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Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: Standardized template with key considerations for a risk/benefit assessment

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ABSTRACT

Replication-deficient adenoviral vectors have been under investigation as a platform technology for vaccine development for several years and have recently been successfully deployed as an effective COVID-19 counter measure. A replication-deficient adenoviral vector based on the simian adenovirus type Y25 and named ChAdOx1 has been evaluated in several clinical trials since 2012.

The Brighton Collaboration Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) was formed to evaluate the safety and other key features of new platform technology vaccines. This manuscript reviews key features of the ChAdOx1-vectored vaccines.

The simian adenovirus Y25 was chosen as a strategy to circumvent pre-existing immunity to common human adenovirus serotypes which could impair immune responses induced by adenoviral vectored vaccines. Deletion of the E1 gene renders the ChAdOx1 vector replication incompetent and further genetic engineering of the E3 and E4 genes allows for increased insertional capability and optimizes vaccine manufacturing processes. ChAdOx1 vectored vaccines can be manufactured in E1 complementing cell lines at scale and are thermostable. The first ChAdOx1 vectored vaccines approved for human use, against SARS-CoV-2, received emergency use authorization in the UK on 30th December 2020, and is now approved in more than 180 countries.

Safety data were compiled from phase I-III clinical trials of ChAdOx1 vectored vaccines expressing different antigens (influenza, tuberculosis, malaria, meningococcal B, prostate cancer, MERS-CoV, Chikungunya, Zika and SARS-CoV-2), conducted by the University of Oxford, as well as post marketing surveillance data for the COVID-19 Oxford-AstraZeneca vaccine. Overall, ChAdOx1 vectored vaccines have been well tolerated. Very rarely, thrombosis with thrombocytopenia syndrome (TTS), capillary leak syndrome (CLS), immune thrombocytopenia (ITP), and Guillain-Barre syndrome (GBS) have been reported following mass administration of the COVID-19 Oxford-AstraZeneca vaccine. The benefits of this COVID-19 vaccination have outweighed the risks of serious adverse events in most settings, especially with mitigation of risks when possible.

Extensive immunogenicity clinical evaluation of ChAdOx1 vectored vaccines reveal strong, durable humoral and cellular immune responses to date; studies to refine the COVID-19 protection (e.g., via homologous/heterologous booster, fractional dose) are also underway.

New prophylactic and therapeutic vaccines based on the ChAdOx1 vector are currently undergoing preclinical and clinical assessment, including vaccines against viral hemorrhagic fevers, Nipah virus, HIV, Hepatitis B, amongst others.

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1. Introduction

The Brighton Collaboration (https://www.brightoncollaboration.org) was launched in 2000 to improve the science of vaccine safety [1]. The Brighton Viral Vector Vaccine Safety Working Group (V3SWG) was formed in 2008 in recognition of the increasing importance of viral vectors for the development of new vaccines and the need to understand their associated safety issues [2]. To better meet the needs of many other platform technologies used to develop vaccines to prevent COVID-19 beyond just vaccines using viral vectors, the V3SWG was renamed to Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group in July 2020. BRAVATO uses a standardized template to describe the key characteristics of novel vaccine vectors, compiled from the latest research, to facilitate scientific discourse among key stakeholders [2].(SeeTable 1.).

Viral vector vaccines are laboratory-generated, chimeric viruses that are based upon replicating or non-replicating virus vectors into which have been spliced genes encoding antigenic proteins for a target pathogen. Consideration of safety issues associated with viral vector vaccines requires a clear understanding of the agents used for construction of the vaccine. These include 1) the wild type virus from which the vector is derived, referred to in the template as "**wild type virus**"; 2) the vector itself before incorporation of the foreign antigen, referred to in the template as "**viral vector**"; and 3) the final recombinant viral vector vaccine, referred to in the template as "**vaccine**". Wild type viruses used as vectors may originate from human or non-human hosts and may have low or high pathogenic potential in humans regardless of species of origin. Viral vectors can originate from attenuated human vaccines, from attenuated human viruses, from human viruses with low pathogenic potential, from animal viruses with low human pathogenic potential, and from vectors (for the expression of proteins) which are then adapted as a viral vector (such as DNA plasmids or baculovirus vector vaccines) to be used as a vaccine in humans or animals. Thus, viral vectors usually, but not always, have properties in a human host that differ from wild type virus from which they were derived. Incorporation of a target antigen into a viral vector to create a vaccine may alter the properties of the vector such that the vaccine may have properties that differ from the vector.

2. Background

2.1. Adenovirus vectors

Adenoviruses have been at the forefront of research in the quest for effective gene transfer vehicles. The dsDNA genome is amenable to manipulation by recombinant DNA techniques, and it is feasible to insert foreign genes into the genome by partial or complete deletion of pre-existing adenovirus genes. Adenoviruses also grow well and to a high titer in a large variety of cell types. Current highly developed vectors based upon adenoviruses are replication incompetent through full deletion of the E1 early gene. Some vectors also have deletion of the E3 gene, and this allows great flexibility in the insertion of foreign DNA. Propagation of these E1 deleted adenovirus vectors is achieved by growing them in vitro in cell lines that have been modified to constitutively produce E1 and thus complement the replication defective E1 deleted adenovirus vectors. Because of the E1 deletion and the resultant replication incompetent phenotype, these vectors have the advantage of not killing the target cell during gene transfer.

While the original line of research into gene transfer was for the transfer of a therapeutic gene into a patient, for example to circumvent a genetic disease, it was soon realized that viral vectors being developed for gene therapy could be used also as vaccine vectors that deliver an antigen for the purpose of inducing an immune response against the encoded antigen [3]. Thus, a whole new era of vaccine development began using adenovirus (and other viruses) as vectors for the delivery of antigens from important disease-causing agents such as HIV, malaria, Ebola and many others.

