

Supplementary materials: Brighton Collaboration standardized templates for benefit-risk assessment of vaccines

Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG)

Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group

The latest version of these templates can be accessed at

<https://brightoncollaboration.us/bravato/>.

Read the specific instructions prior to completing the templates. Contact the Brighton Collaboration here: brightoncollaborationv3swg@gmail.com

Supplementary Table S1. Nucleic acid (RNA and DNA) candidate vaccines

Brighton Collaboration standardized template for risk assessment of nucleic acid (RNA and DNA) vaccines		
1. Authorship	Information	
1.1 Author(s) and affiliation(s)		
1.2. Date completed/updated		
2. Basic vaccine information	Information	Comments/ Concerns
2.1 Vaccine name		
2.2 Nucleic acid type: DNA, RNA, self-amplifying RNA		
2.3 Adjuvant (if applicable)		
2.4 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g. complexing with polymers, encapsulation within microparticles, liposomes)		
2.5 Route and method of delivery (e.g. intramuscular injection, gene gun, electroporation)		
3. Target pathogen and population		
3.1 What is the target pathogen?		
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In elderly		
• In any other special populations		
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 (R_0), and spontaneous mutation)?		
3.4 What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, breast-feeding women (breast-feeding), adult, elderly)?		
3.5 What is known about the natural immune responses, duration, and potential correlates of protective immunity to the target pathogen or the disease?		
3.6 Describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of vaccine transgene and expression		
4.1 Nature of the nucleic acid platform (DNA - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; messenger-RNA, self-replicating, other)		

4.2 Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)		
4.3 Factors enhancing/controlling gene expression		
4.4 Non-expressed features that could have an impact on vaccine efficacy (CpG sequences, other)		
4.5 Other sequence features that may have an impact on safety (e.g. sequences in DNA that might facilitate insertion or recombination)		
4.6 Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		
4.7 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.)?		
5. Delivery and administration		
5.1 Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.4) impact the safety profile of the vaccine?		
<i>* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purposes. For example, among the risks that WHO, FDA, and EMA list for the use of DNA vaccines is the hazard of integration into recipient's chromosomal DNA with the resulting risk of insertional mutagenesis or spreading of antibiotics resistance genes. The probability of chromosomal integration increases if the introduced pDNA has been linearized, and this is the reason that regulatory authorities require the plasmid preparation intended for vaccination or gene therapy to contain a high percentage of supercoiled material (usually >80%). The percentage of supercoiled material is also used as a criterion of DNA vaccine stability at different storage temperatures.</i>		
5.2 Describe how the mode of vaccine delivery may impact safety ** (e.g., electroporation (specify name of device), intradermal needle injection)		
<i>** Also consider the safety impact of multi-dose delivery methods, the use of multi dose vaccine vials, and any special considerations for disposal.</i>		
5.3 How might any co-administered components (e.g. adjuvants, cytokines, immunomodulatory molecules) impact the safety profile?		
5.4 If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety		
6. Toxicology and nonclinical		
6.1 What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?		
6.2 How long does the RNA or DNA persist in vivo (may specify in tissue/serum, proximal/distal to site of administration)?		
6.3 What is the risk of integration of sequences from the platform nucleic acid into the host genome?		
6.4 What is the possible risk of autoimmunity or a harmful immune response?		
6.5 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products		
6.6 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products		
6.7 What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD).) or absence thereof <i>in vitro</i> or in animal models? ¹⁴		

6.8 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?		
7. Human efficacy and other important information		
7.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g. natural history, passive immunization, animal challenge studies)?		
7.2 Describe other key information that may impact benefit-risk		
8. Adverse event (AE) assessment of the vaccine platform (*see instructions):		
8.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, list separately		
8.2 Method(s) used for safety monitoring:		
Spontaneous reports/passive surveillance Yes/No? If yes describe method:		
Diary – Yes/No? If yes, number of days		
Other active surveillance – Yes/No? if yes, describe method (e.g., LTFU) and list the AES solicited:		
8.3 What criteria were used for grading the AEs?		
2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Yes/No		
If no criteria were used for grading, or if other metrics were employed, describe:		
8.4 List and provide frequency of any related or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):		
8.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:		
Describe the control group: _____.		
8.6 List and provide frequency of Adverse Events of Special Interest		
8.7 What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) (if any) in humans?		
8.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study? Yes/No?		
Did it identify any safety issue of concern? Yes/No? If yes, describe.		
9. Overall risk assessment		
9.1 Summarize key safety issues of concern identified to date, if any:		
How should they be addressed going forward		
9.2 What is the potential for causing serious unwanted effects and toxicities in:(Describe the toxicities) (Rate risk as: none, minimal, low, moderate, high, or unknown)		
Healthy humans?		

