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Environmental Risk Assessment (ERA) of Recombinant Viral Vector Vaccines against SARS-CoV-2

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INTRODUCTION

Many efforts have been directed towards the rapid development of effective and safe COVID-19 vaccine candidates by use of a range of vaccine platforms. Two recombinant adenoviral vector vaccines, ChAdOx1-S (AstraZeneca) and Ad26.CoV2.S (Janssen) are authorized for use in European Union (EU). In the EU, vaccines based on recombinant viral vectors are subject to additional regulatory requirements on top of those related to their safety, efficacy and quality control as they are considered genetically modified organism (GMOs). Some of these GMO-associated requirements aim to assess aspects related to potential risks for human health (other than the vaccinee) and the environment, including animal, plants and micro-organisms, what is called « environmental risk assessment (ERA) ». We elaborate on key features of the ERA in relation to several recombinant viral vector COVID-19 vaccine candidates.

Type of viral vector	Key features of the environmental risk assessment proper to viral vector COVID-19 vaccine candidates
Replication deficient viral vectors	
Adenoviral vectors	• Due to larger experience with this vaccine platform, possibility to build on good understanding of the host range, cellular tropism • Predominantly episomal in host cell nuclei; integration into the cell genome: extremely rare event • Probability of replication competent adenoviruses (RCA) emergence reduced during the manufacturing process; should be demonstrated • Emergence of RCA after administration of the vaccine by homologous recombination with parental wt Ad or other related hAd infecting the same host cell: theoretical hazard (never reported with Ad replication-defective vectors) • Shedding of Ad vectors following intramuscular (IM) administration: very rare event • Specific attention to oral and subcutaneous mode of administration (might increase probability of shedding) • Germline transmission: not observed after systemic administration of hAd5 vectors in mouse
Modified Vaccinia Virus Ankara (MVA) vectors	• Highly attenuated orthopoxvirus, not able to replicate in mammalian hosts, no natural reservoir • Widely tested for vaccination or gene therapy, good safety profile in immunocompromised humans and infants • Remains localized in the cytoplams: no integration in the host genome • Importance of the homogeneity and genetic stability of the recombinant MVA vector • Assessment of the probability of recombination events in human hosts: specific attention to monkeypoxvirus who circulates among humans
Recombinant influenza virus vectors	• Backbone is safe and well tolerated after intranasal administration • No shedding data available – transient local shedding expected • Nonreplicative in humans • Possible reassortment events with circulating wt strains – assessment of the reassorted vaccine candidates
Replication competent viral vectors	
Live-attenuated measles virus (MV) vector	• Proven safety profile • Stability of the MV genome • Humans are the only known known reservoir, non-human primates can be infected • Risk of recombination with wt MV is negligible • Most individuals in industrialised countries are immune to wt MV
Vesicular stomatitis virus (VSV)-vectors	• Derived from a vector-borne virus, has several animal hosts • Express the SARS-CoV-2 Spike (S) protein on the surface of the virion • Replicate within the cytoplasm of infected cells and does not integrate into the cellular genome • A better understanding of tropism and biodistribution pattern is still needed and warrants the collection of more shedding data • No shedding data has been reported • Recombination with wt-VSV cannot be excluded and should be evaluate • Shedding data should be collected • Likelihood of transmission from vaccinee to non vaccinated individuals should be assessed
For all viral vectors	**The exogenous inserted gene sequences and its product:** Spike (S) protein and other inserted gene sequences of SARS-CoV-2 have no intrinsic hazardous properties

CONCLUSIONS

Data available on tropism and biodistribution, potential recombination and shedding show that SARS-CoV-2 vaccine based on adenoviral vectors, MVA vectors and measles virus vectors have a good safety profile in regard to their potential risks for human health and the environment.
For influenza vectors, more data are needed to better understand de likelihood of exchange of genetic material with or the complementation by co-infecting wt influenza strains. Considering that Influenza A virus can remain infective for days in humid conditions and has many permissive hosts, such as wild birds and mammals, a precautionary approach is justified when implementing risk management measures,
For VSV vectors, as long as data on biodistribution, shedding and viremia levels are not completed, due consideration is to be given to measures aiming at minimising contact of trial participants with immunocompromised individuals, vulnerable persons or persons who have increased risk of severe COVID-19 disease. Regarding the risk for animals and if shedding data is lacking, human-to-animal transmission can also not be excluded. Risk mitigation measures could be implemented.

REFERENCE

• Baldo, A. et al, *Vaccines* 2021, 9, 453 , https://doi.org/10,3390/vaccines9050453

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