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Review

Viral vector vaccines

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Over the past two years, the SARS-CoV-2 pandemic has highlighted the impact that emerging pathogens can have on global health. The development of new and effective vaccine technologies is vital in the fight against such threats. Viral vectors are a relatively new vaccine platform that relies on recombinant viruses to deliver selected immunogens into the host. In response to the SARS-CoV-2 pandemic, the development and subsequent rollout of adenoviral vector vaccines has shown the utility, impact, scalability and efficacy of this platform. Shown to elicit strong cellular and humoral immune responses in diverse populations, these vaccine vectors will be an important approach against infectious diseases in the future.

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Introduction

A recombinant viral vector was first used almost forty years ago as a vaccine-delivery system, when the gene for hepatitis-B surface antigen was inserted into a modified vaccinia virus [1,2]. Since then, such vaccine vectors have been widely used in veterinary medicine, but before 2020, only five had progressed through clinical trials to licensure and use in humans (Figure 1). However, a number of viral vector vaccines have been developed against a wide variety of infectious-disease pathogens and indeed as vaccine vectors against noninfectious diseases, particularly cancer. Owing to the SARS-CoV-2 pandemic over the last two years, there has been an expansion in the use of adenoviral vector vaccines, with doses given to billions of people worldwide. This has given enormous insight into the safety, immunogenicity and efficacy of adenoviral (Ad) vaccine technology, which will be summarised here alongside a discussion of other viral vector vaccines in use today (Table 1). A more detailed summary of all existing licensed viral vector vaccines can be found in the Supplementary Material.

Immunogenicity

Innate immune response

Using viral vectors as vaccine platforms allows induction of an innate immune response without the need for adjuvant. This response is key for stimulating downstream processing and later adaptive immune responses (Figure 2).

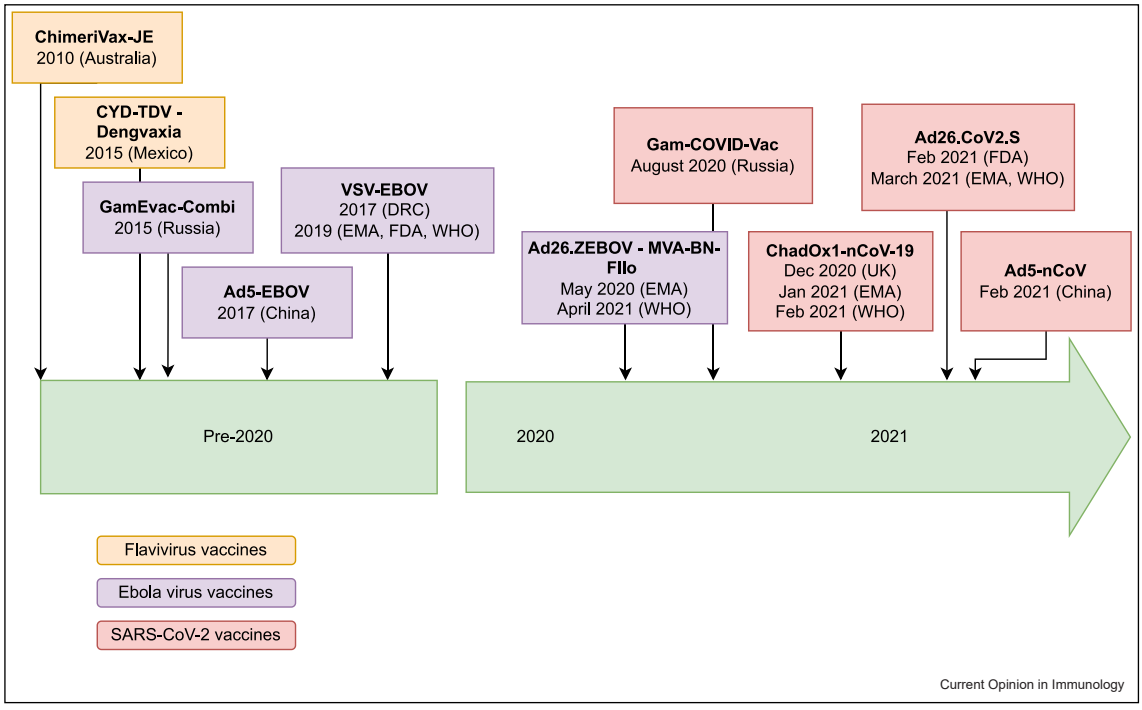
The downstream patterns of signalling from Ad vector recognition involve induction of a proinflammatory response, including cytokine and chemokine production, inducing humoral and cellular responses. Importantly, Ad vectors are able to do this without causing host damage and excess cytokine production. However, the excessive induction of type-I interferons (IFNs) by Ad vectors has been associated with dampened transgene expression and reduced antibody and cellular responses [34,35].