• Immunocompromised humans?		
• Human neonates, infants, children?		
• Pregnancy and in the fetus in humans?		
• Elderly?		
• In any other special populations (e.g., institutionalized people, individuals with associated chronic comorbidity)?		
References		

Supplementary Table S2. Protein candidate vaccines

Brighton Collaboration standardized template for risk assessment of protein vaccine candidates		
1. Authorship	Information	Comments /Concerns
1.1 Author(s) and affiliation(s)		
1.2 Date completed/updated		
2. Basic vaccine information		
2.1 Vaccine name		
2.2 Protein type (e.g., molecular clamp, virus-like particle, peptide) and any special characteristics		
2.3 Type of heterologous expression system used for antigen production (e.g., bacteria, yeast, plants, mammalian or insect cells, chemical synthesis)		
2.4 Adjuvant (if applicable)		
2.5 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g., preservatives (e.g., thimerosal, phenol, benzethonium chloride, 2-phenoxyethanol), complexing with polymers, encapsulation within microparticles, liposomes, depot formulations)		
2.6 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)		
3. Target pathogen and population		
3.1 What is the target pathogen?		
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In elderly		
• In any other special populations		
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 (R_0), and spontaneous mutation)?		
3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, breast-feeding women (breast feeding), adult, elderly)		
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		
3.6 Describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of antigen		
4.1 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence?		
4.2 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.)?		

4.3 Is there homology in the sequence of the vaccine antigen and human proteins?		
5. Adjuvant (if applicable)		
5.1 Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant		
5.2 What is the evidence that an adjuvant improves/boosts/enhances the immune response?		
5.3 What is the mechanism of action of the adjuvant (if known)?		
5.4 How is the adjuvant formulated with the antigen?		
5.5 How might the adjuvant impact the safety profile of the vaccine?		
5.6 Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen		
6. Delivery and administration		
6.1 How might the vaccine formulation (antigen and adjuvant already formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?		
6.2 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety		
6.3 Describe how components of the vaccine formulation that facilitate stability and delivery into cells (Section 2.5) may impact the safety profile of the vaccine		
6.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)		
* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purpose.		
7. Toxicology and nonclinical		
7.1 What is known about biodistribution of the antigen in its final formulation and mode of administration in animal models?		
7.2 How long does the vaccine antigen persist in vivo (may specify in tissue/serum; proximal/distal to site of administration)?		
7.3 What is the possible risk of autoimmunity or a harmful immune response?		
7.4 Summarize the preclinical safety data that support the use of this product in humans including any related information from similar products		
7.5 Summarize the preclinical immunogenicity and efficacy data that support the use of this product in humans including any related information from similar products		
7.6 What is the evidence of disease enhancement or absence thereof <i>in vitro</i> or in animal models? ⁸		
7.7 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?		
8. Human efficacy and other important information		
8.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?		
8.2 Describe other key information that may impact benefit-risk		
9. Adverse event (AE) assessment of the vaccine platform (*see Instructions):		
9.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, list separately.		

9.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance		
• Diary		
• Other active surveillance		
9.3 What criteria were used for grading the AEs?		
• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials		
• If no criteria were used for grading, or if other metrics were employed, describe:		
9.4 List and provide frequency of any or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):		
9.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:		
• Describe the control group: _____.		
9.6. List and provide frequency of Adverse Events of Special Interest		
9.7 What is the evidence of disease enhancement (if any) in humans?		
9.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?		
• Did it identify any safety issue of concern?		
• If so describe:		
10. Overall risk assessment		
10.1 Summarize key safety issues of concern identified to date, if any:		
• How should they be addressed going forward		
10.2 What is the potential for causing serious unwanted effects and toxicities in:		
• Healthy humans?		
• Immunocompromised humans?		
• Human neonates, infants, children?		
• Pregnancy and in the fetus in humans?		
• Elderly?		
• In any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?		
References		