The first adenovirus vectors investigated for gene transfer were based upon the common human serotypes Ad5 and Ad2. However, these vectors suffered from the high prevalence of anti-adenovirus neutralizing antibodies in human sera thus potentially reducing their effectiveness both as therapeutic agents and as viral vaccine vectors. Despite this, the use of Ad5 as a vaccine vector has been pursued and vaccines against HIV [4-7], Ebola [8] and COVID-19 [9] amongst others have been developed and tested in humans. However, in order to bypass pre-existing immunity to Ad5 vectors, vectors based upon other human adenoviruses, especially Ad26, have been developed. An Ad26 based Ebola vaccine, used in conjunction with a Modified Vaccinia Ankara (MVA) vectored Ebola vaccine [10] and an Ad26-vectored COVID-19 vaccine [11] have both been authorized for human use. In addition, the Sputnik V vaccine (Gamaleya, Russia) uses an Ad26 prime and Ad5 boost regimen [12], now used in several countries under local Emergency Use Authorization (EUA).

Adenoviruses from chimpanzees were also being studied by virologists and were soon being investigated for their use as gene transfer vehicles especially as human sera had no or very low reactivity against some of the common chimpanzee adenoviruses being studied as such as C63 and C68. Indeed, the first chimpanzee adenovirus vector to enter clinical trials was a vector based upon AdC63 (ChAd63) and was highly effective in stimulating antimalaria specific T cells in humans when boosted by a distinct viral vector, MVA expressing the same antigen [13]. An AdC68 vector was the first E1 deleted chimpanzee adenovirus vector to be created [14] and has since been demonstrated to be a highly immunogenic vaccine vector in pre-clinical HIV-1 vaccine studies [15].

2.2. ChAdOx1 ***vaccine vector***

In pursuing the development of an adenovirus vector against which there is little pre-existing immunity in humans, a group at the Jenner Institute in Oxford, England focused its attention on the chimpanzee strain Y25, originally characterized in 1969 by Hillis and Goodman [16]. Many of the chimpanzee adenoviruses being studied group phylogenetically with human adenovirus species group E of which human Ad4 is the only member, including the commonly used C63 and C68 isolates and Y25. Interestingly, sera from human trials of a malaria vaccine based upon ChAd63 as a vaccine vector failed to neutralize Y25 even although the sera had very high titer of anti-chAd63 antibodies, showing that Y25 was a distinct serotype from ChAd63 despite both belonging to human adenovirus group E. To investigate further the value of the ChAdY25 vector, the presence of anti-ChAdY25 neutralizing antibodies in UK and Gambian human serum samples was investigated and found to be of low prevalence especially compared to that published for other chimpanzee adenoviruses. At a titer of greater than 1:200, values for neutralizing antibodies were 0% for in UK adult sera (n = 100) and 9% in Gambian adult sera (n = 57). Such data indicated the potential value of a vaccine vector based upon Y25 in human clinical trials [17].

In initial studies at the Jenner Institute, a variety of E1, E3 deleted simian adeno virus vectors were constructed using a bacterial artificial chromosome to facilitate genetic manipulation of genomic clones [17]. Using a specific green fluorescent protein antigen and taking into consideration the infectious titer of clones as well as virus particle number, the antigen immunogenicity of

Table 1
Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates.

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
1. Authorship	**Information**		
1.1. Author(s)	Pedro M Folegatti, Daniel Jenkin, Susan Morris, Sarah Gilbert		
1.2. Date completed/updated	June 10, 2022		
2. Basic vector information	**Information**		
2.1 Vector name	ChAdOx1		
2.2. Vector origin Family/Genus/Species/subtype	E1/E3 deleted Chimpanzee adenovirus Y25 with human Adenovirus serotype 5 E4 orf4, 6 and 6/7 genes (Adenoviridae,Mastadenovirus, Human mastadenovirus E, Chimpanzee adenovirus Y25)		
2.3. Vector replication in humans (replicating or non-replicating)	Non-replicating		
3. Characteristics of the wild type virus from which the vector is derived	**Information**	**Comments/Concerns**	**Reference(s)**
3.1 Name of wild type virus (common name; Family/Genus/Species/subtype)	Chimpanzee adenovirus Y25; Adenoviridae;Mastadenovirus; Human mastadenovirus E; Chimpanzee adenovirus Y25	ChAdOx1 is an E1/E3 deleted Chimpanzee adenovirus Y25 with human Adenovirus serotype 5 E4 orf4, 6 and 6/7 genes	[16,67]
3.2 What is the natural host for the wild type virus?	Chimpanzee (*Pan troglodytes*)	Humans and other mammals are known to be the natural hosts for adenoviruses of the Mastadenovirus genus. However, chimpanzees remain the only natural host known for Chimpanzee adenovirus Y25.	[68,69]
3.3. How is the wild type virus normally transmitted?	Aerosolized droplets or fecal-oral spread		[70,71]
3.4. Does the wild type virus establish a latent or persistent infection?	Yes	Simian hosts may persistently shed the virus from gastrointestinal tract.	[72]
3.5. Does the wild type virus replicate in the nucleus?	Yes	Adenoviruses replicate as linear, extra-chromosomal DNA elements in the nucleus	[73]
3.6. What is the risk of integration into the human genome?	Low risk	Wild type adenovirus DNA is unlikely to integrate into the host genome, as it remains in an episomal state in the nucleus. The European Medicines Agency considers adenoviruses as non-integrating vectors	[74,75]
3.7. List any disease manifestations caused by the wild type virus, the strength of evidence, severity, and duration of disease for the following categories:		There is limited literature available on clinical presentation of simian adenoviruses on natural host and none, to our knowledge, for Chimpanzee adenovirus Y25. There is some evidence of cross species transmission between human and simian adenoviruses from antibody and genetic diversity studies. There is one report of clinical disease in humans with limited onward human-to-human transmission from a new world monkey adenovirus. The clinical implications of human infection from wild type Chimpanzee adenovirus Y25 remain unknown.	[17,70,71,76-78]
In the healthy natural host	Clinically apparent adenovirus infections of the respiratory tract are characterized by cough. Keratoconjunctivitis and diarrhea may also occur. Most animals, but especially adults recover within a week to 10 days. Except in neonates, mortality is generally low	Clinical presentation of Chimpanzee adenovirus Y25 is unknown for natural host	[70,71]
In healthy human host	Unknown		
In immunocompromised humans	Unknown		
In human neonates, infants, children	Unknown		
During pregnancy and in the unborn in humans	Unknown		
In any other special populations?	Unknown		
3.8. What cell types are infected and what receptors are used in the natural host and in humans?	Epithelial and endothelial cells expressing Coxsackievirus and adenovirus receptor (CAR)	Although not fully defined for Y25 other simian adenoviruses, (Ch63 and Ch68) and human adenovirus 4 of species E use CAR for cell entry.	[69,79-81]
3.9. What is known about the mechanisms of immunity to the wild type virus?	Unknown		

Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
3.10 Has disease enhancement been demonstrated with the wild type virus:	No	No disease enhancement has been described for Adenovirus infections. However, enhancement of HIV infection acquisition has been previously reported with a Ad5 vectored vaccine expressing HIV antigens. There is no evidence of COVID-19 enhancement following immunization with Ad5, Ad26 or ChAdOx1 vectored vaccines.	[6,82]
● in vitro?	No		
● in animal models?	No		
● in human hosts?	No		
3.11 Is DE a possible contributor to the pathogenesis of wild type disease	No		
3.12 What is the background prevalence of natural immunity to the virus?	Low level natural immunity to the virus	British and Gambian adults were analyzed using virus neutralization assays against Chimpanzee Y25. The percentage of individuals having a clinically relevant neutralizing titer (defined as a 50% neutralization titer greater than 200) were 0% for Y25 in UK adults (n = 100); and 9% for Y25 in Gambian adults (n = 57).	[17]
3.13 Is there any vaccine available for the wild-type virus? If yes,	No		
● What populations are immunized?	N/A		
● What is the background prevalence of artificial immunity?	N/A	The prevalence of ChAdOx1 vector immunity is likely to increase with deployment of ChAdOx1 nCoV-19 (AZD1222).	
3.14 Is there treatment available for the disease caused by the wild type virus	N/A	Cidofovir is the drug of choice for severe AdV infections in humans, but not all patients require treatment.	[83]
4. Characteristics of the vector from which vaccine(s) may be derived	**Information**	**Comments/ Concerns**	**Reference(s)**
4.1 Describe the source of the vector (e.g. isolation, synthesis)	The wild type chimpanzee adenovirus isolate Y25 was originally obtained from William Hillis, John Hopkins University of Medicine. The virus was passaged in HEK293A cells and purified by CsCl gradient ultracentrifugation. Viral DNA was phenol extracted and cloned into a bacterial artificial chromosome (BAC) containing Y25 LFI/II and RFI by recombination in such a manner as to delete E1 region. The E3 region was deleted by recombineering. The E4 region was modified by recombineering to replace the native E4 orf 4, orf 6 and orf 6/7 with those from Human Adenovirus serotype 5. The E1 region was modified to allow insertion of antigen expression cassette.		[15]
4.2. What is the basis of attenuation/inactivation of the wild type virus to create the vector?	The E1 region encoding the viral transactivator proteins is deleted rendering the vector replication incompetent.		[84]
4.3. What is known about the replication, transmission and pathogenicity of the vector in humans in the following categories:	Non replicating in humans therefore no transmission.		
in healthy people	N/A		
in immunocompromised people	N/A		
in neonates, infants, children	N/A		
during pregnancy and in the unborn	N/A		
in gene therapy experiments	N/A		
in any other special populations	N/A		
4.4. Is the vector replication-competent in non-human species?	No		

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Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
4.5. What is the risk of reversion to virulence or recombination with wild type virus or other agents?	Low risk. Reversion to virulence would require the acquisition of a functional E1 region. Recombination with wild type Y25 is possible but unlikely as Y25 and other simian adenoviruses are not widely distributed in the human population. Recombination with other adenovirus species would require significant homology in the E1 flanking regions. These regions contain essential packaging motifs and other genes, therefore the number of possible recombination events to generate a replication competent virus is very small. Recombination with E1 producer cell lines during manufacturing process is theoretically possible.	Prevalence of virus neutralizing antibodies (titer greater than 1:200) against ChAdY25 in serum samples collected from two human populations in the UK and Gambia was low. The wild type virus is not widely present in the general population Testing for recombinant-competent adenoviruses is conducted at all times ahead of vaccine release.	[17,85]
4.6 Is the vector genetically stable in vitro and/or in vivo?	Yes	The viral vector backbone is genetically stable in vitro.	
4.7. What is the potential for shedding and transmission to humans or other species?	None as this vector does not replicate.		
4.8. Does the vector establish a latent or persistent infection?	No		
4.9. Does the vector replicate in the nucleus?	No		
4.10. What is the risk of integration into the human genome?	Low risk	See 3.6	
4.11. Is there any previous human experience with this or a similar vector (safety and immunogenicity records)?	Yes, multiple phase I/II clinical trials have been conducted or are underway on ChAdOx1 vectored vaccines expressing influenza, tuberculosis, malaria, meningococcal B, hepatitis B, prostate cancer, HIV, MERS-CoV, Chikungunya, Zika, and Plague and SARS-CoV-2. Phase III clinical trials were conducted on ChAdOx1 nCoV-19 and the vaccine has now been deployed to [54] over two billion persons in multiple different countries.	Clinicaltrials.gov: NCT04121494, NCT03681860, NCT03815942, NCT03203421, NCT03590392, NCT04015648, NCT03399578, NCT04170829, NCT04297917, NCT04364035, NCT03204617 ISRCTN46336916, ISRCTN41077863	[42,43,47,48,52,86]
4.12. What cell types are infected and what receptors are used in humans?	See 3.8		
4.13. What is known about the mechanisms of immunity to the vector?	Neutralizing antibodies to ChAdOx1 are induced post prime vaccinations. A homologous second dose does not seem to boost these responses against the vector. A homologous second dose is able to significantly boost binding and neutralizing antibodies to the vaccine antigen. The impact of anti-vector immunity on antibody and cellular responses to different vaccine antigens remains unclear and further work is required but appears to be low.		[87,88]
4.14 Has disease enhancement been demonstrated with the vector:	No		
● in vitro?	No	Antibody dependent enhancement to Dengue has been assessed in vitro for a ChAdOx1 vectored vaccine expressing Zika virus antigens	[23]
● in animal models?	No	ChAdOx1 vectored vaccines expressing Nipah, MERS-CoV and SARS-CoV-2 antigens have been used in pre-clinical challenge or natural transmission studies in mice, camels and Non-Human-Primates with no evidence of disease enhancement.	[22,26,27,45,89]
● in human hosts?	No	There has been no evidence of disease enhancement to date, either from clinical trials of ChAdOx1 nCoV-19 or from COVID-19 vaccine roll-out	[52]
4.15. Is there antiviral treatment available for disease manifestations caused by the vector?	See 3.14		
4.16. Can the vector accommodate multigenic inserts or will several vectors be required for multigenic vaccines?	This vector can accommodate multigenic inserts but with a limit on transgene size up to 8kbp, include the required promoter and terminator sequences		

Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
5. Characteristics of vector-based vaccine(s)	**Information**	**Comments/ Concerns**	**Reference(s)**
5.1. What is the target pathogen?	Any pathogen expressing proteins that would generate a protective immune response	Multiple clinical trials have been conducted or are underway on ChAdOx1 vectored vaccines expressing influenza, tuberculosis, malaria, meningococcal B, hepatitis B, prostate cancer, HIV, MERS-CoV, Chikungunya, Zika, Plague, and SARS-CoV-2. Pre-clinical work which is expected to lead into clinical trials in the near future include ChAdOx1 vectored vaccines expressing Ebola (Bivalent), Crimean-Congo Hemorrhagic Fever, Nipah and Lassa antigens.	See 4.11 [22,24,25]
5.2. What is the identity and source of the transgene?	All transgenes are synthesized and cloned into a shuttle vector containing the promoter and poly A sequence. The expression cassette is inserted into the adenovirus BAC by recombination.	Cytoplasm-evolved genes were not optimized for nuclear expression in ChAdOx1 vectored vaccines. Transcriptomics and proteomics data of ChAdOx1 nCoV-19 gene expression in human cell lines show that rare transgene transcripts with aberrant splice patterns can be detected at a very low level. However, no protein is transcribed from them. Aberrant splicing, therefore, seems to be a theoretical concern only	[90]
5.3. Is the transgene likely to induce immunity to all strains/ genotypes of the target pathogen?	This is dependent on the transgene used.	For ChAdOx1 MERS, consistent neutralizing activity has been observed across different MERS-CoV isolates. Pre-clinical work on a ChAdOx1 vectored vaccine expressing Nipah virus antigens have shown cross protection against homologous and heterologous challenge (Nipah Bangladesh and Malaysia). Decreased neutralizing activity has been observed across different SARS-CoV-2 variants of concern compared to the original strain.	[22,84,91,92]
5.4. Where in the vector genome is the transgene inserted?	Insertion at the E1 locus for single valent vaccines or E1 and E4 for multivalent vaccines.		
5.5. Does the insertion of the transgene involve deletion or other rearrangement of any vector genome sequences?	The E3 genes are deleted in addition to E1 genes. E3 gene products are immunomodulatory and non-essential for in vitro vector growth.		
5.6. How is the transgene expression controlled (transcriptional promoters, etc.)?	Cytomegalovirus immediate early promoter with or without intron A sequence. Polyadenylation sequence is from bovine growth hormone gene or SV40.		
5.7. Does insertion or expression of the transgene affect the pathogenicity or phenotype of the vector?	No, the vector remains structurally the same. Deletion of E1, to allow for insertion of the transgene, renders the virus replication incompetent.		
5.8. Is the vaccine replication-competent in humans or other species?	No		
5.9. What is the risk of reversion to virulence or recombination with wild type or other agents?	See 4.5		
5.10. Is the vaccine genetically stable in vitro and/or in vivo?	This depends on the size of the expression cassette and the nature of the transgene product.	See 4.6	
5.11. What is the potential for shedding and transmission to humans or other species?	None as this vector does not replicate.		
5.12. Does the vaccine establish a latent or persistent infection?	No		
5.13. Does the vaccine replicate in the nucleus?	No		
5.14. What is the risk of integration into the human genome?	Low risk	See 3.6	
5.15. List any disease manifestations caused by the vaccine in humans, the strength of evidence, severity, and duration of disease for the following categories:	See 4.11.		

(*continued on next page*)

Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
In healthy people	Dose dependent reactogenicity following several ChAdOx1 vectored vaccines have been reported as part phase I clinical trials. Commonly reported adverse events include local (injection site pain) and systemic (headache, fatigue, feverishness/chills, malaise). Most adverse events have been mild or moderate in severity and self-limiting in nature. Onset of local and systemic AEs usually take place within 24–48 h post vaccine administration. Objective fever (T $\geq$ 38oC) has been reported in approximately 7.6% of individuals. A second dose is markedly less reactogenic. A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with COVID-19 Vaccine ChAdOx1 nCoV-19 during post-authorization use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. Very rare cases of Guillan-Barre Syndrome and Capillary Leak Syndrome have been observed following vaccination with COVID-19 Vaccine ChAdOx1 nCoV-19 during post-authorization use		[42,43,46,47,86,93]
In immunocompromised people	There are ongoing clinical trials of ChAdOx1 vectored vaccines (HIV and SARS-CoV-2 antigens) in people living with well controlled HIV, with no safety concerns reported to date. Compared with participants without HIV, no difference was found in magnitude or persistence of SARS-CoV-2 spike-specific humoral or cellular responses	NCT04444674, NCT04400838, NCT03204617, NCT04364035, NCT04805216, NCT04878822	[94]
In neonates, infants, children	There is an ongoing clinical trial of ChAdOx1 nCoV-19 in children aged between 6 and 17. No safety concerns have been reported to date.	ISRCTN15638344	
During pregnancy and in the unborn	Not assessed	Accidental pregnancies have occurred during COVID-19 clinical trials. Pregnant volunteers are being followed until 3 months post live birth and pregnancy outcomes being recorded, which will generate some data on safety of ChAdOx1 vectored vaccines during pregnancy and in the unborn. A pregnancy registry of women exposed to the ChAdOx1 vectored COVID-19 vaccine immediately before or during pregnancy as part of an international consortium is planned. A DART study has been completed and maternal immunization studies are now planned.	Unpublished
In any other special populations	Older adults with comorbidities have been included in clinical trials of ChAdOx1 vectored vaccines (Influenza and SARS-CoV-2 antigens). The reactogenicity profile is milder in older age groups after prime compared to young adults, with similar immune responses after a second dose. ChAdOx1 vectored vaccines have been administered to adults with Prostate Cancer with similar reactogenicity profile. Clinical trials of ChAdOx1 vectored vaccines in chronic Hepatitis B and HPV patients are underway.	NCT04607850, NCT04297917	[43,48,53]
5.16. What cell types are infected and what receptors are used in humans?	See 3.8	Any transgene expressed from the vaccine would not alter cell tropism Adenoviruses are comprised of a protein capsid and do not incorporate foreign proteins into their structure.	

Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
5.17. What is known about the mechanisms of immunity to the vaccine?	Immune responses will vary depending on the antigen. ChAdOx1 vectored vaccines have consistently shown to induce binding and neutralizing antibodies and T-cell responses.		[18,42,43,46-48,53,86,93]
5.18 Has disease enhancement been demonstrated with the vaccine:	No		
● in vitro?	See 4.14		
● in animal models?	See 4.14		
● in human hosts?	See 4.14		
5.19 What is known about the effect of pre-existing immunity, including both natural immunity and repeat administration of the vector or the vaccine, on 'take', safety or efficacy in any animal model or human studies using this vector?	See 4.13. Vaccine reactogenicity does not seem to vary according to target disease serostatus at baseline or pre-existing anti-vector responses.		[93]
5.20. Is the vaccine transmissible in humans or other species (including arthropods) and/or stable in the environment?	No		
5.21. Are there antiviral or other treatments available for disease manifestations caused by the vaccine?	See 3.14. Prophylactic paracetamol has been shown to reduce severity of AEs reported post vaccine administration. There are currently no robust data to inform clinical management of vaccine induced immune thrombocytopenia and thrombosis. In the absence of published evidence, there are pragmatic guidelines based on experience of managing the initial cases, alternative similar conditions and the theoretical risks and benefits of interventions. As evidence emerges, recommendations are expected to change. Patient management should be individualized according to specific circumstances.		[46]
5.22. Vaccine formulation	Liquid solution for injection. Known thermostability at 2–8 °C		
5.23. Proposed route of vaccine administration	Intramuscular		
5.24 Target populations for the vaccine (e.g pediatric, maternal, adult, elderly etc.)	Currently adults aged over 18 Pediatric studies are in progress and maternal immunization studies are planned.		
6. Toxicology and potency (Pharmacology) of the vector	**Information**	**Comments/ Concerns**	**Reference(s)**
6.1. What is known about the replication, transmission and pathogenicity of the vector in and between animals?	Non-replicating vector so no transmission regardless of species.		
6.2. For replicating vectors, has a comparative virulence and viral kinetic study been conducted in permissive and susceptible species? (yes/no) If not, what species would be used for such a study? Is it feasible to conduct such a study?	n/a		
6.3. Does an animal model relevant to assess attenuation exist?	No	Replication competent adenovirus assays are conducted in permissive cells alongside examination for the presence of virus-induced cytopathic effect.	
6.4. Does an animal model for safety including immuno-compromised animals exist?	Standard toxicology studies conducted in mice		Unpublished
6.5. Does an animal model for reproductive toxicity exist?	A DART study has been completed in mice with no detrimental effects observed in pregnancy, embryofetal development, parturition or post-natal development	See reference for further details	[95]
6.6. Does an animal model for immunogenicity and efficacy exists?	Mice, target species (e.g., Camel for MERS-CoV; sheep/cattle/goat for Rift Valley Fever), Non-Human-Primates, hamsters, ferrets, guinea pigs, cats.		[22,26,27,32,35,45,47,89]
6.7 Does an animal model for antibody enhanced disease or immune complex disease exist?	Immunopathology studies have been conducted in mice and NHPs following challenge studies of MERS-CoV and SARS-CoV-2. However, there are no established models to assess disease enhancement.		[26,27,45]