Employing bioinformatic techniques to investigate transcriptional changes induced by viral vectors can give new insight into the activation of innate immune pathways by viral vectors. In a study by Sheerin et al using a mouse immunisation model, Ad vectors induced expression of genes involved in TLR2 stimulation and natural killer (NK) cell activation, whereas modified vaccinia Ankara (MVA) vectors induced expression of type-1 IFN genes [36]. Collingnon et al evaluated cytokine responses and gene expression patterns to characterise innate responses following vaccination with the ChAd155 vector vaccines in preclinical studies. The authors showed that the vaccine induced a bimodal pattern of innate cell-population changes characterised by IFN-associated signatures [37].

Adaptive immune response

The ability of viral vectors to infect host cells, and express heterologous antigen, allows for antigen presentation and

Figure 1



Timeline showing licensing of viral vector vaccines approved for use in humans. Before 2020, only five viral vectors were licensed for use in humans, and only one by the World Health Organisation. Since 2020, five further viral vector vaccines (all containing adenoviral vector vaccines) have been licensed for human use, including three which have been licensed by the WHO.

activation of host MHC pathways via direct and cross-presentation, inducing a robust cellular response (Figure 3). The amount and duration of antigen expression correlate with CD8+ T-cell-protective immunity [35]. This potent T-cell activation has led to prior targeting of viral vector vaccines against intracellular pathogens, for example, HIV and malaria where such responses to such vaccines have correlated with protection [38].

Recent work has confirmed the strong and durable CD4+ and CD8+ antigen-specific T-cell responses that are generated following viral vector vaccines against other pathogens such as SARS-CoV-2, Ebola and RSV [4,11,39–41]. The T-cell response following viral vector vaccination appears to be a Th-1-biased response, characterised by IFN-y and TNF-alpha production [27,41–43]. Strong transgene expression by Ad vector vaccines also allows robust mono- and polyfunctional CD8+ T-cell responses [42,44].

These specific T-cell responses may also contribute to protection and reduction in disease severity. For example, when examining these SARS-CoV-2-specific T-cell responses following acute COVID-19 infection, they appear to inversely correlate with COVID-19 disease severity [45,46]. Additionally, SARS-CoV-2 spike-specific follicular helper T cells correlate with neutralising antibody responses [47]. T-cell epitopes also appear to remain relatively preserved in COVID-19 variants of concern (VoC), leading to limited T-cell escape following infection or vaccination [48–50]. Given that these VoC have significant mutations in spike protein, leading to evasion of the neutralising antibody response [51–53], the ability of Ad vector vaccines to induce a broad cellular response may be important in sustaining protection from SARS-CoV-2.

As described above, although T-cell-mediated immunity plays a role in reducing disease severity, a neutralising antibody response often correlates with protection against infection. High levels of neutralising antibodies are induced by vesicular stomatitis virus (VSV), MVA and Ad viral vector vaccines against Ebola virus [23,27,54,55] and following Ad vector vaccines against SARS-CoV-2 [12,39,42]. When investigating correlates of protection against SARS-CoV-2 following ChAdOx1-nCoV-19 vaccination higher anti-spike IgG, anti-receptor-binding protein IgG and neutralising antibody titres were all associated with lower risk of symptomatic disease [56]. All four Ad viral vector vaccines (Ad26.COV2.S, ChAdOx1-nCoV-19, Gam-COVID-Vac and Ad5-nCoV) are effective in protecting against symptomatic COVID-19 (66.9%, 66.7%, 91.6% and 57.5%, respectively) [11,12,21,57,58].