Supplementary Table S3. Viral vector candidate vaccines

Brighton Collaboration standardized template for risk assessment of viral vector vaccine candidates		
1. Authorship and affiliation	Information	Comments /Concerns
1.1. Author(s) and affiliation		
1.2. Date completed/updated		
2. Basic vector information		
2.1 Vector name		
2.2. Vector origin Family/Genus/Species/subtype		
2.3. Vector replication in humans (replicating or non-replicating)		
3. Characteristics of the wild type virus from which the vector is derived		
3.1 Name of wild type virus (common name; Family/Genus/Species/subtype)		
3.2 What is the natural host for the wild type virus?		
3.3. How is the wild type virus normally transmitted?		
3.4. Does the wild type virus establish a latent or persistent infection?		
3.5. Does the wild type virus replicate in the nucleus?		
3.6. What is the risk of integration into the human genome?		
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:		
• In the healthy natural host		
• In laboratory hosts (specify species)		
• In healthy human host		
• In immunocompromised humans		
• In breast milk, human neonates, infants, children		
• During pregnancy and in the unborn in humans		
• In any other special populations?		
3.8. What cell types are infected and what receptors are used in the natural host and in humans?		
3.9. What is known about the mechanisms of immunity to the wild type virus?		
3.10 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the wild type virus:		
• In vitro?		
• In animal models?		
• In human hosts?		
3.11 Is disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) a possible vaccine-induced contributor to the pathogenesis of wild type disease		
3.12 What is the background prevalence of natural immunity to the virus?		

3.13 Is there any vaccine available for the wild-type virus? If yes,		
• • What populations are immunized?		
• • What is the background prevalence of artificial immunity?		
3.14 Is there treatment available for the disease caused by the wild type virus		
4. Characteristics of the vector from which vaccine(s) may be derived		
4.1 Describe the source of the vector (e.g., isolation, synthesis)		
4.2. What is the basis of attenuation/inactivation of the wild type virus to create the vector?		
4.3. What is known about the replication, transmission and pathogenicity of the vector in humans in the following categories:		
• In healthy people		
• In immunocompromised people		
• In breast milk, neonates, infants, children		
• During pregnancy and in the fetus		
• In gene therapy experiments		
• In any other special populations		
4.4. Is the vector replication-competent in non-human species?		
4.5. What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
4.6 Is the vector genetically stable in vitro and/or in vivo?		
4.7. What is the potential for shedding and transmission, including arthropod borne transmission, to humans or other species?		
4.8. Does the vector establish a latent or persistent infection?		
4.9. Does the vector replicate in the nucleus?		
4.10. What is the risk of integration into the human genome?		
4.11. Is there any previous human experience with this or a similar vector (safety and immunogenicity records)?		
4.12. What cell types are infected and what receptors are used in humans?		
4.13. What is known about the mechanisms of immunity to the vector?		
4.14 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vector?		
• • In vitro?		
• • In animal models?		
• • In human hosts?		
4.15. Is there antiviral treatment available for disease manifestations caused by the vector?		
4.16. Can the vector accommodate multigenic inserts or will several vectors be required for multigenic vaccines?		
5. Toxicology and potency (pharmacology) of the vector		
5.1. What is known about the replication, transmission and pathogenicity of the vector in and between animals?		
5.2. 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?		
5.3. Does an animal model relevant to assess attenuation exist?		
5.4. Does an animal model for safety including immuno-compromised animals exist?		

5.5. Does an animal model for reproductive toxicity exist?		
5.6. Does an animal model for immunogenicity and efficacy exists?		
5.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) or immune complex disease exist?		
5.8. What is known about biodistribution in animal models or in humans, including neurovirulence and/or neuroinvasion?		
5.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:		
• Small animal models?		
• Nonhuman primates (NHP)?		
• Human?		
5.10. Have challenge or efficacy studies been conducted in subjects with:		
• Immunocompromised conditions including HIV?		
• Other diseases?		
5.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes? Is there evidence for interaction/interference?		
6. Adverse event (AE) assessment of the vector (*see Instructions):		
6.1. Approximately how many humans have received any vaccine using this viral vector to date? If variants of the vector, list separately.		
6.2. Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance: Yes/No – If yes, describe method		
• Diary: Yes/No – If yes, number of days: Yes/No – If yes, describe method and list the AE's solicited		
• Other active surveillance		
6.3. What criteria were 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 -- Yes/No		
• If no criteria were used for grading, or if other metrics were employed, describe:		
6.4. List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see instructions in full publication):		
6.5. List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:		
• Describe the control group: .		
6.6. List and provide frequency of Adverse Events of Special Interest		
6.7. Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study? Yes/No		
• Did it identify any safety issue of concern? Yes/No		
• If so describe:		
7. Overall risk assessment of the vector		
7.1. Summarize key safety issues of concern identified to date, if any:		
• How should they be addressed going forward:		

