis B surface S antigen (HBsAg)	Licensed	[47]
	PreHevbrio	VLP	Hepatitis B surface S antigen, pre-S1 antigen and pre-S2 antigen	Licensed	[47,70]
Hepatitis E	Hecolin	VLP	p239 truncated capsid protein	Licensed	[45,71,48]
HPV	Gardasil	VLP	L1 capsid protein types 6, 11, 16, and 18	Licensed	[45,68]
	Gardasil9	VLP	L1 capsid protein types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Licensed	[45,47,72]
	Cervarix	VLP	L1 capsid protein types 16 and 18	Licensed	[45,73]
	Cecolin	VLP	L1 capsid protein types 16 and 18	Licensed	[47]
	Walrinvax	VLP	L1 capsid protein types 16 and 18	Licensed	[74]
Malaria	Mosquirix (RTS,S/AS01)	VLP	*Plasmodium falciparum* circumsporozoite protein	Licensed	[45,75,48]
	R21/Matrix M	VLP	*Plasmodium falciparum* circumsporozoite protein	Licensed	[76,77]
Japanese encephalitis virus	ChimeriVax-JE (Imojev)	Yellow fever virus	Membrane (prM) and envelope (E) proteins	Licensed	[23,25]
HIV	THV01	Lentivirus	Gap/pol/nef	Phase 1/2	[78]
	Ad26.ENVA.01	Ad26	Env	Phase 1	[79]
	Ad26.Mos.HIV + MVA	Ad26 + MVA	Gag/pol/env	Phase 2	[80]
	ALVAC-HIV	Canarypox	Env/gag/pol	Phase 3 (RV144 trial)	[81,82,83,84]
Influenza	VXA-A1.1	Ad5	HA	Phase 2	[85,86]
	MVA- NP + M1 (VTP-100)	MVA	NP + M1	Phase 1/2a	[87,88,89]
	Quadrivalent VLP influenza vaccine	VLP	HA	Phase 3	[47,90]
SARS-CoV-2	Ad26.Cov2-S	Ad26	S prefusion stabilized conformation	Licensed	[91–93]
	Gam-COVID-Vac (Sputnik)	Ad26 + Ad5 (booster)	S full-length	Licensed	[94]
	ChAdOx1 nCov-19	Chimpanzee CHAdOx1	S full-length	Licensed	[95,96]
	Ad5-nCov (Convidecia)	Ad5	S full-length	Licensed	[97]
	NVX-Cov2373	VLP	S full-length	Licensed	[98]
	Covifenz	VLP	S full-length	Licensed	[99]
	GRAd-COV2	Gorilla adenovirus	S prefusion conformation	Phase 2	[100]
	hAd5-*S*-Fusion + N-ETDS	Ad5	S + N proteins	Phase 1b	[101]
	LYB001	VLP	RBD of S protein	Phase 2/3	[47]
	NDV-HXP-S	NDV	Stabilized version of S protein	Phase 2/3 (HXP-GPOvac, licensed in Thailand)	[42,102,103,104]

Abbreviations: Ad, adenovirus; EBOV, Ebola virus; HA, hemagglutinin; HBsAg, Hepatitis B surface antigen; HIV, Human immunodeficiency virus; HPV, human papillomavirus; MVA, Modified Vaccinia Ankara; NDV, Newcastle disease virus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; VLP, Virus-like-particle.

Paramyxoviridae, Rhabdoviridae, Flaviviridae, Togaviridae, and *Parvoviridae*, with adenoviruses and retroviruses being the most widely used vectors [25]. However, those vectors selected for designing vaccines are done so depending on the characteristics of the gene to be inserted and safety concerns related to the presence of pre-existing immunity, viral replication, and genetic stability [24]. Five of the main types of viral vectors that have been selected for designing viral-based vaccines are summarized below (Table 2).

3. Main viral vectors used to develop vaccines

3.1. Adenoviral vectors

Adenovirus (Ad) vectors have been widely used as tools in gene therapy [105,106] and represent one of the most commonly used vaccine platforms [107]. The *Adenoviridae* family comprises non-enveloped viruses with double-stranded linear DNA ranging from 26 to 45 kb in length. The genome contains five early transcription genes (E1A, E1B, E2, E3, and E4), four intermediate transcription units (IX, IVa2, L4 intermediate, and E2 late), five late units (L1-L5) and two inverted terminal repeat (ITR) sequences at both ends [108]. The icosahedral capsid is made up of three major proteins, fiber, penton, and hexon, the latter being the most abundant protein