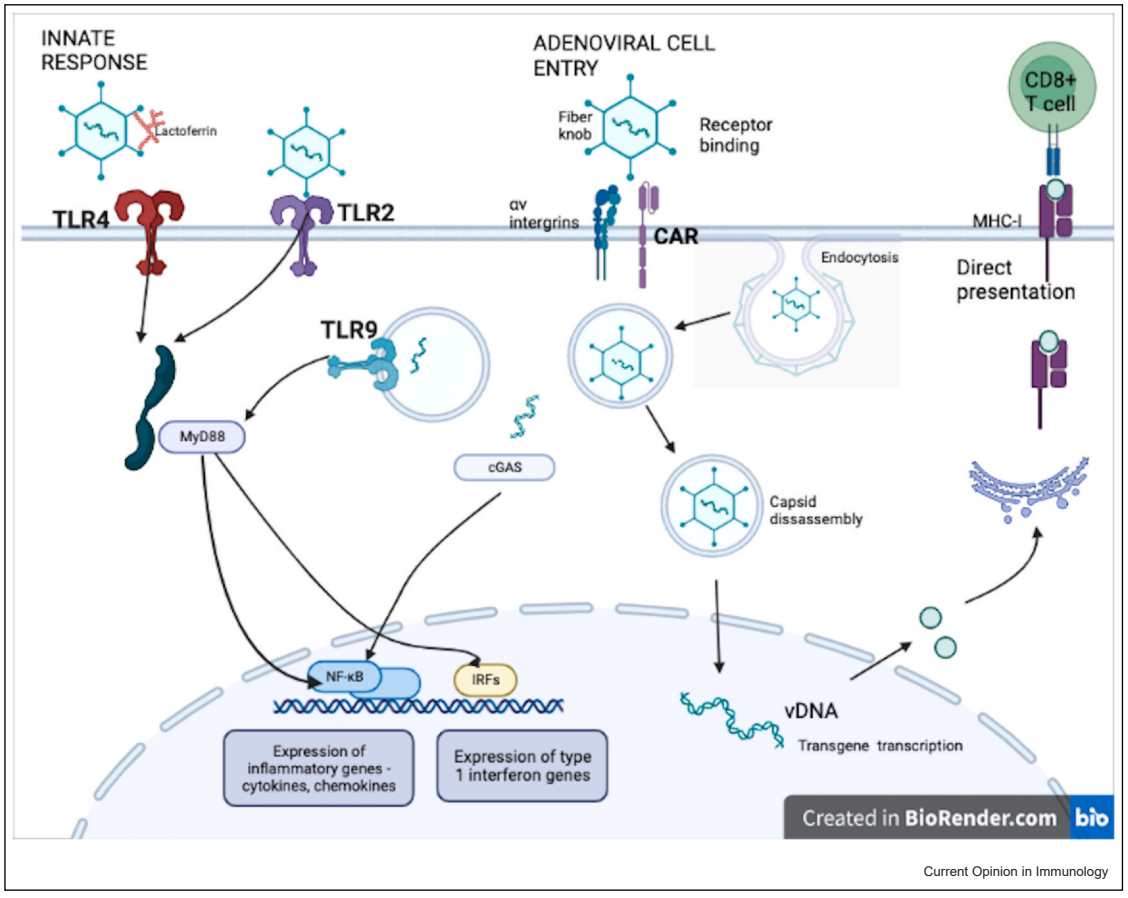
Table 1

Currently licensed viral vector vaccines for use in humans.