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Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
6.8. What is known about biodistribution in animal models or in humans?	Biodistribution studies in mice have been conducted for ChAdOx1 vectored vaccines expressing Hepatitis B and SARS-CoV-2 antigens. No shedding was detected in urine or fecal samples. Virus was primarily detected at the injection site immediately after injection, and at draining lymph nodes. Distribution to some samples of other tissues (liver, lung, spleen, bone marrow, heart, liver, ovary and testes) was noted on day 2. The levels of ChAdOx1 vector DNA and the number of tissues with detectable levels of ChAdOx1 vector DNA decreased from Day 2 to later timepoints (day 29 and day 56), indicating elimination.	Biodistribution studies are more informative when a replication-competent virus is administered since the amount of virus present in the subject (experimental animal or human volunteer) will increase following injection, and some viruses have a known propensity to accumulate in particular organs. However, replication-deficient viruses are known to infect cells at the injection site, and although some infectious viral particles may drain to local lymph nodes and travel through the blood to other sites in the body, concentrations of virus at these sites are very low after dilution in the blood and other tissues.	[96]
6.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:			
Small animal models?	Binding and Neutralizing antibodies and T-cell responses		[22,23,26,27,32,34,35,44,89,97]
Nonhuman primates (NHP)?	Binding and Neutralizing antibodies and T-cell responses		[27,45]
Human?	Binding and Neutralizing antibodies and T-cell responses		[18,42,43,46-48,53,86,93]
6.10. Have challenge or efficacy studies been conducted in subjects with:			
HIV?	No	Safety and immunogenicity studies have been conducted (See 5.15)	
Other diseases?	No		
6.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes? Is there evidence for interaction/ interference?	Clinical trials of simultaneous vaccine administration of 2 ChAdOx1 vectored vaccines expressing 2 different transgenes (Zika and Chikungunya) are planned. Participants who previously received any ChAdOx1 vectored vaccines have been invited to receive ChAdOx1 nCoV-19 as part of a phase II COVID-19 vaccine trial, with no differences in binding antibody titres compared to ChAdOx1 naïve individuals.	NCT04015648, NCT04440774, NCT04400838	[88]
7. Adverse Event (AE) Assessment of the Vector (*see Instructions):	**Information**	**Comments/ Concerns**	**Reference(s)**
7.1. Approximately how many humans have received this viral vector vaccine to date? If variants of the vector, please list separately. _____	Over 30,000 people as part of clinical trials and [54] over two billion persons as part of COVID-19 vaccine roll out in more than 180 countries	NCT04121494, NCT03681860, NCT03815942, NCT03203421, ISRCTN46336916, NCT04170829, NCT03590392, NCT04015648, NCT04440774, NCT04297917, NCT04778904, NCT04607850, NCT03204617, NCT04364035, ISRCTN89951424, PACTR202005681895696, ISRCTN15638344, NCT04516746, CTRI/2020/08/027170, NCT04568031	[42,43,46-48,52,53,86]
7.2. Method(s) used for safety monitoring:			
Spontaneous reports/passive surveillance	Yes	Post implementation surveillance from regulatory agencies	
Diary	Yes	28 days_____	
● Other active surveillance	Yes	SAEs and AESIs at each follow-up visit_____	
7.3. What criteria was used for grading the AE's?			
2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	No		
If no or other, please describe:	Toxicity grading scales have been adapted from the 2007 US FDA Guidance		
7.4. List and provide frequency of any related or possibly related serious* AE's observed: (*see Instructions):	Pre-introduction clinical trials: short segment, spinal cord demyelination (n = 1) Post-introduction: 1) Thrombosis with Thrombocytopenia Syndrome (TTS; also known as vaccine-induced immune thrombotic thrombocytopenia (VITT)); 2) Capillary Leak Syndrome (CLS); 3) Immune Thrombocytopenia (ITP); 4) Guillain-Barre Syndrome (GBS);	1) ~ 2/100,000 doses reporting rate to passive surveillance; 2) six cases reported to European and two cases to Australian authorities; 3) safety signal; 4) ~ 1/100,000 doses reporting rate to passive surveillance	[52,98-101,109]

Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates			
7.5. List and provide frequency of any serious, unexpected AE:	See 7.4		
7.6. List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control group:	Pre-introduction clinical trials: Transient mild haematological changes from baseline of no clinical significance are expected following ChAdOx1 vectored vaccines (leucopenia, neutropenia, lymphopenia or thrombocytopenia) Post-Introduction: See 7.4		
Describe the control group: _____.	Pre-Introduction: MenACWY and/or normal saline		
7.7. List and provide frequency of Adverse Events of Special Interest	Pre-Introduction: Serious adverse events and adverse events of special interest balanced across the study arms Post-Introduction: See 7.4		[52]
7.8. Did Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes		
Did it identify any safety issue of concern?	No		
If so describe:			
8. Overall Risk Assessment of the Vector	**Information**	**Comments/ Concerns**	**Reference(s)**
8.1. Please summarize key safety issues of concern identified to date, if any:	Pre-Introduction: No significant safety issues were identified in clinical trials of ChAdOx1 vectored vaccines. One clinical trial participant developed short segment spinal cord demyelination episode 14 days post a booster dose of ChAdOx1 nCoV-19 which was deemed possibly related to the vaccine. Post-Introduction: TTS, in some cases accompanied by bleeding, has been observed very rarely following post-authorization vaccination. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia Mortality reduced from ~ 50% to < 5% with early treatment. The majority of these cases occurred within the first three weeks following vaccination Very rare cases events of CLS, ITP, and GBS Guillain-Barre Syndrome and Capillary Leak Syndromedemyelinating disorders have been reported following vaccination with COVID-19 Vaccine ChAdOx1 nCoV-19/AstraZeneca. A causal relationship has not been established.	TTS seems to occur primarily after the first dose. TTS after the second dose seems to occur within background expected rates The benefits of protection against severe COVID-19 and death outweighs the risks of vaccine induced TTS in most settings, especially with mitigation of risks when possible. There is currently insufficient evidence as to whether TTS is associated more broadly with adenovirus vectors or are specific to the ChAd and Ad26 COVID vaccines.	[52,57,102-104]
how should they be addressed going forward:	All of the identified risks should be treated as AESIs in clinical trials of ChAdOx1 vectored vaccines TTS: Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia. CLS: Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted. Individuals with a known history of CLS	While there is currently a lack of robust data to definitively establish standard of care of TTS, similarities to heparin induced thrombocytopenia, expert opinion, and case reports suggest, at the time of writing, that management should include the use of non-heparin-based anticoagulants and consideration of treatment with IVIG. However, heparin should not be withheld in acute VITT if no other therapeutic option is available. Patient management should be individualized according to specific circumstances.	[99,105-108]

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Table 1 (*continued*)

Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) Standardized Template V2.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Candidates		
	should not receive this vaccine. ITP: If an individual has a history of ITP, the risk of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination GBS (Guillain-Barre Syndrome Demyelinating disorders): Healthcare professionals should be alert of demyelinating disorders signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.	
8.2. What is the potential for causing serious unwanted effects and toxicities in:		**Please rate risk as: none, minimal, low, moderate, high, or unknown**
healthy humans?	TTS, CLS, ITP and GBS	Low
● immunocompromised humans?	TTS, CLS, ITP and GBS	Unknown
● ● Human neonates, infants, children?	TTS, CLS, ITP and GBS	Unknown
● ● pregnancy and in the unborn in humans?	TTS, CLS, ITP and GBS	Unknown
● in any other special populations.	TTS, CLS, ITP and GBS	Low
8.3. What is the potential for shedding and transmission in risk groups?		None, as the vector is replication deficient

ChAdY25 was shown to be equivalent to that of ChAd63 and AdC68 in both single dose and heterologous prime-boost vaccine regimens. The ChAdY25 vector has the E3 region deleted in addition to E1 that renders it replication incompetent and allows for increased insertional capability. In addition, the E4 region is a chimeric of Ad5 and Y25 to enhance growth of ChAdY25 in HEK293 cells. For future studies the vector was named ChAdOx1 [17].