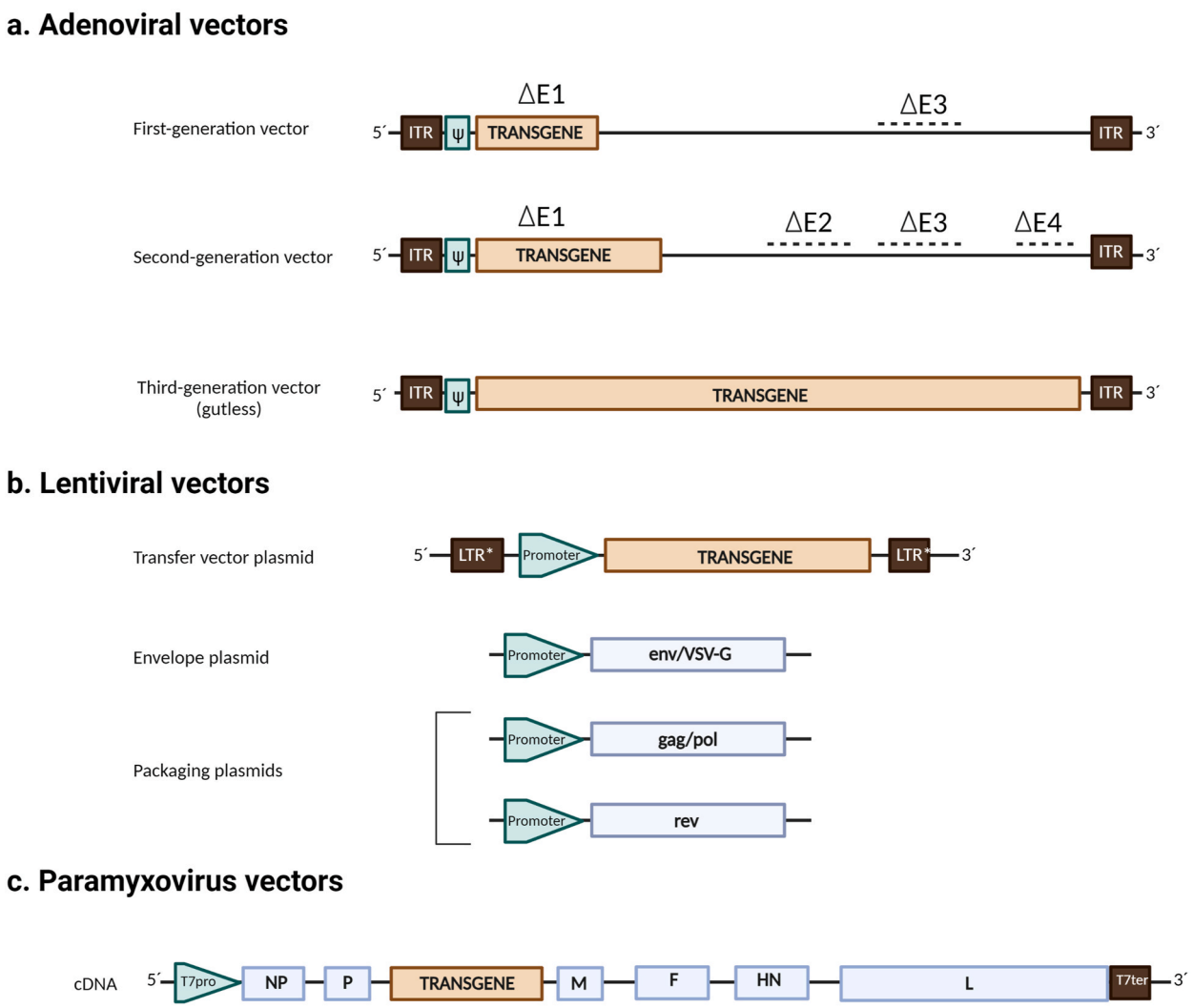

Fig. 1. Schematic representation of different viral-based vectors: (a) Adenoviral vectors. In first-generation vectors, E1A, E1B, and E3 genes from the adenovirus genome are deleted; in second-generation vectors, E2 and E4 genes are additionally deleted; in third-generation vectors or gutless vectors, most of the viral genes are deleted, except for the packaging signal Ψ and the ITR sequences. (b) Lentiviral vectors. A third-generation lentiviral vector containing the transfer vector plasmid (with the lentiviral 5′ and 3′ LTRs modified to be self-inactivating and the transgene); the envelope plasmid containing a promoter and the HIV env or VSG-G in a pseudotyped lentiviral particle; and two packaging plasmids encoding gag or pol and rev respectively are shown. (c) Paramyxovirus vectors. NDV vector is shown. The T7 promoter system is employed for the rescue of NDV from cloned DNA (cDNA). NDV, Newcastle disease virus; T7Pro, T7 polymerase promotor; T7ter T7 terminal sequence. ITR, inverted terminal repeat; Ψ, packaging signal; LTR*, Self-inactivating long terminal repeat. Created with BioRender.com.

containing the main neutralizing epitopes [109]. There are more than 100 different human adenoviral serotypes [105] classified into seven different species (A–G). Originally, Ad5 and Ad2 were the serotypes most widely used to construct vectors, as they are the easiest to manipulate and production and immunogenicity are high [105]. However, owing to preexisting immunity [110], Ad5 has been replaced by other serotypes with lower seroprevalence such as Ad6, Ad26, and Ad35 [107,79,81,111–113]. Additionally, simian-derived adenoviral vectors have also been developed against different pathogens and diseases [107,114], including influenza [115], HIV [116–118], Ebola [119,64]), SARS-CoV-2 [95,100,120], and malaria [121].

The advantages of using adenoviral vectors include an increased capacity for transgene transduction, broad cell tropism, the ability to infect both dividing and non-dividing cells, as well as antigen-presenting cells, and their lack of integration into the host genome (Table 2). Moreover, recombinant genomes exhibit stable maintenance across successive passages, which facilitates rapid and large-scale production and results in the generation of high-titer stable stocks [26]. As mentioned above, the main disadvantage of adenoviral vectors is pre-existing immunity [27] and the immunogenicity of the vector itself. This occurs because adenoviruses are highly immunogenic and elicit high titers of neutralizing antibodies against Ad major capsid proteins [28,29].

