List of questions to be considered

Accelerated assessment of the risk of disease enhancement with COVID-19 vaccines:
A Coalition for Epidemic Preparedness Innovation (CEPI)/Brighton Collaboration (BC) scientific working meeting. Mar. 12-13, 2020.

1- What can we learn from prior experience with enhanced disease following vaccination? From RSV? From Dengue?	
ANIMAL MODELS:	
2- In view of the fact that Coronavirus vaccines have never been used in humans, how can animal models help assess the risk of vaccine-related enhanced disease ?	
3- Are murine models relevant to this issue?	
○ Which mouse strain?	
○ Will hACE2 transduced or transgenic murine models be needed? If so, which source (Jackson?)	
○ SARS differs from COVID-19. What is the relevance of previous observations made with SARS in murine models. Comparative pathology SARS vs COVID-19	

○ Can post-immunization immunological data obtained in mice be sufficiently predictive? If so, which data (e.g. IgG isotypes, Th2 markers, vaccine antigen specific IgE) of the relative risk of disease enhancement, even in the absence of viral challenge ?	
○ Will mice give indications on the risk of immune complex or T-cell mediated immunopathology?	
○ Are there other small animal models that could be useful (e.g. rabbit, ferrets) for safety assessment.	
4- Are NHPs more relevant for this issue.	
○ Comparative pathology of SARS vs COVID-19 in various NHPs (Rhesus, Cynomolgus?)	
○ Can post-immunization immunological data be sufficiently indicative (e.g. pattern of immune response, neutralizing vs non-neutralizing antibodies, antibody affinity, T-cell response markers?) of the relative risk of disease enhancement, with or without viral challenge ? If yes, which primate model would be optimal?	
○ After challenge, which clinical follow-up? Inflammation markers?	
○ Are CT scan studies needed, as done for MERS?	
○ Histopathology ? timing?	
○ Which virus source to be used for challenge?	
○ Timing of challenge vs immunization? How can we mimic vaccination in the context of an on-going outbreak?	
○ Potential sites for NHP trials	

VACCINE COMPOSITION	
5- Can an appropriate selection of a vaccine antigenic structure reduce the risk of vaccine-related enhanced disease ?	
○ How can structural studies help to define optimal vaccine antigens?	
○ Truncated Spike protein?	
○ RBD peptides? Conjugated?	
○ Can In vitro assessment be helpful?	
6. What about the role of adjuvants? Which ones? What about other modifiers of the immune response aimed to minimize the risk of enhanced disease?	
o What can be expected of different adjuvants with sub-unit vaccines?	
CLINICAL STUDIES	
7. From what has been observed in animal models	
○ What are the priority immunological markers to analyze during a phase 1 trial to assess the relative safety of a candidate vaccine in relation to disease enhancement (antibody specificity? Neutralizing vs non-neutralizing?, IgG isotypes, T-cell markers? Gene-expression micro-arrays?	
○ Should such NHP studies be done before or parallel to initial phase 1 trials? When in clinical development should data from challenge studies become available?	
8. What about doing clinical trials in high risk areas for natural transmission?	
9. Importance of cross-reactive coronavirus antibodies and T-cells in disease immunopathology?	