The ChAdOx1 vector has been advocated for use in potential pandemic outbreaks by establishing vaccine candidates for stockpiling vaccines for emergency deployment. To this end, vaccines against a variety of infectious diseases and prostate cancer have been targeted [18]. Animal studies have been performed and multiple phase I/II clinical trials have been conducted or are underway on ChAdOx1 vectored vaccines expressing influenza, tuberculosis, malaria, meningococcal B, hepatitis B, prostate cancer, HIV, MERS-CoV, Chikungunya, Zika, Rift Valley Fever, HPV, and SARS-CoV-2. In addition, phase III clinical trials have been conducted on a ChAdOx1 nCoV-19 vaccine that is now being used extensively worldwide to combat the Covid-19 pandemic.

2.3. Pre-clinical studies of vaccines based upon the ChAdOx1 vector

Several pre-clinical studies have been performed using the ChAdOx1 vector including preliminary research of vaccine candidates for use in potential pandemic situations. Studies in small animal models have shown good potential of a number of ChAdOx1 vectored vaccines including those encoding antigens from influenza virus [19-21], Nipah virus [22], Zika virus [23], Lassa virus [24], filoviruses [25], MERS-Cov virus [26], SARS-CoV-2 virus [27-29], blue tongue virus [30], Rift Valley fever virus [31-33], Chikungunya virus [34,35], Human Immunodeficiency virus (HIV) [36,37], Human papilloma virus (HPV) [38], Hepatitis C virus [39,40] and Hepatitis B virus [41]. In some studies, large animals specific for the viral disease of concern were used, for example, pigs for ChAdOx1 expressing influenza virus haemagglutinin, sheep for the ChAdOx1 vector expressing blue tongue virus antigens, and sheep, cattle, dromedary camels and goats for ChAdOx1 expressing Rift Valley fever virus antigens. Some of the studies incorporated a heterologous vaccination regimen priming with the ChAdOx1 vector vaccine and boosting with an MVA vectored vaccine expressing the same antigen [43,47,48]. In all cases a robust immune response was obtained and in several of the studies protection from live viral challenge was demonstrated.

2.4. Clinical studies of vaccines based upon the ChAdOx1 vector

Ongoing but unpublished trials are not listed here.

2.4.1. Influenza

The first human trial of a vaccine based upon ChAdOx1 assessed the safety and T cell responses of the vector expressing influenza virus conserved antigens nucleoprotein and matrix protein 1 (NP and M1) [42]. These antigens were chosen for a study designed to assess a universal flu vaccine. Prior to immunization, no to little immunity to the ChAdOx1 vector was detected in the subjects and post-immunization most subjects sero-converted, or the titer of anti-vector neutralizing antibodies increased to varying degrees. ChAdOx1 NP + M1 was administered at doses ranging from 5×10^8 to 5×10^{10} viral particles (vp). The vaccine was well tolerated with no serious adverse events (AEs); however, at the highest dose (5×10^{10} virus particles), a higher level of local and systemic reactions was observed in two volunteers and so the next highest level of 2.5×10^{10} virus particles was deemed appropriate for further human studies of the vaccine.

In a long-term (18 months) clinical study, a two-dose heterologous vaccination regimen of MVA-NP + M1/ChAdOx1-NP + M1 (at

2.5 × 10^{10} vp) was safe and immunogenic in young and older adults [43].

2.4.2. Middle east respiratory syndrome (MERS)

Progressing from a successful demonstration of the immunogenicity of ChAdOx1 vectored MERS-CoV vaccine in mice [26,44], and of protective immunity in rhesus macaques [45], the safety and immunogenicity of a ChAdOx1 vaccine expressing the MERS-CoV surface spike glycoprotein was assessed in a phase I trial [46]. The vaccine was found to be safe and well tolerated at all dose levels tested (5 × 10^9, 2.5 × 10^{10}, and 5 × 10^{10} vp), and a single dose elicited both humoral and cell responses to the MERS-CoV virus.

2.4.3. Tuberculosis

A human phase I trial evaluated the safety and immunogenicity of a heterologous vaccination regimen of ChAdOx1-85A prime (5 × 10^9 and 2.5 × 10^{10} vp) /MVA-85A boost. Local and systemic AEs were mild to moderate. A small number of subjects (2/12) experienced severe pain at the vaccination site following MVA-85A vaccination at day 56, and a small number of subjects (4/42) experienced severe systemic reactions including severe fatigue, feverishness, headache, myalgia, or malaise at differing stages of the vaccination regimen. No Serious Adverse Events (SAEs) were reported. Vaccination with ChAdOx1-85A induced Ag85A-specific IFN-γ responses that could be boosted with heterologous MVA-85A vaccination, although the T-cell responses observed after a single dose of ChAdOx1-85A were not boosted by a second homologous dose [47].

2.4.4. Prostate cancer

In a phase I study, ChAdOx1 (2.5 × 10^{10} vp) and MVA expressing the oncofetal self-antigen 5 T4 were administered to low-risk and intermediate-risk prostate cancer subjects following a heterologous prime/boost regimen. Both vaccines were well tolerated with the majority of systemic AEs graded as mild and which usually resolved within 7 days post-vaccination. There were no reported SAEs related to the vaccines. The vaccines were immunogenic and elicited CD8 + and CD4 + polyfunctional 5 T4-specific T cells [48].