Depending on viral genome editing, Ad vectors are classified into first-, second-, or third-generation vectors (Fig. 1a). However, genes responsible for viral replication, E1B and E1A, have been removed from first-generation vectors. In addition, the insertion of a foreign gene through homologous recombination and the deletion of the E3 gene has led to an increase in the size of the transgene from 5 to 8 kb [122]. Also, the deletion of the E3 product promotes immunization as it is essential for suppressing the host's immunological response. In second-generation Ad vectors, the deletion of the E4 and E2 regions increases transgene capacity and reduces toxicity in host cells [26,123,124]. The third generation of Ad vectors, called gutless vectors or helper-dependent vectors, have most of their structural and functional genes deleted except for the packaging signal Ψ and the ITR sequences that are essential for virus packaging (Fig. 1a). These vectors can accommodate transgenes up to 35 kb in size [123–125]. The helper-dependent vectors have an improved safety profile while maintaining the immune response [126].

Ad vectors are usually replication-deficient. In addition, single-cycle Ad vectors are designed by deleting the IIIa capsid cement protein [127,128]; for example, those used for vaccines against the Ebola virus [111] and SARS-CoV-2 [129]. Several preclinical studies using animal models have led to good immune responses, making the development of single-cycle Ad vectors for human vaccination quite promising [18].

Vaccines using Ad vector technology have been developed for a wide range of pathogens (Table 3). Some of the Ad vector vaccines are still being studied, whereas vaccines against the Ebola virus and SARS-CoV-2 have already been commercialized, as we will discuss in the following sections.

3.2. Retroviral vectors

After adenoviruses, lentiviruses are the second most commonly used vector for viral vector design [31]. Lentiviruses, such as HIV type 1 (HIV-1), are included in the *Retroviridae* family, which is a family of enveloped single-stranded RNA viruses. Upon entry into the host cell, RNA is reverse transcribed into DNA and integrated into chromosomal DNA [130]. The genome encodes three essential genes (*gag*, *pol*, and *env*) and several regulatory and accessory genes for small six proteins (*tat, rev, vif, vpr, vpu,* and *nef)* that are essential for viral replication, infection, and inactivation of host restriction systems [131]. The *gag* gene encodes structural proteins, the *pol* gene encodes the protease, the reverse transcriptase enzyme characteristic of this group, and the integrase needed for the integration of viral DNA into the host's genome. The *env* gene encodes the envelope (Env) glycoprotein, gp160, which undergoes proteolytic cleavage to produce the gp120 and gp41 transmembrane glycoproteins [131].

Lentivirus vectors have great potential for immunization because they optimally transduce dendritic cells and efficiently stimulate T and B lymphocytes (for more information on immune responses to lentiviral vectors, see the review in Ref. [32]). Preclinical studies have shown that lentiviral vectors elicit robust and durable humoral and T-cell responses, providing effective protection against many infectious diseases [33]. Other advantages that have led to the widespread use of lentiviral vectors include their enhanced capacity to carry large transgenes (<8 kb), their integration into the host's genome that ensures high and long-lasting transgene expression, their high transduction efficiency both in dividing and non-dividing cells, and their low genotoxicity and immunogenicity, including low anti-vector immunity [32]. However, the widespread use of lentiviral vectors may be hindered by relatively high production costs and the technical challenges associated with large-scale manufacturing [33]. The main disadvantages derive from their integration, which can induce oncogenesis [31] (Table 2), although lentiviral-based gene therapy clinical studies have suggested the risk of insertional mutagenesis is low [33]. Additionally, the site of proviral integration for lentivirus is not random but relatively nonspecific. For HIV, the preference for site integration includes actively transcribed genes but not promoter regions [132]. Nevertheless, non-integrating lentiviral vectors have been generated for vaccination by mutating the viral integrase [33,34].

Most of the lentivirus vectors have been generated from HIV. First-generation lentiviral vectors were developed using a three-plasmid expression system [133], which comprises the packaging plasmid carrying gag and pol genes and the accessory and regulatory genes; the envelope plasmid; and the transfer plasmid with the transgene cassette flanked by lentiviral long terminal repeat (LTR) sequences (Fig. 1b). The cell tropism of lentiviral vectors can be modified by pseudotyping, which consequently increases the tropism of the virus. In pseudotyped vectors, the viral receptor binding protein Env is replaced by a heterologous envelope glycoprotein, with the G protein of the rhabdovirus vesicular stomatitis virus (VSV-G) being one of the most commonly used [31]. The absence of preexisting immunity to pseudotyped lentiviral vectors, coupled with their low pro-inflammatory properties, renders them suitable candidates for mucosal vaccination strategies [33]. Second-generation lentiviral vectors were made safer by deleting accessory virulent genes *vif*, *vpr*, *vpu*, and *nef* from the packaging plasmid. Third-generation lentiviral vectors currently used for gene delivery also induce strong immunity through vaccination [134,135]. In the third-generation vectors, the viral genome is separated into

three different plasmids (gag/pol, rev, and env or VSV-G). To prevent transcription of the entire HIV genome, the transgene is included in an additional plasmid containing lentiviral LTR sequences modified for self-inactivation [31,136] (Fig. 1b).

The use of lentiviral vectors as cancer vaccines is being also studied, particularly for melanoma, lymphoma, and prostate cancer [31,32,33,137]. As will be discussed in the next section, many lentiviral vectors against different pathogens, such as influenza virus [138], West Nile virus [139], HIV-1 [140,141], and SARS-CoV-2 [142], have been designed.

3.3. Adeno-associated virus vectors

After adenoviruses and lentiviruses, adeno-associated viruses (AAVs) are the third most widely used viral vectors [35,36]. AAVs are non-enveloped single-stranded DNA viruses that belong to the *Parvoviridae* family. AAVs are dependent viruses because they require a helper virus, such as adenovirus or herpes simplex virus, to replicate. Most of the AAV vectors have been used in gene therapy [37]. AAV vectors can infect both dividing and non-dividing cells and carry transgenes of up to 5 kb in size. AAV vectors persist predominantly as episomes and integrate into chromosome 19 at a lower frequency [38]. Their advantages are the lack of pathogenicity, broad tropism, low immunogenicity, ease of production, and the ability to establish long-term transgene expression. The main drawback is the small size of the transgene (Table 2). For the construction of an AAV-based vector, the viral replication (rep) and structural (cap) genes are replaced by the transgene expression cassette (transgene along with promoter and regulatory elements) flanked by AAV ITRs.

