Summary Document

Topic: Evaluating the Burden-of-Disease Endpoint to Assess Vaccine Efficacy

Version: 1.0; Dated 23 October 2020

Disclaimer: This document provides a summary of key points from the literature, guidelines or other documents from experts on the subject matter, including from national and multilateral organizations and authorities. This document does not aim to be exhaustive. Due to the rapidly evolving situation, this summary document may not include latest evidence and updates are likely. New versions will be issued when significant new information becomes available. Its purpose is to support organizations and institutions involved in the development of COVID-19 vaccines. It is the responsibility of each vaccine developer to review available evidence, take into account relevant guidance and recommendations, and to seek scientific advice from regulatory agencies as appropriate.

Prepared by: Edde Loeliger and Bob Small for CEPI COVID-19 Clinical Working Group

For questions and feedback, please write to: bob.small@cepi.net, or edde.loeliger@cepi.net

Overview:

In this Summary Document, we evaluate, from a clinical perspective, the burden of disease (BOD) endpoint recently proposed by Mehrotra et.al. for its suitability as a primary endpoint for assessing COVID-19 (C-19) vaccine efficacy (VE) in a multiple endpoint approach. This summary document does not intend to recommend a specific BOD endpoint definition. The example 0,1,2,3,4 score in the table is there for illustration only.

The BOD endpoint was developed for vaccines that may affect both disease incidence and disease severity. C-19 vaccines may not be able to prevent infection per se, but may be able to attenuate disease severity in individuals with breakthrough disease. In interventional efficacy trials, vaccine-attenuated disease (VAD) has the effect of lowering VE in preventing C-19, in which VE = 1 – RR and RR represents the rate ratio of vaccine to placebo. If using the BOD endpoint, the VE_{BOD} in reducing C-19 *incidence* and disease severity, is a simple, useful, and interpretable statistic when expressed as VE = 1 – RR, in which RR represents the rate ratio of the BOD score vaccine to placebo.

The effect of VAD in interventional trials is that it gradually lowers VE against milder disease manifestations. Typically for vaccines associated with VAD, VE is greatest against death > critical disease > severe disease > moderate disease > mild disease. This lowers the overall VE point estimate, significantly impacting the sample size of C-19 cases required. The lower (lowest) efficacy against mild disease, however, does not necessarily imply that the vaccine has less biological *activity* against mild disease. The effect of VAD on VE is illustrated with a purely hypothetical example that shows that despite preventing disease in 88% of people who would have had mild disease if unvaccinated, the VE against mild disease is lowest with only 50%, because of the way VE is mathematically calculated. In the example, this is due to accumulation of 23 VAD cases that were classified as mild C-19, out of the total of 30 mild C-19 cases. The purpose of the example is to illustrate the effect of VAD by "opening the black box" also showing 1 severe VAD case out total of 3 severe C-19 cases, and 6 moderate VAD cases out of 10 moderate C-19 cases, explaining the gradual lowering of VE against milder disease manifestations.

The answer to VAD in interventional trials is to accept a relatively low VE point estimate for success. In the sample size calculations, low VE assumptions significantly increase the number of C-19 cases required for success. This could prove problematic during a pandemic with public health intervention that aim to prevent infection potentially slowing down accrual of C-19 cases. The purpose of this document is to stimulate the discussion around the BOD as an alternative way of addressing VAD that might speed-up demonstration of VE, and to explain that inclusion of moderate disease might be critical to its added value when used as a dual or triple primary endpoint, because of the relatively low incidence of severe C-19.

The burden of disease (BOD) endpoint was developed for vaccines that may affect both disease incidence and disease severity[1]. It was recently proposed by Mehrotra et.al. for assessing COVID-19 (C-19) vaccine efficacy (VE)[2]. The BOD endpoint seems particularly valuable for C-19, because C-19 vaccines, like other respiratory and mucosal virus vaccines, may not be able to prevent infection per se, and therefore could be associated with vaccine-attenuated disease (VAD), i.e. reduced disease severity in individuals with breakthrough disease following vaccination. The BOD endpoint has previously been accepted as a primary endpoint[3] to support efficacy claims to regulatory authorities[4].