Vector class	Vector	Vaccine	Target pathogen	Encoded antigen	Developer	Clinical trials
Adenoviruses	Ad5	Ad5-nCoV (Convidecia)	SARS-CoV-2	Spike protein	CanSino Biologics (China)	[3,4]
		Ad5-EBOV	Ebola virus	Zaire strain (Makona) of glycoprotein	CanSino Biologics Inc	[5–7]
	Ad26	Ad26. CoV	SARS-CoV-2	Pre-fusion- stabilised spike protein	Janssen Pharmaceutical Companies	[8,9]
		Sputnik light	SARS-CoV-2	Spike protein	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)	[10]
	ChAdOx1	ChAdOx1- nCoV-19 (Covishield, Vaxzevria)	SARS-CoV-2	Spike protein with tissue plasminogen leader sequence	University of Oxford/AstraZeneca	[11–13]
Rhabdoviruses	VSV	VSV-EBOV (rVSV-ZEBOV, Ervebo)	Ebola virus	Zaire strain (Kikwit 1995) of glycoprotein	Merck	[14,15]
Flaviviruses	YF 17D	ChimeriVax-JE (Imojev)	Japanese encephalitis	Viral envelope (prM and E) of JE strain SA14–14–2	Sanofi Pasteur	[16–18]
		CYD-TDV (Dengvaxia)	Dengue	prM and E genes of DENV 1–4	Sanofi Pasteur	[19,20]
Heterologous regimens	Ad5/Ad26	Gam-COVID-Vac (Sputnik V)	SARS-CoV-2	Both spike proteins	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)	[21,22]
	VSV/Ad5	GamEvac-Combi	Ebola virus	Both glycoproteins	Gamaleya Research Institute of Epidemiology and Microbiology (Russia)	[23]
	Ad26/MVA	Ad26. ZEBOV (Zabdeno) MVA-BN-Filo (Mvabea)	Ebola virus	Ad26 — Zaire strain MVA — glycoproteins from the Zaire Ebola virus (Mayinga strain), Sudan virus (Gulu strain) and Marburg virus (Musoke strain), and the nucleoprotein from the Tai Forest virus	Janssen Pharmaceutical Companies	[24–28]

Viral vector vaccines utilise the capacity of viruses to infect cells and induce broad immune responses. Heterologous antigens are expressed by the virus, usually from genes engineered into the viral genome, and induce antigen-specific humoral and cellular immune responses. Viral vectors themselves can be replication-deficient, replication-competent or attenuated. Replication of the virus inside cells allows ongoing amplification of the vaccine antigen and improved immunogenicity, but must be balanced against the risk of increased adverse events or even disease in the host, particularly in the immunocompromised, resulting in some preference for use of replication-incompetent vectors.