Several vaccine candidates based on AAV vectors encoding antigens against pathogens, such as henipavirus, dengue virus, human papillomavirus (HPV), HIV, Ebola virus (EBOV), influenza virus [143], and SARS-CoV-2 [144–146], have been evaluated in different studies. Additionally, many AAV-based vectors have been developed for passive immunization strategies to deliver genes of neutralizing antibodies. This strategy generates sustained expression of the antibodies against several pathogens, such as HIV [13, 147–149], influenza virus [150,151], and respiratory syncytial virus (RSV) [152], for which vaccines are not yet available or are less effective. For instance, the intranasal delivery of an AAV serotype 9 vector expressing the recombinant monoclonal antibody palivizumab has been shown to effectively protect against RSV challenge in mouse models [152].

3.4. Rhabdoviral vectors

A large number of preclinical and clinical studies for vaccine candidates based on rhabdoviral vectors, including some commercialized viral vector vaccines, have been conducted (Table 3). However, not as many studies have been conducted on adenovirus, AAV, and lentivirus vectors. The *Rhabdoviridae* family comprises enveloped viruses with a typical bullet shape that have a non-segmented negative-sense single-stranded RNA genome. The genome encodes five structural proteins: nucleocapsid (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and large polymerase (L) [153]. The use of reverse genetics has allowed negative-strand RNA viruses to be rescued from cloned DNA [154]. This system was first developed for the rescue of the rabies virus from cDNA in 1994 [155]. The modular organization of its genome facilitates genetic modification and offers greater manipulation compared to the majority of more complex DNA and plus-stranded RNA viruses [39].

Advantages of using rhabdoviral vectors include transgene size (up to 6 kb), which allows the expression of multiple antigens of a multivalent rhabdoviral vaccine, cytoplasmic replication, which decreases the possibility of viral integration into the host genome, low or absent preexisting immunity, and high-titer replication in tissue culture (Table 2).

Rhabdovirus-based vaccine candidates mostly use rabies virus and VSV [39]. Many rhabdovirus-based vectors are attenuated replication-competent [40] although single-cycle vectors have also been designed [21]. In addition, in VSV-based pseudotyped vectors, the G protein (the main contributor to viral neurotropism) is replaced by another glycoprotein [156]. Replication-defective rhabdovirus vector vaccines are however less immunogenic [39].

A considerable number of recombinant rabies viruses have been developed for their use as vaccine vectors against several pathogens such as HIV [40], lymphocytic choriomeningitis virus, Ebola and Marburg viruses, Lassa fever virus, Rift Valley fever virus, and SARS-CoV-2 [39]. In particular, the rabies-vectored vaccine, expressing the Lassa fever virus glycoprotein complex, is an inactivated dual candidate vaccine against both Lassa fever and rabies viruses. This vector induces durable humoral responses against the Lassa fever virus and the rabies virus in both mouse and guinea pig models and provides efficient protection against the Lassa fever virus [157].

Unlike rabies, VSV causes disease in cattle, horses, and swine but not in humans [39]. Recombinant VSV encoding foreign proteins are excellent candidates for vaccine vectors against HIV, EBOV, tuberculosis, and SARS-CoV-2, among others [158–161]. One of the first successful trials using VSV vectors involved the vaccination of mice using a VSV-based vector encoding influenza virus hemagglutinin antigen [162]. Rhabdovirus-based vaccine candidates against the deadly emerging paramyxoviruses, Hendra and Nipah viruses, have also been developed [158,163]. In many cases, the receptor-binding G glycoprotein is replaced by the immunogen [18]. As mentioned above, the G glycoprotein of VSV can be incorporated in pseudotyped lentiviral vectors [31].

At least two recombinant VSV-based vaccines against Ebola have been approved for human use, namely rVSV-ZEBOV [58,59] and GamEvac-Combi, which combines recombinant VSV and Ad5 expressing the envelope glycoprotein of EBOV [61,62] (Table 3).

3.5. Paramyxovirus vectors

The *Paramyxoviridae* family comprises enveloped viruses with a negative-sense single-strand RNA genome. The organization of the paramyxovirus genome is similar to that of the rhabdovirus and encodes five structural proteins: nucleocapsid (NP), phosphoprotein (P), matrix protein (M), attachment glycoprotein (HN/G), and large polymerase (L) (Fig. 1c). Also similar to rhabdovirus, the modular

genome of paramyxovirus facilitates its manipulation by reverse genetics. The measles virus (MV) was first rescued in 1995 [164] and the NDV in 1999 [165]. Many of the paramyxovirus-based vaccine vectors are based on MV, human parainfluenza virus 3 (HPIV3), and NDV.

Paramyxovirus-based vectors offer several advantages. They do not integrate into the genome of target cells but replicate exclusively in the cytoplasm without a DNA intermediate. They can accommodate an insert size of 6 kb, provide high and stable expression of heterologous genes, have the potential for mucosal vaccination, and are easy and cost-effective to manufacture. In the case of NDV-vectored vaccines, their egg-based nature makes them suitable for large-scale production (Table 2).