VAD cases after C-19 vaccination may impede the rapid demonstration of VE. VE is defined as the proportionate reduction of the C-19 incidence in vaccinees compared to controls and typically expressed as VE= 100 x (1-RR), in which RR represents the rate ratio vaccine to placebo. The accumulation of C-19 VAD cases in the vaccine arm would significantly reduce VE against milder disease manifestations, which in turn would significantly increase the number of cases required to reject the null hypothesis, thereby delaying demonstration of VE. To allow for VAD cases, the boundaries defining success for VE have been set low by some agencies. The WHO and FDA define statistical success as a C-19 VE point estimate of at least 50% with a lower bound of the confidence interval for the VE point estimate of >30%. The large number of cases required for low VE assumptions could prove difficult to obtain during the pandemic with public-health interventions aiming to reduce SARS-CoV-2 infections, rendering the lowering of the VE target to address VAD when speed is of essence, potentially counterproductive.

An important aspect of vaccines associated with VAD is that they are expected show higher efficacy in preventing severe disease compared to mild disease. This would make a primary endpoint of prevention of severe C-19 attractive if not for the epidemiology of C-19 showing that the incidence of severe C-19 is much lower than mild or moderate C-19, likely requiring larger trials than those currently ongoing.

The higher VE against severe than moderate and mild disease is primarily caused by accumulation of VAD cases in the vaccine arm, as conceptually illustrated in Figure 1, and visualized with a hypothetical example in Table 1 in which 200 subjects became SARS-CoV-2-infected in each the placebo and vaccine arm. For the purpose of the conceptual visualization, the example assumes that infections cannot be prevented at all; that in 10% of people the vaccine does not reduce disease severity; that in 10-20% the vaccine reduces severity by one category; and that 70-80% of people drop two or more severity categories, or become asymptomatic. The example shows that although VE is highest against critical disease (90%), only in one person (10%) in this severity category, symptomatic C-19 was prevented (i.e. one person became asymptomatic), despite a reduction of disease severity in 90% of subjects. VE decreases for each decreasing C-19 severity, having the lowest VE against mild disease (50%) despite being most effective in preventing C-19 cases (90%) in the mild C-19 category. As a result, the accumulation of VAD cases that are mild will be greater than those that are moderate with even fewer severe cases, explaining the declining VE against decreasing disease severity. The true vaccine effect on individual cases is illustrated in the vaccine arm 'black-box' outcome in Table 1.

Table 1: The impact of VAD on C-19 vaccine efficacy – hypothetical 'black-box' illustration [© AE.Loeliger]

C-19 disease severity		Placebo arm		Vaccine arm		VE	C-19 cases averted
Endpoint	BOD score	Cases (n)	BOD score	Cases (n)	BOD score	100*(1-RR)	n/n*100
Critical C-19	4	10	40	1	4	**90%**	10%
Severe C-19	3	20	60	3	9	**85%**	20%
Moderate C-19	2	40	80	10	20	**75%**	70%
Mild C-19	1	60	60	30	30	**50%**	88%
Asymptomatic SARS-CoV-2 +	0	70	0	156	0	**-123%**	NA
Burden of Disease (BOD)			240		63	**74%**	
Severe/critical		30		4		**87%**	
Moderate/severe/critical		70		14		**80%**	
Mild/moderate/severe/critical		130		44		**66%**	
All SARS-CoV-2 Infections		200		200		**0%**	

Vaccine arm "black-box" outcome		
Critical n=10	Critical	1
	Severe (=VAD)	1
	Moderate (=VAD)	2
	Mild (=VAD)	5
	Asymptomatic	1
Severe n=20	Severe	2
	Moderate (=VAD)	4
	Mild (=VAD)	10
	Asymptomatic	4
Moderate n=40	Moderate	4
	Mild (=VAD)	8
	Asymptomatic	28
Mild n=60	Mild	7
	Asymptomatic	53
Asymptomatic	Asymptomatic	70

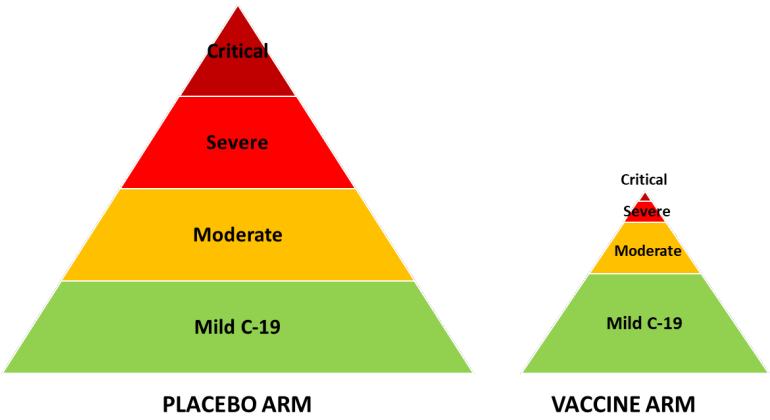
The BOD endpoint takes the distribution of severity into account, assigning a value for each severity grade. In the example in Table 1, asymptomatic infection, mild C-19, moderate, C-19, severe C-19, and critical C-19 are scored as 0, 1, 2, 3, and 4 respectively. The BOD score in each arm is the sum of the scores assigned to each case. The VE_{BOD} is defined as the relative reduction in the burden of disease score in the vaccine group as compared to the score in the placebo group and calculated as VE= 100 x (1-RR), in which RR represents the rate ratio of the BOD score vaccine to placebo[5]. This provides a simple, useful, and interpretable VE_{BOD} statistic.