Figure 2

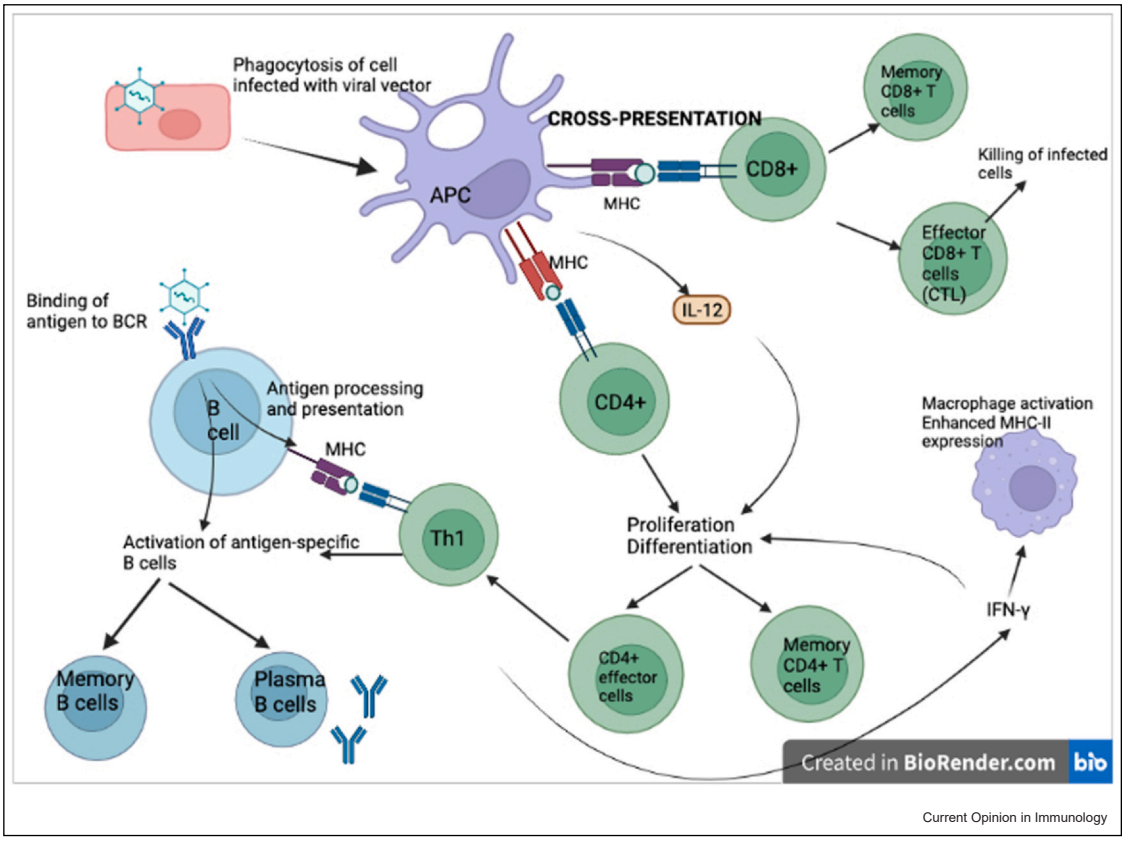


Induction of innate and adaptive immune responses by adenoviral vector vaccines. Adenoviral binding occurs via the fibre protein of the Ad capsid to infection receptors, such as the coxsackievirus–adenovirus receptor (CAR) and CD46, activating entry to the cell. Secondary attachment is mediated by RGD loops on the penton protein of the Ad capsid to integrins. These binding processes themselves can trigger innate immunity, but it is the pathogen-associated molecular patterns of adenoviruses, which are recognised by cell pattern-recognition receptors (PRRs), for example, toll-like receptors (TLRs). Ad vectors are recognised by TLR2 and TLR4, which are surface receptors, and TLR9, an endosomally located receptor that senses the Ad vector genome in endosomes [29,30]. The binding of lactoferrin, a host defence peptide, to Ad vectors, appears to activate an innate immune response via TLR4-mediated internalisation [31]. Intracellular adaptor proteins, such as MyD88, are vital for TLR signal transduction and induction of antigen-specific T-cell responses via activation of NF-κB transcription factors following Ad vector vaccine [32]. Further, PRRs such as the cytosol DNA sensor cGAS and the receptor RIG-I area are also important for inducing innate immune signals following Ad vector vaccination [33].

Non-neutralising antibodies are also recognised as important mediators of antipathogen immunity and in preclinical studies Fc-mediated functions were shown to contribute to protection against SARS-CoV-2 [59,60] and Ebola [61]. Systems' serology work has shown that Ad vector vaccines are able to induce antibody-dependent functional activities, including antibody-dependent neutrophil phagocytosis and antibody-dependent monocyte phagocytosis [8]. In a comparison of vaccine responses from phase-I and phase-II studies in humans using different HIV vaccines, Ad viral vectors induced a more potent IgG1 and IgG3 response than pox-virus vectors, leading to higher levels of functional antibody activity, including antibody-dependent cellular phagocytosis [62].