Due to the large success of using live attenuated MV [166], its use as a vaccine vector was initiated early in the area of viral vector-based vaccinology. Different measles virus-based vectors have been used in pre-clinical and clinical trials against a wide range of pathogens and viruses such as HIV, RSV, Dengue, SARS-CoV, MERS-CoV, Chikungunya, Ebola and Zika, hepatitis B, West Nile and SARS-CoV-2, among others [30,166,167].

Naturally occurring avirulent NDV strains are widely used as live attenuated vaccines in the poultry industry. NDV-vectored vaccines have also been developed for veterinary use [41]. Furthermore, the use of NDV-based vectors is safe in humans due to a restricted host range and the absence of pre-existing immunity [41]. NDV-based vectors have been designed to carry antigens from EBOV, influenza virus, HIV, SARS-CoV, and Nipah virus, among others [41,168–170]. The use of NDV vectors encoding the S protein of SARS-CoV-2 has also been described [42,102,103] (Table 3).

HPIV3-based vector vaccines have been developed against EBOV [171], RSV [172–174], and SARS-CoV [175], including a vaccine candidate for pediatric COVID-19 vaccination [176], but not to the extent of MV and NDV vector vaccines.

4. Virus-like particles

VLPs are nanoparticles formed from the self-assembly of viral structural proteins that mimic viral particles [44,177,178]. VLPs do not contain genetic material and, therefore, are replication-incompetent and non-infectious. This significantly improves their safety profiles over live attenuated vaccines or recombinant viral vectors, as more copies of immunogens are not synthesized like in the case of viral vector vaccines. VLPs can be categorized into two groups: non-enveloped and enveloped. Non-enveloped VLPs lack an outer lipid envelope, whereas enveloped VLPs possess a membrane envelope derived from the host cell that allows glycoprotein antigens to be incorporated into the lipid membrane. Both non-enveloped and enveloped VLPs can be single or multi-layered and assembled from single or multiple proteins [177,45,66]. One example of a simple non-enveloped VLP is the HPV VLP vaccine, which consists of a single layer. Influenza VLPs are a well-established example of enveloped VLPs [45,66].

VLPs carry specific viral epitopes of their own or foreign antigens (chimeric VLPs), which safely stimulate humoral and cellular immune responses [46,47] and elicit robust immunogenicity. VLPs often exhibit antigenic similarity to the virus from which they originate. They present antigens in an organized and highly repetitive manner, thereby triggering efficient humoral and cellular immune responses [179] due to the optimal stimulation of B cells by particles with repetitive surfaces. Moreover, VLPs possess the capability to activate T-helper cells, as they naturally encode T-helper cell epitopes that activate the cellular immune response. The immune system can be further activated by loading VLPs with specific pathogen-associated molecular patterns (PAMPs) into VLPs such as single-stranded RNA or CpG oligodeoxynucleotides (CpG-ODNs) [47]. This feature also enhances the immunogenicity of VLPs even at lower doses [180].

More than 100 viral proteins from 35 viral families, including enveloped and non-enveloped viruses, have been shown to assemble into VLPs [181]. This explains why the use of VLPs provides a versatile emerging platform for creating vaccines that provide an alternative to the use of viral vectors. The application of this technology has experienced significant growth in recent years due to the diverse types of vaccines that have been designed as well as their clinical use [44,47]. Usually, lower doses of antigen are adequate for inducing a similar protective response as compared to subunit vaccines [46]. The spontaneous assembly of viral proteins into VLPs ensures rapid and efficient production, allowing VLPs to be manufactured economically on a large-scale [47] (Table 2). In addition to vaccination against infectious diseases and cancer [45], VLPs can also be used as vehicles of drugs, dyes, or nanomaterials for their use in nanomedicine [45,182].

VLPs are developed through the molecular cloning of viral structural genes into an expression vector, followed by the expression of these genes in an expression system. About 30 % of VLPs are produced in bacteria [183], although different expression systems such as baculovirus/insect cells, mammalian cells, and plants are also used. The *Escherichia coli* expression system is notable for its ease of use and cost-effectiveness. However, its utility is limited for the production of non-enveloped VLP due to the absence of a post-translational modification (PTM) system [45]. Production in yeast has low production and maintenance costs, but the ability to introduce PTMs, (e.g., glycosylation, phosphorylation) is limited. Conversely, baculovirus-insect cell and mammalian-cell systems have the advantage of eliciting more complete PTM modifications [66], facilitating the production of both enveloped and non-enveloped VLPs, including the assembly of multi-protein VLPs [45,66]. Additionally, plant expression systems have emerged as versatile and promising platforms for reducing protein production costs [99,90]. For a review of the different approaches for designing, producing, and developing VLP-based vaccines see Refs. [177,178,45,66,181].

The first VLP-based vaccine, Recombivax HB, was licensed in 1986 for its use in humans. It is a hepatitis B VLP-based vaccine produced in yeast that was first developed in 1982 [66,67,68]. Since then, several VLP-based vaccines have been commercialized (Table 3). Engerix-B is another vaccine against the hepatitis B virus that is also produced in yeast [45,69]. Gardasil and Gardasil9 are additional examples of commercialized VLP-based vaccines produced in yeast that carry the L1 protein of HPV [45,47,68,72]. Recent studies have resulted in the successful production of HIV-based VLPs carrying Gag and p17 and p24 proteins [45]. The two recently approved malaria vaccines, RTS, S/AS01 (Mosquirix), and R21/Matrix M, utilize the hepatitis B surface antigen (HBsAg) VLP as a

platform to display malaria epitopes on the surface of VLPs formed in yeast [75–77].

