

Draft framework for the evaluation of new vaccines

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Advancing the development of pan-
sarbecovirus vaccines

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Goals

Increase supply of vaccines that likely meet TPP criteria

for effectiveness against severe disease

- Unless they confer major offsetting advantages, they should be as “**variant-resistant**” as current vaccines
- Under certain circumstances, a new vaccine could be considered for EUL based on an **already-authorized comparator vaccine**
- When these circumstances are not met, **additional data would be needed** prior to EUL

For this presentation, we consider demonstration of effectiveness, **assuming that safety has already been addressed**

Considerations

Neutralizing immune responses appear to mediate protection and levels can predict protection against symptomatic disease

After neutralizing antibodies wane, other responses can take over and maintain protection against severe disease

Non-neutralizing responses appear to play a greater role in vaccine protection against variants

Non-neutralizing protective responses can include:

- Cell-mediated immunity (T cells and memory B cells)

- Fc dependent (non-neutralizing) humoral responses

Ideally, new vaccines would induce both neutralizing and non-neutralizing protective responses

This framework provides an approach to considering vaccines for EUL based on:

- information about their mechanisms of action**
- immune responses relative to those of an already-authorized comparator vaccine**

The is intended to apply to all SARS-CoV-2 vaccines:

1. intended as new vaccines,
2. as “booster” vaccines,
3. as variant-specific vaccines, or
4. as pan-sarbecovirus vaccines (which may have additional breadth of coverage, but should also be capable of preventing severe disease caused by currently circulating variants).

The framework described above provides an **alternative to placebo-controlled clinical trials** to demonstrate clinical effectiveness for certain vaccines that meet the specified criteria

Because comparisons are made under defined conditions, relative to a vaccine with known effectiveness against circulating variants, the use of neutralizing antibody titers does not strictly follow the definition of a serological correlate of protection.

However, the choice of comparator must be well-justified based on an understanding of immunologic responses to the new vaccine and to the comparator.

Key questions

- 1. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?**
 - If new vaccine has less viral sequence, it may present fewer important cellular or non-neutralizing humoral epitopes
 - Any impact of 2-P mutation likely will be captured in magnitude of humoral response (so does not influence assessment of breadth)
- 2. Is the predicted/likely CMI response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?**
 - CMI responses appear to confer longer term protection and increase resistance of immune response to new variants
- 3. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?**

What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?

In the absence of randomized controlled trials, it is **critical to be able to make direct or indirect comparisons of immune responses** induced by a new vaccine with those induced by other vaccines of known effectiveness.

- The current evidence about effectiveness of existing vaccines against circulating variants is the most current data available about vaccine effectiveness
- The degree of effectiveness of the comparator affects the standard that a new vaccine is expected to meet.

Is the predicted/likely CMI response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?

If neutralizing immune responses are to be used for immunobridging, it is important that these **neutralizing responses will be predictive of other protective responses induced by the new vaccine**, relative to those associated with neutralizing responses of the comparator vaccine.

- For example, if the new vaccine and the comparator both use the same platform, it is highly likely that a given neutralizing response will predict a proportional cellular or non-neutralizing response for both vaccines.

If the platforms are different, then there should be data indicating that the **non-neutralizing protective responses** (i.e., cellular, non-neutralizing humoral, and mucosal responses) **of the new vaccine will be at least as strong as those of the comparator vaccine.**

What is the breadth of antigenic composition relative to the proposed comparator? 9

If the breadth of antigenic composition is lower for the new vaccine than for the comparator, it is likely that the new vaccine will not induce responses to as many cell-mediated and non-neutralizing humoral epitopes as the comparator.

Unless there were clear data that indicated considerably stronger and more durable neutralizing responses to the new vaccine vs. the comparator, the absence of these cellular or non-neutralizing humoral epitopes would be expected to make the new vaccine less resilient to waning of neutralizing responses and to new variants.

Thus, there would be a presumption against immunobridging to a comparator with broader antigenic composition.

Additional point

The table in the next slide is intended to show conditions under which there could be general agreement as to the regulatory pathway for EUL.

