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Review

Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) standardized template for collection of key information for benefit-risk assessment of live-attenuated viral vaccines

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ABSTRACT

Several live-attenuated viral vaccine candidates are among the COVID-19 vaccines in development. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) has prepared a standardized template to describe the key considerations for the benefit-risk assessment of live-attenuated viral vaccines. This will help key stakeholders assess potential safety issues and understand the benefit-risk of such vaccines. The standardized and structured assessment provided by the template would also help to contribute to improved communication and support public acceptance of licensed live-attenuated viral vaccines.

Contents

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[1] See Acknowledgement for other V3SWG members.

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1. Introduction:

The Brighton Collaboration (www.brightoncollaboration.org) was launched in 2000 to improve the science of vaccine safety [1]. The Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October 2008 to improve the ability of key stakeholders to anticipate potential safety issues and meaningfully assess or interpret safety data, thereby facilitating broader acceptance when viral vaccines are licensed [2]. One of the tools developed by the V3SWG is a standardized template describing the key considerations for benefit-risk assessment of viral vaccines. Completed by the vaccine developers/sponsors, it will be peer reviewed by the V3SWG and published. The information on the template may facilitate communication of otherwise complex and highly technical data among key stakeholders (some of whom may lack subspecialized training in biotechnology) and increase the transparency, comparability, and comprehension of essential information. A similar template has been used for the standardized risk-assessment of several new viral vector vaccines [3-5], including some targeting Ebola. The WHO Global Advisory Committee on Vaccine Safety (GACVS) endorsed the use of the template for other new candidate Ebola vaccines "as it is a structured approach to vaccine safety" [6].

In 2020, the development of vaccines for COVID-19 is occurring with unprecedented speed [7]. The pace and volume of development make a deliberate and systematic approach that is accessible and understandable to a diversity of stakeholders all the more important. Live-attenuated viral vaccine candidates are among the COVID-19 vaccines in development [8]. The Brighton Collaboration V3SWG has therefore developed a specific template for live-attenuated vaccines that vaccine developers and other key stakeholders can use to evaluate and communicate the benefit-risk of such vaccines. See Supplementary Material for definitions and additional guidance for completing this template.

Live-attenuated viral vaccines are among the most successful types of vaccines developed to date. They consist of a modified version of the virus against which protection is sought. The vaccine viruses replicate in the vaccinee; while generally not causing disease nor symptoms, and are able to stimulate a protective immune response [9]. In the development of such a vaccine, attenuation and immunogenicity have to be balanced carefully [10,11]. Live-attenuated vaccines are usually contraindicated in individuals with impaired immunity. Additionally, some live-attenuated viral vaccines are shed from vaccinees and could present a risk to unvaccinated individuals with impaired immunity.

Live-attenuated viral vaccines have been classically developed by multiple passages of a wild type specimen in vitro in a variety of cell lines, in vivo in animals or *in ovo*, whereas today live-attenuated vaccines are generally created by genetic engineering. For viruses with segmented genomes, live-attenuated vaccine viruses have been generated by directed or engineered reassortment of the genomes of different strains.

The success of live-attenuated vaccines is based on the fact that the immune response to the attenuated vaccine virus mimics closely the response resulting from natural infection. Examples of successful live-attenuated viral vaccines include those targeting polio, mumps, measles and rubella; now part of childhood immunisation programmes; and influenza, varicella, yellow fever and, of course, vaccinia, that was used for the eradication of smallpox [10,11].

Compared with other types of vaccines, attenuated viral vaccines usually require considerably more time to develop and test. This is due to the need to demonstrate not only safety and immunogenicity in the vaccinees; but also to demonstrate safety in immunologically vulnerable populations, such as infants and the immunosuppressed, as well as lack of transmission and/or occurrence of disease particularly in vulnerable contacts of the vaccine; such as immunosuppressed or pregnant contacts. Additionally, while transmission to contacts may even be seen as a benefit in some mass vaccination programs, there are potential concerns about reversion to less attenuated variants if there is ongoing transmission of the vaccine in the community. In some instances there may be a need to demonstrate lack of transmission to non-human animals.