Hecolin is the only vaccine that can effectively prevent hepatitis E [45,71]. It was the first VLP vaccine produced in bacteria carrying a p239 truncated capsid protein of the hepatitis E virus [45]. Phase 3 clinical trials have confirmed the high immunogenicity and efficacy of Hecolin, demonstrating its ability to induce significant titers of hepatitis E virus antibodies. Furthermore, the utilization of the *E.coli* expression system has facilitated cost-effective production. Hecolin obtained regulatory approval in China in 2011 [71, 48]. Recently, it has been approved as a third-generation hepatitis B vaccine, PreHevBio, that is manufactured in mammalian cells [47, 70]. Vaccines against malaria, influenza, HPV, and West Nile viruses are other examples of VLP vaccine candidates produced in bacteria [45,68,48]. The baculovirus/insect cell system is the preferred system for VLP production because it facilitates high expression of multiprotein VLPs with many PTMs. This is the case of Cervarix, an HPV vaccine, containing the L1 capsid protein of HPV 16 and HPV 18 [45,73].

Different VLP-based vaccines against the viruses SARS-CoV-2 [47,99,98,184–186], influenza A [90,187], EBOV [188,189]), adenovirus-7 [190], HPV, HIV-1, hepatitis B, SARS-CoV, dengue, rabies, rotavirus, norovirus, and malaria [45,47,75,76,48,74] have been recently approved or are currently being tested in clinical trials (Table 3).

5. Viral vector vaccines against major infectious diseases and pathogens

In this section, we will summarize some of the novel vaccine vectors that have been licensed for the prevention of major diseases or that are being tested in several clinical trials.

5.1. Ebola virus vaccine

Ebola is an emerging disease caused by the filovirus EBOV that has caused multiple outbreaks in West and Central African countries and has led to mortality rates between 25 and 90 % [191]. To date, the licensed Ebola vaccines available are based on viral vectors encoding the GP glycoprotein of the EBV (Table 3). Adv5-EBOV was the first EBV vaccine approved in China in 2017, which is based on an Ad5 vector [25]. The Ervebo or rVSV-ZEBOV vaccine is a live attenuated recombinant VSV-based vector vaccine in which the G protein of VSV is replaced by the GP protein of the Zaire species of EBV. rVSV-ZEBOV was the first *anti*-EBOV vaccine approved by the FDA in 2019 [58,59]. Preclinical studies have shown that Ervebo confers protection against lethal EBOV challenge in both mice and non-human primates, which is primarily mediated by *anti*-GP antibodies [60]. The vaccine, originally developed by the Public Health Agency of Canada, is administered as a single 1 mL dose and has been administered to over 200,000 individuals during an outbreak lasting from 2018 to 2020 [58]. The third EBOV vaccine is a two-dose combination of Zabdeno (Ad26.ZEBOV), an adenoviral vector (Ad26), and Mvabea (MVA-BN-Filo) with a Modified Vaccinia Ankara (MVA) vector that encodes GP proteins of different EBOV species [59,63]. GamEvac-Combi is a heterologous vectored vaccine licensed for emergency use, which combines recombinant VSV and Ad5 expressing the envelope glycoprotein of the EBOV [61,62].

In addition, many Ebola vaccine candidates are being studied in either pre-clinical or clinical trials [192] that include vaccines using paramyxovirus vectors [169,170,171], VSV and rabies virus vectors [65,193], cytomegalovirus vectors [194,195], and VLP-based vaccines [188,189,196].

5.2. Influenza virus vaccine

Influenza is a disease caused by viruses from the *Orthomyxoviridae* family that affects 15 % of the world's population and causes up to 645,000 deaths per year [197]. The three main genera that infect humans are influenza A, B, and C. Orthomyxoviruses have a negative-sense, single-stranded, and segmented RNA genome that can frequently lead to new variants due to genetic mutations and genome reassortment. This feature complicates the production of effective vaccines. Many avian influenza viruses present in poultry and wild birds constitute a zoonotic threat to humans. In addition to the emergence of different seasonal variants of the virus, influenza viruses are strong candidates for causing future pandemics. Influenza A is the main target for the development of recombinant vaccines, with the hemagglutinin (HA) of the viral envelope being the main antigenic target. Additionally, NA, M1, M2, NP, and the viral RNA polymerase complex immunogens can also be included in the vector [115].

Different viral-vectored influenza A vaccines based mainly on alphavirus, poxvirus, and adenovirus have progressed into the clinical trial stage [197]. Also, the use of paramyxovirus, adeno-associated virus, and herpesvirus as vaccine vectors has been considered [87]. In particular, vaccines based on Ad5 and Ad4 adenoviruses, as well as on non-human adenoviral vectors (Chimpanzee AdC7, AdC68, and ChadOx1; bovine BAdV-3; and porcine PAV-3), are being studied in pre-clinical and clinical trials [115]. Ad5-vectored vaccines have been reported to generate a stronger and more efficient immune response against the influenza virus in single doses [198]. The ChAdOX vector encoding NP and M1 genes from the influenza virus has completed two phase 1 clinical trials [115]. VXA-A1.1 is an adjuvanted adenoviral-based influenza vaccine from an Ad5 vector encoding the HA immunogen that is administered using double-stranded RNA as an adjuvant [85]. The VXA-A1.1 vaccine has also completed a phase 2 clinical trial [86].

Furthermore, several vaccines based on MVA vectors have been studied and tested in animal models and clinical trials. For example, an MVA-NP + M1 vaccine (VTP-100 vector) expressing the NP and M1 protein of influenza A [88] was assayed in phase 1/2a clinical trials [87,89] but without success [199,43]. Moreover, the alphavirus Venezuelan equine encephalitis virus has been tested as an influenza vaccine vector [197,87]. Lentivirus vectors have been also designed as influenza virus platform vaccines and tested in preclinical trials. Specifically, the HA and NP antigens of the influenza virus were delivered using an integrase-defective lentiviral vector. Mice immunized with this vector had a sustained production of functional antibodies against the surface proteins of the

influenza virus, along with eliciting functional T-cell responses, which are capable of neutralizing virus infectivity [138].