7.2. What is the potential for causing serious unwanted effects and toxicities in:		
• Healthy humans? -- Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
• Immunocompromised humans? -- Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
• Breast milk, human neonates, infants, children? -- Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
• Pregnancy and in the fetus in humans? -- Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
• Elderly -- Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
• In any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
7.3. What is the potential for shedding and transmission in risk groups?		
8. Target pathogen and population for the vaccine		
8.1 What is the target pathogen for the vaccine?		
8.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In elderly		
• In any other special populations		
8.3 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 (R_0), and intrinsic mutation)?		
8.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, breast-feeding women (breast feeding), adult, elderly)		
8.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		
8.6 Describe any other key information about the target pathogen or population that may inform benefit-risk		
9. Characteristics of the vaccine		
9.1 Vaccine name		
9.2. What is the identity and source of the transgene?		
9.3. Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		
9.4. Where in the vector genome is the transgene inserted?		
9.5. Does the insertion of the transgene involve deletion or other rearrangement of any vector genome sequences?		
9.6. How is the transgene expression controlled (transcriptional promoters, etc.)?		
9.7. Does insertion or expression of the transgene affect the pathogenicity or phenotype of the vector?		

9.8. Is the vaccine replication-competent in humans or other species?		
9.9. What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
9.10. Is the vaccine genetically stable in vitro and/or in vivo?		
9.11. What is the potential for shedding and transmission to humans or other species?		
9.12. Does the vaccine establish a latent or persistent infection?		
9.13. Does the vaccine replicate in the nucleus?		
9.14. What is the risk of integration into the human genome?		
9.15. List any disease manifestations caused by the vaccine in humans, the strength of evidence, severity, and duration of disease for the following categories:		
• In healthy people		
• In immunocompromised people		
• In breast milk, neonates, infants, children		
• During pregnancy and in the fetus		
• In any other special populations		
9.16. What cell types are infected and what receptors are used in humans?		
9.17. What is known about the mechanisms of immunity to the vaccine?		
9.18 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vaccine?		
• In vitro?		
• In animal models?		
• In human hosts?		
9.19 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?		
9.20. Is the vaccine transmissible in humans or other species (including arthropods) and/or stable in the environment?		
9.21. Are there antiviral or other treatments available for disease manifestations caused by the vaccine?		
9.22. Vaccine formulation		
9.23. Proposed route and method of vaccine delivery (e.g., oral, intramuscular injection microneedles, skin patch, intranasal, mucosal)		
9.24. Target populations for the vaccine (e.g., pediatric, maternal, adult, elderly etc.)		
10. Toxicology and potency (pharmacology) of the vaccine		
10.1. What is known about the replication, transmission and pathogenicity of the vaccine in and between animals?		
10.2. 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?		
10.3. Does an animal model relevant to assess attenuation exist?		
10.4. Does an animal model for safety including immuno-compromised animals exist?		
10.5. Does an animal model for reproductive toxicity exist?		
10.6. Does an animal model for immunogenicity and efficacy exists?		

10.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) or immune complex disease exist?		
10.8. What is known about biodistribution in animal models or in humans, including neurovirulence and/or neuroinvasion?		
10.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:		
• Small animal models?		
• Nonhuman primates (NHP)?		
• Human?		
10.10. Have challenge or efficacy studies been conducted in subjects with:		
• Immunocompromised conditions including HIV?		
• Other diseases?		
10.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes? Is there evidence for interaction/interference?		
11. Adverse event (AE) assessment of the vaccine (*see Instructions):		
11.1. Approximately how many humans have received this viral vector vaccine to date? If variants of the vector, list separately.		
11.2. Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance: Yes/No, if yes, describe method		
• Diary: Yes/No, if yes, number of days		
• Other active surveillance: Yes/No, If yes, describe method and list the AEs solicited		
11.3. What criteria were 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: Yes/No		
• If no criteria were used for grading, or if other metrics were employed, describe:		
11.4. List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see Instructions):		
11.5. List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:		
• Describe the control group: .		
11.6. List and provide frequency of Adverse Events of Special Interest		
11.7. Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study? Yes/No		
• Did it identify any safety issue of concern? Yes/No		
• If so describe:		
12. Overall risk assessment of the vaccine		
12.1. Summarize key safety issues of concern identified to date, if any:		
• How should they be addressed going forward:		
12.2. What is the potential for causing serious unwanted effects and toxicities in:		
• Healthy humans? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		