2.4.5. Chikungunya virus

ChAdOx1 expressing the Chikungunya virus (CHIKV) full-length structural polyprotein comprising capsid, E3, E2, 6 k and E1 was evaluated in a first-in-human trial of 24 adult healthy volunteers. A single intramuscular injection was safe at all doses tested (5 × 10^9, 2.5 × 10^{10}, and 5 × 10^{10} vp) with no serious adverse reactions reported. The vaccine induced IgG and T-cell responses against the structural antigens and broadly neutralizing antibodies against the four CHIKV lineages were found in all participants [49].

2.4.6. Sars-CoV-2

ChAdOx1 nCoV-19 was constructed to express a full-length wild type spike glycoprotein of SARS-CoV-2. The expressed glycoprotein has been shown to undergo native-like post-translational processing and assembly and adopt the trimeric prefusion conformation on the surface of cells [50]. In pre-clinical studies in mice and rhesus macaques, the vaccine was immunogenic, eliciting robust humoral and cell-mediated responses in mice and a balanced humoral and cellular response in rhesus macaques with no evidence of immune-enhanced disease after viral challenge of vaccinated SARS-CoV-2 infected animals [27]. A phase I/II study showed an acceptable safety profile when administered at a 5 × 10^{10} vp dose with local and systemic reactions involving pain, feeling feverish, chills, muscle ache, headache and malaise, and no SAEs related to the vaccine [51]. In a phase III trial, overall vaccine efficacy against virologically confirmed symptomatic SARS-CoV-2 infection was 70.4% and the vaccine had a good safety profile, with SAEs and AEs of special interest balanced across the study arms [52]. Further studies in older adults showed the vaccine to be tolerated better in older than in younger adults with all age groups demonstrating similar immunogenicity [53].

The ChAdOx1 nCoV-19 vaccine is now on the WHO Emergency Use Listing (EUL) and has been granted EUA in over 180 countries with more than two billion doses distributed [54].

2.5. Post-Introduction safety experience

While not identified in clinical trials involving thousands of participants, vaccination of many millions of people with adenoviral vector-based vaccines against SARS-CoV-2, including the ChAdOx1 nCoV-19 vaccine and the Janssen COVID-19 vaccine, have resulted in the identification of very rare, serious, and potentially fatal adverse events such as thrombosis with thrombocytopenia syndrome [TTS; also known as vaccine-induced immune thrombotic thrombocytopenia (VITT)], with similarities to heparin-induced thrombocytopenia. TTS is manifested by venous or arterial thrombosis including unusual sites, such as cerebral venous sinus thrombosis and/or splanchnic vein thrombosis, in combination with thrombocytopenia [55,56]. A geographical difference was observed in the risk for TTS as indicated by the reporting rate (cases per million doses administered per 21 days) in different countries suggesting multifactorial role in the development of TTS. [109] No definitive mechanism has been established to explain such rare events to date, but early treatment (ideally with specialists) can reduce mortality from ∼ 50% to < 5% [57]. The observation of anti-Platelet Factor 4 (PF4) antibodies in TTS patients following immunization with the ChAdOx1 nCoV-19 vaccine has led to hypothesis that they may be involved in platelet aggregation with resultant thrombocytopenia and/or thrombosis [55,58,59]. Other hypotheses invokes unintended and unanticipated splicing of the nascent SARS-CoV-2 spike mRNA generating erratic and toxic spike protein structures or accidental intravascular injection.

Following a very small number of cases of capillary leak syndrome (CLS) following ChAdOx1 nCoV-19 vaccine administration, the EMA has announced that people who have previously had CLS must not be vaccinated with Vaxzevria (formerly COVID-19 Vaccine AstraZeneca; brand names of the ChAdOx1 nCov-19 vaccine)) and that CLS should be added to the product information as a new side effect of the vaccine [60]. Very rare cases of Thrombocytopenia including Immune Thrombocytopenia (ITP) and Guillain-Barre syndrome (GBS) have also been reported and a warning has also been added to the Vaxzevria EMA product information [61,62]. See section 7.4 of Table for latest estimated rates of these adverse events of special interest.

Several post-authorization safety studies (PASS) to assess these safety signals have been added to the Vaxzevria Risk Management Plan (RMP) [63]. Results from the self-controlled case series analysis and population based cohort study generally showed small increased risk of TTS-associated outcomes among ChAdOx1 vaccinees compared to controls, but lower risk compared to SARS-CoV-2 infection in the same population [64-66]. Extensive immunogenicity studies reveal strong, durable humoral and cellular immune responses to date; studies to refine the COVID-19 protection (e.g., via homologous/heterologous booster, fractional dose) are also underway. The results of ongoing evaluation of ChAdOx1-based vaccines by stringent regulatory bodies and recommendations for their use are publicly available.

New prophylactic and therapeutic vaccines based on the ChAdOx1 vector are currently undergoing pre-clinical and clinical assessment, including vaccines against viral hemorrhagic fevers, Nipah, HIV, Hepatitis B, amongst others.

3. Conclusion

ChAdOx1 has shown a consistent safety and immunogenicity profile in over 30,000 people who took part in clinical trials of ChAdOx1 vectored vaccines expressing different antigens. Over 2 billion doses of the ChAdOx1 COVID-19 have been distributed to more than 180 countries. In most settings, the benefit/risk balance remains positive in the context of the very rare serious adverse reactions identified during widespread use of the ChAdOx1 nCoV-19 vaccine, compared to risks of severe COVID-19 and COVID-19 death. Evaluation of ChAdOx1-based vaccines is continuing as part of ongoing clinical trials and regulatory surveillance systems.

4. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official positions of any participants organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

The BRAVATO authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The University of Oxford has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. SG is a cofounder of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1 vectored vaccines and a patent application covering the SARS-CoV-2 vaccine (PCT/GB2012/000467). PMF is a consultant to Vaccitech and received funding from the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior, Brazil (finance code 001). AstraZeneca reviewed the final manuscript but the authors retained editorial control.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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