Finally, many preclinical and clinical trials in phases 1, 2, and 3 have tested the efficacy of VLP-based vaccines for influenza vaccination [187], including influenza B vaccines [200]. A phase 3 trial assessed the quadrivalent plant-based VLP vaccine against influenza virus. The vaccine was formulated to include HA proteins from four different strains and was produced using *Nicotiana benthamiana* as the manufacturing platform. Results from the study highlighted the immunogenicity and safety of this plant-derived VLP influenza vaccine [90]. VLP-derived vaccines expressing HA and different NA subtypes have been proposed as a promising platform for developing a universal influenza A vaccine [201].

5.3. HIV-1 vaccine

HIV was first identified in the 1980s when it caused a worldwide public health threat. The virus belongs to the *Retroviridae* family which, as previously mentioned, contains enveloped viruses with a single-stranded RNA genome that is reverse transcribed to DNA during the viral life cycle [131]. Two main HIV species infect humans, namely HIV-1 and HIV-2. The main antigenic protein is the viral envelope glycoprotein, Env or gp160, which is proteolytically activated into the receptor-binding protein gp120 and the fusion protein gp41. Two main characteristics of the Env protein confer an escape mechanism against neutralizing antibodies and non-neutralizing humoral and cellular responses. The exposed epitopes are hypervariable with a high mutation rate and the protein(s) has a high degree of glycosylation that leaves the epitopes inaccessible [81,118]. Thus, no effective vaccine against HIV has yet been commercialized despite exhaustive research.

Different viral vectors have been designed for HIV vaccination [202]. Viral vector HIV vaccines aim to stimulate both humoral and cellular immune responses against conserved epitopes of the Env protein (stimulation of the production of neutralizing antibodies) or the Gag, Pol, and Nef proteins (stimulation of T cell response) [202]. In addition, adenoviral vectors have been widely used. For example, STEP and Phambili phase 2b trials have tested Ad5-derived vaccines encoding the *gag*, *pol*, and *nef* genes from HIV-1 clade B [82]. Due to preexisting immunity against these vectors, the results have been discouraging [203] and have led to the design of vectors with different Ad serotypes, such as Ad26, Ad35, or chimpanzee adenoviruses, that have been tested in several clinical trials [110,79, 81,116–118,80].

In addition to adenoviral vectors, several HIV vaccines have been designed based on other types of vectors such as lentiviral vectors. THV01 is a lentiviral vaccine generated from a third-generation lentiviral vector. It is a replication-defective and self-inactivating vector that encodes segments of the HIV Gag, Pol, and Nef proteins. Phase 1/2 clinical trials have shown that this vector is highly immunogenic [78]. The NDV paramyxovirus-based vectors expressing both gp160 Env and p55 Gag proteins have been tested in preclinical studies [41]. The canarypox ALVAC-HIV vector, encoding *env*, *gag*, and *pol* genes, has also been tested in a phase 3 RV144 trial [81,82]. In this study, the viral vector was combined with a booster and a recombinant gp120 protein vaccine. This trial produced modest results for HIV immunization [83]. Several ongoing efficacy trials are currently underway to further elucidate the findings of the RV144 trial [81], including research on the efficacy of various adjuvants [84].

5.4. SARS-CoV-2 vaccine

SARS-CoV-2, the etiological agent of the recent COVID-19 pandemic, is a zoonotic respiratory virus belonging to the *Coronaviridae* family of enveloped viruses with positive single-stranded RNA. The surface spike S glycoprotein is the main target for the design of vaccines against SARS-CoV-2. This protein is essential for virus entry into target cells owing to its receptor-binding and fusion activities on subunits S1 and S2, respectively [204].

The development of safe and effective vaccines against SARS-CoV-2 has been accomplished rapidly and successfully. Additionally, a large number of SARS-CoV-2 vaccines using different platforms, including viral vector and VLP-based vaccines, are currently being developed.

Many vaccines are based on replication-incompetent adenovirus vectors that encode different versions of the S protein or epitopes such as the receptor-binding domain (RBD). To date, four adenoviral vector vaccines have been approved (Table 3). The Janssen (Johnson & Johnson) Ad26.COV2–S SARS-CoV-2 vaccine is a replication-incompetent Ad26 vector that encodes the pre-fusion conformation of the full-length S protein, which was approved for its use worldwide in 2021 [91–93]. The Gam-COVID-Vac or Sputnik vaccine consists of a heterologous regimen based on an Ad26 vector and an Ad5 booster, both encoding the full-length S protein that was approved in Russia as an emergency vaccine in the spring of 2021 [94]. The Oxford/AstraZeneca vaccine is based on a chimpanzee adenoviral vector (ChAdOx1 nCov-19) containing the transgene that encodes the protein S [95,96]. The Convidecia vaccine is based on Ad5 (Ad5-nCov9) and was developed by CanSino in China [97].

Additionally, a large number of preclinical and clinical trials are currently being conducted. AdCOVID is an Ad5-vectored vaccine that expresses the RBD region of the S protein. This vector can effectively elicit mucosal immunity in mice [205]. A second-generation Ad vector, hAd5-*S*-Fusion + N-ETDS, encodes both the spike and N proteins. This vector aims to immunize and protect against possible new emerging variants and is currently in phase 1 clinical trials [101]. GRAd-COV2 is a first-generation gorilla adenovirus vector that encodes the S protein stabilized in its pre-fusion conformation that has been tested in phase 2 clinical trials [100].