● Immunocompromised humans? - Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
● Breast milk, human neonates, infants, children? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
● Pregnancy and in the fetus in humans? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
● Elderly? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
● In any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)? Describe toxicities –Rate risk as: none, minimal, ow, moderate, high, or unknown		
12.3. What is the potential for shedding and transmission in risk groups?		
13. Any other information concerning either the viral vector or the vaccine		
References		

Supplementary Table S4. Live attenuated viral candidate vaccines

Brighton Collaboration standardized template for risk assessment of live attenuated viral candidate vaccines		
1. Authorship	Information	Comments /Concerns
1.1 Author(s) and affiliation(s)		
1.2 Date completed/updated		
2. Basic vaccine information		
2.1 Vaccine name		
2.2 Virus name, genus, family strains/serotypes, origin (e.g., geography, patient, asymptomatic infection), and any other specific characteristics, such as genetic modifications		
2.3 Method of attenuation		
2.4 Substrate for vaccine virus growth and method of production (e.g., nature of substrate, cell line, eggs, bioreactor, microcarriers, etc.)		
2.5 Final vaccine formulation components		
2.6 Route and method of delivery (e.g., oral, intramuscular injection, microneedles, skin patch, intranasal, other mucosal)		
3. Target pathogen and population		
3.1 What is the target pathogen?		
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In elderly		
• In any other special populations		
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)?		
3.4 Does the target pathogen establish a latent or persistent infection?		
3.5 Does the target pathogen virus replicate in the nucleus?		
3.6 What is the risk of integration into the human genome?		
3.7 What sections of the population are most affected by the target pathogen (e.g., paediatric, pregnant, breast-feeding women (breast feeding), adult, elderly)		
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 Describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of attenuated vaccine virus		
4.1 Describe the source of the virus or virus strains (e.g., isolation, synthesis)		

4.2. How does attenuated virus differ from the pathogen?		
Method of attenuation and validation		
4.3 Does the vaccine establish a latent or persistent infection?		
4.4 Does the vaccine virus replicate in the nucleus?		
4.5 What is the risk of integration into the human genome?		
4.6. What is known about the replication of vaccine virus in humans in the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In any other special populations		
4.7. What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
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?		
5. Delivery and administration		
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?		
5.2 If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety		
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		
5.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral, or combination thereof)		
<i>* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed relevant for safety purpose.</i>		
6. Toxicology and nonclinical		
6.1 Will the vaccine virus express or replicate in non-human species?		
6.2 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products		
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		
6.4 What is the evidence of disease enhancement or absence thereof in vitro or in animal models? ¹³		
6.5 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?		
6.6 What is the evidence that the vaccine has generated a beneficial immune response in:		
• Animal models?		
• Nonhuman primates (NHP)?		

7. Human efficacy and other important information		
7.1 What is known about the replication of vaccine virus in humans in the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In gene therapy experiments		
• In any other special populations		
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)?		
7.3 Can the vaccine virus protect against multiple strains or serotypes or will separate strains be required for multigenic vaccines?		
• Was evidence generated?		
• 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.)?		
7.4 Is there any previous human experience with this vaccine (safety and immunogenicity records)?		
• Any evidence for or against disease enhancement?		
7.5 Describe other key information that may impact benefit-risk		
8. Adverse event (AE) assessment of the vaccine platform (*see Instructions):		
8.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine, list separately.		
8.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance		
• Diary		
• Other active surveillance		
8.3 What criteria were used for grading the AEs?		
• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials		
• If no criteria were used for grading, or if other metrics were employed, describe:		
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):		
8.5 List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control groups:		
• Describe the control group: _____.		
8.6 List and provide frequency of Adverse Events of Special Interest		
8.7 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?		
• Did it identify any safety issue of concern?		