Conditions not on the slide may require further discussion, but for now, vaccines and studies not meeting these conditions would need to be considered for other types of clinical evaluations.

The table presents a possible framework for evaluating new vaccines, based on scenarios that consider the effectiveness of the comparator against severe disease caused by circulating variants and the likelihood that humoral responses to a new vaccine will predict cellular responses.

Depending on careful/detailed assessment of these factors, proposed approaches to evaluating the new vaccine are presented.

Key questions	Status of evidence in relation to key questions				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	Meets preferred TPP criteria (90%)	Meets acceptable TPP criteria (70-80%)	Comparator authorized but no longer meets TPP criteria (<70%)	As in Scenarios 1,2 or 3	Meets preferred TPP criteria (90%)
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?	Similar (e.g., same platform) or better	Similar (e.g., same platform) or better	Similar or better	Lower	Clearly better CMI or mucosal response vs circulating VOC plus supportive animal data
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?	Similar or better	Similar or better	Similar or better	Lower	Lower
	≡	≡	≡	≡	≡
What additional data do we need to authorize the new vaccine?	NI Nabs to circulating variants	Unambiguous superiority Nabs to circulating variants	Super-Superiority Nabs to circulating variants	<i>Results as in Scenarios 1, 2, or 3 PLUS Additional clinical data*</i>	Additional clinical data (e.g. in deployment studies or human challenge data if feasible)
Comments on vaccine effectiveness			<i>Duration of effectiveness may not exceed that of comparator vaccine unless CMI response is better</i>	<i>Low CMI may lead to short duration of effectiveness</i>	

VACCINES THAT DON'T MEET ANY OF THESE CRITERIA WOULD NEED TO BE TESTED IN CLINICAL TRIALS

Key questions	Status of evidence in relation to key questions				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	Meets preferred TPP criteria (90%)	Meets acceptable TPP criteria (70-80%)	Comparator authorized but no longer meets TPP criteria (<70%)	Scenarios 1-3 contemplate potential immunobridging, where there is high likelihood that the neutralizing immune response to the new vaccine will also predict other protective immune responses relative to the comparator. As more experience is gained, or where stronger data exist, it may become possible to employ less conservative criteria.	
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?	Similar (e.g., same platform) or better	Similar (e.g., same platform) or better	Similar or better		
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?	Similar or better	Similar or better	Similar or better		
What additional data do we need to authorize the new vaccine?	NI Nabs to circulating variants	Unambiguous superiority Nabs to circulating variants	Super-Superiority Nabs to circulating variants		
Comments on vaccine effectiveness			Duration of effectiveness may not exceed that of comparator vaccine unless CMI response is better		

VACCINES THAT DON'T MEET ANY OF THESE CRITERIA WOULD NEED TO BE TESTED IN CLINICAL TRIALS

Key questions	Status of evidence in relation to key questions			Scenarios 1-3 Where the comparator is highly effective (>90%) against severe disease caused by circulating variants, a non-inferiority comparison may be made. - Where the comparator is moderately effective (>70%), a superiority comparison should be made because of uncertainties in the actual effectiveness in the comparator and because non-inferiority comparisons allow for the possibility that the new vaccine is actually not as effective as the comparator. - If the comparator was previously EUL listed, but is no longer 70% effective (e.g., due reduced protection against circulating variants), a superiority margin acceptable to regulators and WHO to provide reasonable assurance that the new vaccine would meet the TPP criteria would be needed. Assuming criteria under Scenarios 1-3 were met, a product could be considered for EUL, with plans for post-marketing studies.
	Scenario 1	Scenario 2	Scenario 3	
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	Meets preferred TPP criteria (90%)	Meets acceptable TPP criteria (70-80%)	Comparator authorized but no longer meets TPP criteria (<70%)	
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?	Similar (e.g., same platform) or better	Similar (e.g., same platform) or better	Similar or better	
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?	Similar or better	Similar or better	Similar or better	
What additional data do we need to authorize the new vaccine?	NI Nabs to circulating variants	Unambiguous superiority Nabs to circulating variants	Super-Superiority Nabs to circulating variants	
Comments on vaccine effectiveness			Duration of effectiveness may not exceed that of comparator vaccine unless CMI response is better	