A lentiviral vector encoding a full-length, membrane-anchored form of the spike S glycoprotein has been shown to confer protection against SARS-CoV-2 in preclinical animal models following intranasal vaccination [142]. NDV-based vectors expressing the S protein have also been designed against SARS-CoV-2 and tested in phase 1, 2, and 3 clinical trials [42,102,103]. The NDV-HXP-S vector contains an enhanced immunogen version of the S protein that maintains the spike in a stable pre-fusion conformation. This vaccine can be efficiently produced at a low cost in embryonated chicken eggs. NDV-HXP-S is applicable as both a live vaccine [103] and as an

inactivated vaccine [102]. Phase 1 clinical trials have shown the NDV-HXP-S vector is both safe and highly immunogenic when administered via intramuscular or intranasal routes [102,103]. In Thailand, the inactivated NDV-HXP-S vaccine has received emergency use authorization [104]. The rhabdovirus VSV has been also used as a vaccine vector against SARS-CoV-2, using the well-developed platform for the design of an Ebola vaccine. These vectors express the S protein, either in its native unmodified non-stabilized conformation or in an optimized prefusion-stabilized conformation, and the nucleocapsid [159,161,206]. A great number of MVA-based vaccine candidates against SARS-CoV-2 have been designed and tested in preclinical and clinical trials [207].

Additionally, VLP platforms derived from different viruses such as influenza [184], NDV [186], and Moloney murine leukemia virus [185], among others, are also used for SARS-CoV-2 vaccine development. VLP-based SARS-CoV-2 vaccines are currently in preclinical and clinical studies, with the Novavax NVX-Cov2373 vaccine being the only commercialized VLP vaccine against SARS-CoV-2 [98]. Recently, the plant-made SARS-CoV-2 VLP vaccine Covifenz has been approved in Canada [99].

6. Concluding remarks

Viral vectors were first used for gene therapy, where the first vaccine was a vaccinia virus vector vaccine developed in the 1980s. Since then, many viral vector vaccines have been engineered for human vaccination and have emerged as new platforms to solve the limitations of conventional vaccines. The extensive use of adenoviral vectors for vaccination against COVID-19 has proven that this technology is both safe and effective. In addition, viral vectors facilitate the re-engineering of new viral vectors in response to new variants and emerging viruses and can be used for large-scale production.

Adenoviral vectors are the most commonly used vectors in both clinical trials and approved vaccines. Due to Ad5 seroprevalence, other less common human and simian serotypes are used as vectors. However, replication-deficient vectors are preferred due to safety concerns. In addition, the genes necessary for viral replication of the vector and the genes that prevent a host immune response are often removed. A large amount of research in this field has led to the design of third-generation vectors, mainly adenoviral and lentiviral vectors, leading to an increase in the size of the transgene and improved safety profiles.

Some viral vector vaccines have been licensed for human vaccination, however, many preclinical and clinical trials using viral vector vaccine candidates are still ongoing. Viral vector vaccines have been tested in a single trial and have produced modest results for HIV immunization. Thus, the development of vaccines against pathogens for which there is no effective traditional vaccine, such as HIV, hepatitis C virus, and Ebola virus among others, is critical.

VLPs are an emerging and versatile vaccine platform that, in recent years, has been significantly used to produce several commercialized vaccines. In this sense, VLP-derived vaccines have been proposed as a promising solution for fighting emerging viruses and for developing a universal influenza A vaccine.

The rapid development of COVID-19 vaccines for worldwide vaccination using viral vectors and other technologies, such as mRNA and protein subunit vaccines, has highlighted the success of these technologies. This success underlines the importance of having the right platforms based on previous research and validates the effectiveness of viral vectors against emerging viruses and pandemic outbreaks.

7. Perspectives

The enormous potential of viral vector- and VLP-based vaccines drives the continuous design of new vaccines. A large number of vaccines against important pathogens, such as influenza, HIV, RSV, Ebola virus, and SARS-CoV-2, are currently being developed and some are at the preclinical or clinical trial stage. However, despite the significant progress that have been made in developing viral vector- and VLP-based vaccines many challenges still need to be addressed. Specifically, further research is essential to improve their safety profile, addressing concerns related to preexisting immunity, potential integration into the host cell genome, and the generation of virulent phenotypes. Additionally, it is crucial to develop effective vaccines against major human pathogens or diseases such as HIV, Epstein-Barr virus, hepatitis C virus, and tuberculosis. Efforts should also focus on creating a universal influenza vaccine and developing new vectors to immunize against emerging variants. Moreover, improving multivalent vaccines, overcoming challenges in expanding the use of viral vectors for passive immunization, and advancing the application of viral vectors for prophylactic or therapeutic cancer vaccines are critical areas for future research.

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Declaration of competing interest

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Abbreviations

AAVs	Adeno-associated viruses
Ad	Adenovirus
ChAd	Chimpanzee adenovirus
COVID-19	Coronavirus disease 2019
EBOV	Ebola virus
HbsAg	Hepatitis B surface antigen
HIV-1	Human immunodeficiency virus-1
HPIV3	Human parainfluenza virus-3
HPV	Human papilomavirus
ITR	Inverted terminal repeat
LTR	Long terminal repeat
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MV	Measles virus
MVA	Modified Vaccinia Ankara
NDV	Newcastle disease virus
PTMs	Post-translational modifications
RBD	Receptor binding domain
RSV	Respiratory syncytial virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
VLPs	Virus-like particles

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