If so describe:		
9. Overall risk assessment		
9.1 Summarize key safety issues of concern identified to date, if any: how should they be addressed going forward		
9.2 What is the potential for causing serious unwanted effects and toxicities in:		
Healthy humans?		
Immunocompromised humans?		
Human neonates, infants, children?		
Pregnancy and in the fetus in humans?		
Elderly?		
In any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?		
References		

Supplementary Table S5. Inactivated viral candidate vaccines

Brighton Collaboration standardized template for risk assessment of inactivated viral candidate vaccines		
1. Authorship and affiliation	Information	Comments /Concerns
1.1 Author(s) and affiliation (s)		
1.2 Date completed/updated		
2. Basic vaccine information		
2.1 Vaccine name		
2.2 Virus name, genus, family, strains/serotypes, origin (e.g., geography, patient, asymptomatic), and any other specific characteristics such as genetic modifications		
2.3 Substrate for vaccine virus growth (e.g., cell substrate, eggs, animal, etc.)		
2.4 Inactivation method		
2.5 Adjuvant (if applicable)		
2.6 Final vaccine formulation components		
2.7 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)		
3. Target pathogen and population		
3.1 What is the target pathogen?		
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people		
• In immunocompromised people		
• In neonates, infants, children		
• During pregnancy and in the fetus		
• In elderly		
• In any other special populations		
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 (R_0), and spontaneous mutation)?		
3.4 What sections of the population are most affected by the target pathogen (e.g., paediatric, pregnant, breast-feeding women (breast feeding), adult, elderly)		
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		
3.6 Describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of antigen		

4.1 Virus strains, sequence (including homology among strains), source, propagation, disruption, whole virus or subunit/sub-virion (if applicable)?		
4.2 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence?		
4.3 What is known about the immune response to the vaccine in animals and/or humans (binding, neutralizing antibody, functional, and, B-cell, T-cell memory, etc.)?		
5. Inactivation method(s)		
5.1 Method/s (e.g., thermal, beta propiolactone, UV, formaldehyde, ionizing radiation) and potential impact on safety		
5.2 At what stage of the downstream process is inactivation/s performed and why?		
5.3 QC/confirmation method/log reduction in viability		
5.4 Could the inactivation method/s compromise the antigenic structure of the vaccine (e.g., conformation of the protein antigens)		
6. Adjuvant (optional, if applicable)		
6.1 Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant		
6.2 What is the evidence that an adjuvant improves/boosts/enhances the immune response?		
6.3 What is the mechanism of action of the adjuvant (if known)?		
6.4 How is the adjuvant formulated with the antigen?		
6.5 How might the adjuvant impact the safety profile of the vaccine?		
6.6 Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen		
7. Delivery and administration		
7.1 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral, or combination thereof)		
7.2 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety		
8. Toxicology and nonclinical		
8.1 What is the possible risk of autoimmunity or a harmful immune response?		
8.2 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products		
8.3 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products		
8.4 What is the evidence of disease enhancement or absence thereof <i>in vitro</i> or in animal models? ¹³		

8.5 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?		
9. Human efficacy and other important information		
9.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?		
9.2 Describe other key information that may impact benefit-risk		
10. Adverse event (AE) assessment of the vaccine platform (*see instructions):		
10.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine, list separately.		
10.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance		
• Diary		
• Other active surveillance		
10.3 What criteria were used for grading the AEs?		
• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials		
• If no criteria were used for grading, or if other metrics were employed, describe:		
10.4 List and provide frequency of any related or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):		
10.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control groups:		
• Describe the control group: _____.		
10.6 List and provide frequency of Adverse Events of Special Interest		
10.7 What is the evidence of disease enhancement (if any) in humans?		
10.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?		
• Did it identify any safety issue of concern?		
• If so describe:		
11. Overall risk assessment		
11.1 Summarize key safety issues of concern identified to date, if any:		
• How should they be addressed going forward		
11.2 What is the potential for causing serious unwanted effects and toxicities in:		
• Healthy humans?		
• Immunocompromised humans?		
• Human neonates, infants, children?		

• Pregnancy and in the fetus in humans?		
• Elderly?		
• In any other special populations (e.g., institutionalized populations, individuals with associated chronic comorbidity)?		
References		