Induction of a mucosal immune response is likely to play an important role in protection against respiratory pathogens. Provine et al showed that in ChAdOx1-nCoV-19-immunised mice, mucosal-associated invariant T cells were induced, which correlated with vaccine-mediated T-cell responses [63]. Mucosal administration of an Ad vaccine may also induce stronger mucosal immune responses. Lapuente et al showed that mice given an intranasal Ad vector vaccine (either Ad19a or Ad5) boost following an intramuscular plasmid DNA or mRNA prime induced high levels of mucosal IgA and lung-resident tissue-resident memory T cells, in addition to systemic responses, leading to enhanced mucosal neutralisation [64]. Human trials of mucosal Ad vector vaccines against SARS-CoV-2 are underway with phase-I

Figure 3



Adaptive immune response to adenoviral vector vaccines. Cross-presentation of antigen occurs in antigen-presenting cells, for example, dendritic cells following phagocytosis of infected cells. Antigen is presented via MHC molecules to T cells, stimulating proliferation and differentiation of CD4+ and CD8 + T cells. B cells are activated to antigen-specific memory B cells and plasma B cells via T-dependent and T-independent mechanisms. Binding of native antigen to the B-cell receptor (BCR) delivers biochemical signals that initiate B-cell activation independent of T cells. T-cell-dependent activation occurs when the BCR internalises the antigen that is endocytosed and processed into peptides presented by class-II MHC molecules. T-helper cells recognise these and stimulate B-cell activation.

data from an aerosolised Ad5.nCoV vaccine showing two doses elicit a neutralising antibody response similar to one dose of IM injection [65].

Pre-existing immunity

Pre-existing immunity against the Ad vector has the potential to reduce immunogenicity and subsequent protective effect of these vaccine vectors [66]. Multiple studies have shown that existing anti-Ad-neutralising antibodies are inversely correlated with immunological response to vaccine vector [3,6,67]. This is particularly relevant with Ad5-based vector vaccines, given their high seroprevalence in some populations [68]. However, repeated doses of Ad26 vector vaccination against HIV are able to boost both cellular and humoral immune responses, despite the presence of high Ad26-neutralising antibodies following prime vaccination [69] and following vaccination with ChAdOx1-nCoV-19-neutralising antibodies did not correlate with spike-specific antibody responses or T-cell responses following boost vaccination [12].

To circumvent the issue of antivector immunity less-prevalent adenoviruses, nonhuman adenoviruses or chimeric adenoviruses that express modifications to the hexon major capsid protein have been increasingly used over recent years [9,70–72]. Higher dosing regimens can also be used to overcome pre-existing vector immunity in the population, but when used with Ad5-nCoV, these higher doses caused increased reactogenicity with limited benefit in immunogenicity [3].

Prime-boost regimens

The use of heterologous prime-boost viral vector regimens may overcome the development of antivector immunity and be more immunogenic than homologous regimens [21,73–76]. The use of Ad26 encoding the GP of the Zaire strain of Ebola, followed by an MVA boost, was shown to provide 100% protection against lethal

Ebola when administered to nonhuman primates [77]. This heterologous prime-boost regimen has now been shown to induce strong and durable immune responses in human trials persisting for at least 1 year in both endemic and nonendemic populations [26,27].

Combining viral vectors takes advantage of the differential ability of vectors to prime or boost immune responses. For example, adenoviruses have been shown to prime effective and durable potent B- and T-cell responses, and MVA is able to significantly boost immune responses, but elicits limited humoral responses as a prime [78,79]. However, recent transcriptional data show that an Ad vector boost on an MVA prime appears to augment the molecular response compared with an MVA boost on an Ad prime, including stimulation of preferential TLRs and increased IFN-γ signalling [36], suggesting that further exploration of this area is needed for future vaccine development.

Heterologous prime-boost vaccine schedules using different vaccine platforms have also been evaluated. For example, in vaccines against SARS-CoV-2, a prime dose of adenoviral vector vaccine has been boosted with an mRNA vaccine, which appears to increase vaccine efficacy and immunogenicity against symptomatic infection compared with homologous Ad vaccination [80–83]. In preclinical studies, an MVA booster following mRNA vaccine enhanced specific T-cell responses against HIV-1 [84].