The V3SWG intends that this template focuses on key questions related to the essential safety and benefit-risk issues relevant for the intrinsic properties of the vaccine components. Although we recognize that other aspects of manufacturing, quality, and implementation can play an important role in the safety of a vaccine, we have chosen to keep some of those issues out of scope of this template in order to summarize the most useful information for stakeholders.

The latest version of the template can be accessed on https://brightoncollaboration.us/v3swg/. Developers of live-attenuated vaccines are encouraged to complete the template for their vaccine candidate and collaborate with the V3SWG. The draft template will be shared for review by the V3SWG and submitted for publication. Similarly, updates to the template by the vaccine developer should be submitted to the Brighton Collaboration website for V3SWG review.

2. Specific Instructions for completing the V3SWG Template:

- Please read these instructions before you complete the nine sections. Send questions to: bc-coordinator@taskforce.org
- The first section entitled "Authorship" should include your name and the latest date completing the form. If you are working with someone else to complete this form, their name should be provided as well. If you are updating the form, please provide the updated date. These co-authors will be included in the final published template in Vaccine once reviewed and approved by the V3SWG and in subsequent Wiki updates on the V3SWG website.
- Sections 2-8 collect information regarding the basic vaccine information (Section 2), the target pathogen and population (Section 3), characteristics of attenuated vaccine virus (Section 4), delivery and administration (Section 5), toxicology and nonclinical (Section 6), and human efficacy and other important information (Section 7). Depending on the vaccine, some sections may be redundant or not applicable. In cases of redundancies, an answer may simply refer to the answer in a previous section.
- Answer questions by responding in the column entitled 'Information.' If you have any comments or concerns regarding the question or your answer to the question, note these in the 'Comments/Concerns' column. Finally, please provide references in the 'Reference' column. More than one reference can be used per question. You can simply write the first author's last name, first name initials, and year of publication (e.g., Lewis

Brighton Collaboration
Standardized Template for Collection of Key Information for Benefit- Risk Assessment of Live Attenuated Viral Vaccines
For regular version, see https://brightoncollaboration.us/v3swg/.

1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Attenuated Vaccine Virus	5. Delivery and Administration	6. Toxicology and Nonclinical	7. Human Efficacy and Other Important Information	**8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):**	**9. Overall Risk Assessment**
1.1 Author(s) and affiliation(s)	**2.1** Vaccine name	**3.1** What is the target pathogen?	**4.1** Describe the source of the virus or virus strains (e.g. isolation, synthesis)	**5.1** How might the vaccine formulation (antigen and diluent and/or any other co-administered component formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?	**6.1** Will the vaccine virus express or replicate in non-human species?	**7.1** What is known about the replication of vaccine virus in humans in the following categories:	**8.1** Approximately how many humans have received this vaccine to date? If variants of the vaccine, please list separately.	**9.1** Please summarize key safety issues of concern identified to date, if any:
1.2 Date completed/ updated	**2.2** Virus name, genus, family strains/serotypes, origin (e.g., geography, patient, asymptomatic infection), and any other specific characteristics, such as genetic modifications	**3.2** What are the disease manifestations caused by the target pathogen in humans, for the following categories:	**4.2** How does attenuated virus differ from the pathogen?	**5.2** If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety	**6.2** Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products	● in healthy people	**8.2** Method(s) used for safety monitoring:	● how should they be addressed going forward
	2.3 Method of attenuation	● In healthy people	● Method of attenuation and validation	**5.3** Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.5) impact the safety profile of the vaccine	**6.3** Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products	● in immunocompromised people	● Spontaneous reports/passive surveillance	**9.2** What is the potential for causing serious unwanted effects and toxicities in:
	2.4 Substrate for vaccine virus growth and method of production (e.g., nature of substrate, cell line, eggs, bioreactor, microcarriers, etc.)	● In immunocompromised people	**4.3** Does the vaccine establish a latent or persistent infection?	**5.4** Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral, or combination thereof)	**6.4** What is the evidence of disease enhancement or absence thereof in vitro or in animal models?[8]	● in neonates, infants, children	● Diary	● healthy humans?
	2.5 Final vaccine formulation components	● In neonates, infants, children	**4.4** Does the vaccine virus replicate in the nucleus?		**6.5** Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?	● during pregnancy and in the fetus	● Other active surveillance	● immunocompromised humans?
	2.6 Route and method of delivery (e.g., oral, intramuscular injection, microneedles, skin patch, intranasal, other mucosal)	●During pregnancy and in the fetus	**4.5** What is the risk of integration into the human genome?		**6.6** What is the evidence that the vaccine has generated a beneficial immune response in:	● in gene therapy experiments	**8.3** What criteria were used for grading the AEs?	● human neonates, infants, children?
		●In elderly	**4.6** What is known about the replication of vaccine virus in humans in the following categories:		● Animal models?	● in any other special populations	● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and	● pregnancy and in the fetus in humans?