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Key questions	Status of evidence in relation to key questions		
	Scenario 1	Scenario 2	Scenario 3
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	Meets preferred TPP criteria (90%)	Meets acceptable TPP criteria (70-80%)	Comparator authorized but no longer meets TPP criteria (<70%)
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?	Similar (e.g., same platform) or better	Similar (e.g., same platform) or better	Similar or better
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?	Similar or better	Similar or better	Similar or better
	⌵	⌵	⌵
What additional data do we need to authorize the new vaccine?	NI Nabs to circulating variants	Unambiguous superiority Nabs to circulating variants	Super-Superiority Nabs to circulating variants
Comments on vaccine effectiveness			<i>Duration of effectiveness may not exceed that of comparator vaccine unless CMI response is better</i>

To ensure that evidence on protection against symptomatic and severe infections are provided, neutralizing antibodies, binding antibodies and cell mediated immunity data should be provided and compared appropriately.

The margin of non-inferiority should be -10% and the lower bound of the 95% confidence interval around the geometric mean (GMT) ratio should be at least 0.67. Reverse distribution curves should also be provided.

Additional analyses of immune responses elicited by the candidate vaccine versus the comparator vaccine against past variants of concern may be useful, though it should be clear that the current comparators are all based on antigens that have not circulated for many months, and thus this comparison should not be a basis for decision-making.

VACCINES THAT DON'T MEET ANY OF THESE CRITERIA WOULD NEED TO BE TESTED IN CLINICAL TRIALS

Key questions		Status of evidence in relation to key questions	
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	Scenario 4 contemplates a situation where a new vaccine has a high neutralizing response and strong preclinical data, but there is significant uncertainty about whether or not the cellular or non-neutralizing responses would be sufficient for robustness to new variants or for longer term protection once neutralizing responses would wane.	Scenario 4	Scenario 5
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?		As in Scenarios 1,2 or 3	Meets preferred TPP criteria (90%)
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?		Lower	Clearly better CMI or mucosal response vs circulating VOC plus supportive animal data
		Lower	Lower
What additional data do we need to authorize the new vaccine?		Results as in Scenarios 1, 2, or 3 PLUS Additional clinical data*	Additional clinical data (e.g. in deployment studies or human challenge data if feasible)
Comments on vaccine effectiveness		Low CMI may lead to short duration of effectiveness	
VACCINES THAT DON'T MEET ANY OF THESE CRITERIA WOULD NEED TO BE TESTED IN CLINICAL TRIALS			

Key questions	Status of evidence in relation to key questions	
	Scenario 5 contemplates a situation where humoral responses are weaker, but there are strong immunological and preclinical data to support likely vaccine effectiveness. Under these circumstances, additional data would be needed before an EUL could be granted.	Scenario 5
1. What is the effectiveness or efficacy of the comparator vs. severe disease caused by circulating VOC, relative to TPP criteria?	<p>Such data could come from:</p> <ul style="list-style-type: none"> ○ human challenge studies (if a suitable challenge strain were available) or ○ from (“in-deployment studies” of effectiveness against severe disease performed with the support of WHO and countries seeking to rapidly evaluate and deploy promising new vaccines) which would allow randomized data to be collected rapidly during initial deployment of vaccine to large numbers of people in controlled settings. <p>Vaccines that proved inadequately effective during “in-deployment studies” would not receive EUL.</p>	Meets preferred TPP criteria (90%)
2. Is the predicted/likely non-neutralizing response using the new vaccine likely to be similarly proportional to the humoral response vs. the comparator vaccine?		Clearly better CMI or mucosal response vs circulating VOC plus supportive animal data
3. What is the breadth of antigenic composition relative to proposed comparator that is already EUL-authorized?		Lower
What additional data do we need to authorize the new vaccine?		Additional clinical data (e.g. in deployment studies or human challenge data if feasible)
<i>Comments on vaccine effectiveness</i>		
VACCINES THAT DON'T MEET ANY OF THESE CRITERIA WOULD NEED TO BE TESTED IN CLINICAL TRIALS		