Improving immunogenicity

Various methods have been used to further increase the immunogenicity of Ad vectors by enhancing transgene expression and boosting cellular responses. These include the use of endogenous promoters, co-expression of immune-stimulatory molecules and genetic-fusion adjuvants [85,86] Rollier et al added the Toll-like receptor signalling molecule, TRIF-related adaptor molecule (TRAM), to an adenovirus-based vaccine, showing that co-expression of TRAM and antigen increased the transgene specific CD8+ T-cell responses in mice, but this did not translate into studies in primates [87].

A further way to enhance immunogenicity of viral vectors is to increase immunogen production from vaccine vector. Self-replication via replication-competent vectors allows significant antigen production and may be necessary to induce immunity against some pathogens. The safe use of a replication-competent VSV vector against Ebola virus, VSV-EBOV, in HIV patients, showed that such vectors can be used in immunocompromised patients [88]. An alternative is the use of single-cycle virus vectors, which allow the virus to self-amplify in one additional round of genome replication, circumvent this issue and represent a potential therapy for future viral vector vaccines [89,90].

Harnessing the specific tropism of certain viruses to deliver antigens to desired cell types is a further potential mechanism of improving immunogenicity against certain pathogens. For example, Viktorova et al used a recombinant Newcastle virus, a virus with mucosal tropism, to express proteins from poliovirus, which stimulated systemic and mucosal responses [91].

Safety

Adenoviral vector vaccines have now been given to billions of people worldwide. Two vaccines (Ad26.COV2.S and ChadOx1-nCoV-19) have been associated with a very rare clotting disorder, thrombosis with thrombocytopaenia syndrome (TTS). This syndrome is characterised by the presence of antiplatelet factor-4 antibodies, although the risk factors for developing TTS and the exact pathogenesis remain unclear [92]. There may be an underlying geographical or genetic link, given variations in the rates of TTS across different populations [93].

Conclusion and future directions

Over the past two years, viral vector vaccines have been used as a cornerstone of the control of SARS-CoV-2 in the pandemic, particularly in low- and middle-income countries. The application of newer techniques such as bioinformatics and systems' serology during this time has provided extensive knowledge on the immunogenicity of the adenoviral vaccine platform.

Although significant advances have been made, further understanding of the spectrum of immune responses stimulated by adenoviral vectors is still needed. Understanding of the mechanism underlying antivector immunity, particularly following repeated dosing, will be vital going forward as vaccines against multiple different pathogens are developed using the same vectors. Evaluating the long-term duration of humoral and cellular responses following widespread Ad vector administration for SARS-CoV-2, and their relationship to vaccine efficacy, will be important in providing invaluable insights into the persistence of immune responses afforded by these vaccine vectors.

Despite the excellent immunogenicity and efficacy of the approved viral vector vaccines, there remains scope to improve immunogenicity. The use of genetic or molecular adjuvants may be a useful strategy, particularly in vaccine vectors that only induce weak or short transgene expression. In addition, the use of heterologous prime-boost regimens, by combining either different viral vectors or different technologies such as mRNA vaccines, has been shown to improve immunogenicity of

homologous regimens, and is likely to play an important role in viral vector vaccine regimens going forward. The use of mucosal viral vector vaccines to induce site-specific immune responses may significantly improve protection, particularly against mucosal pathogens, and clinical trial data from such vaccines are eagerly awaited.

Viral vector vaccines have been a major component of the successful response to the SARS-CoV-2 pandemic. Given their safety, immunogenicity and ability to be modified and scaled up at pace, they will remain an important technology for infectious-disease control in the future.

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Conflict of interest statement
AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts. AJP is a National Institute for Health Research Senior Investigator. TL is named as an inventor on a patent application covering ChAdOx1-nCoV-19. Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1-nCoV-19. All other authors declare no competing interests.

Supporting information
Supplementary data associated with this article can be found in the online version at doi:10.1016/j.coi.2022.102210.

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- • of special interest
- •• of outstanding interest

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