(*continued on next page*)

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1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Attenuated Vaccine Virus	5. Delivery and Administration	6. Toxicology and Nonclinical	7. Human Efficacy and Other Important Information	**8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):**	**9. Overall Risk Assessment**
							Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	
		● In any other special populations	● in healthy people		● Nonhuman primates (NHP)?	**7.2** What is the evidence that the vaccine generates a protective immune response in humans (e.g. natural history, passive immunization, animal challenge studies)?	● If no criteria were used for grading, or if other metrics were employed, please describe:	● elderly?
		3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g., incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio (R0), and extent of natural mutation)?	● in immunocompromised people			**7.3** Can the vaccine virus protect against multiple strains or serotypes or will separate strains be required for multigenic vaccines?	**8.4** List and provide frequency of any related or possibly related serious* AEs, as well as any severe, expected or unexpected, AEs observed: (*see Instructions):	● in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?
		3.4 Does the target pathogen establish a latent or persistent infection?	● in neonates, infants, children			● Was there evidence generated?	**8.5** List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control groups:	
		3.5 Does the target pathogen virus replicate in the nucleus?	● during pregnancy and in the fetus			● What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	● Describe the control group: _____.	
		3.6 What is the risk of integration into the human genome?	● in any other special populations			**7.4** Is there any previous human experience with this vaccine (safety and immunogenicity records)?	**8.6** List and provide frequency of Adverse Events of Special Interest	
		3.7 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast feeding), adult, elderly)	**4.7** What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?			● Any evidence for or against disease enhancement ?	**8.7** Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	

(*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit- Risk Assessment of Live Attenuated Viral Vaccines For regular version, see https://brightoncollaboration.us/v3swg/.							
1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Attenuated Vaccine Virus	5. Delivery and Administration	6. Toxicology and Nonclinical	7. Human Efficacy and Other Important Information	**8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):**	**9. Overall Risk Assessment**
		3.8 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease? **3.9** Please describe any other key information about the target pathogen or population that may inform benefit-risk	**4.8** What is the potential for shedding and transmission to humans or other species? **4.9** Is the vaccine virus genetically stable in vitro and/or in vivo?			**7.5** Describe other key information that may impact benefit-risk	● Did it identify any safety issue of concern? ● If so describe:	

* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed relevant for safety purpose.

MH, 2003) in the "Reference" column here, but please provide the full citation for the reference at the end of the form. Unpublished data are acceptable, though we do wish for you to include the source and contact information.

- Sections 8 and 9 have column titles that differ from preceding sections intended to provide a summary assessment of adverse effects and toxicity of the vaccine. Please summarize adverse effects and toxicities as requested and rate the risk in the following fashion: none, minimal, low, moderate, high, or unknown. If there is insufficient data for use of the platform in humans to accurately make these assessments, please state so in response to the questions.
- When completing information on adverse effects in Section 9, please provide as many details as possible based on the Brighton Collaboration Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies [12].
- If a literature search was conducted to complete any of the Sections (strongly encouraged), please add the following information in the Reference(s) column: 1) time period covered (e.g., month/year to month/year); 2) Medical Subject Headings (MeSH) terms used; 3) the number of references found; and 4) the actual references with relevant information used. For prior published templates, please search PubMed for "Brighton Collaboration V3SWG".

3. 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 participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

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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