For C-19 vaccines, the BOD endpoint could be considered as a primary endpoint in a multiple endpoint approach. A multiple endpoint approach differs from a composite or co-primary endpoint approach and is useful when demonstration of a treatment effect on at least one of several primary endpoints is sufficient, irrespective of which one comes first[6]. For C-19 vaccines the BOD endpoint could be considered as a dual primary endpoint together with clinically symptomatic C-19 regardless of disease severity, or as part of a triple primary endpoint that includes in addition, the endpoint of moderate to severe/critical C-19. According to Mehrotra et. al. the statistical penalty for closely related multiple endpoints for C-19 is relatively small. They reported that extensive simulations over a range of options gave critical thresholds rising from 1.96 in the case of a single endpoint to 2.07 and 2.15 for dual or triple primary endpoints.

BOD endpoints in published C-19 Phase 3 efficacy protocols have been defined as exploratory and secondary efficacy endpoints respectively. When included as a dual or triple *primary* endpoint, the inclusion of a moderate C-19 severity grade in the BOD score will be important to increase its added value, because of the low proportion of people that develop severe C-19. With the lack of global consensus on the definitions of moderate or severe C-19, WHO's severity grading would be useful and pragmatic, defining moderate disease as pneumonia, diagnosed by the presence of one or more symptoms of new onset, persistent cough, dyspnoea, or fever, without meeting the criteria of severe pneumonia that would classify as severe C-19[7]. Moderate disease, when defined as clinical or radiographic evidence of pneumonia without the presence of severe pneumonia, is present in up to 40% of symptomatic C-19, depending on age and other risk factors in the clinical-trial cohort.

The C-19 BOD efficacy endpoint allows vaccine-attenuated C-19 cases to be counted as reduced disease severity, instead of vaccine failure in preventing C-19. The corresponding efficacy objective is (demonstration of the efficacy in the) reduction of (virologically confirmed) C-19 incidence and disease severity. It is pertinent because of the difficulty of accruing C-19 cases during a pandemic with public-health interventions, when rapid demonstration of VE is paramount. When a moderate disease category is included, the BOD endpoint effectively addresses the low incidence of severe disease increasing its added value. The concern of translating VE_{BOD} of, for example, 66% in reducing C-19 incidence and severity in a transparent label claim is not fundamentally different from translating a VE claim of 66% in preventing first C-19 cases following vaccination, if in the latter as shown in the example in Table 1, the 66% is made up of 87% VE against severe or critical C-19, 75% VE against moderate C19, and 50% VE against mild C-19. The acceptable minimum VE_{BOD} point estimate and definitions for the different C-19 severity categories should be defined in dialogue with the competent authorities.

Figure 1



References:

[1] Chang MN, Guess HA, Heyse JF. Reduction in burden of illness: a new efficacy measure for prevention trials. Stat Med 1994;13:1807-14

[2] Devan V. Mehrotra, Holly E. Janes , Thomas R. Fleming , Paula W. Annunziato et al. Clinical Endpoints for Evaluating Efficacy in COVID-19 Vaccine Trials. Annals of Internal Medicine 0;0 [Epub ahead of print 22 October 2020]. Doi: https://doi.org/10.7326/M20-6169

[3] The Shingles prevention study: Oxman MN et.al A vaccine to prevent Herpes Zoster and postherpetic neuralgia in older adults. N. Engl. J Med 2005; 352:2271-84

[4] EMA 2006: Zostavax EPAR scientific discussion; available from https://www.ema.europa.eu/en/documents/scientific-discussion/zostavax-epar-scientific-discussion_en.pdf (accessed 11 October 2020)

[5] Callegaro A, Curran D, Matthews S. Burden-of-illness vaccine efficacy. Pharmaceutical Statistics 2020; 19:636-645

[6] FDA 2017: Multiple endpoints for clinical trials; draft guidance for industry; available from https://www.fda.gov/media/102657/download (accessed 11 October 2020)

[7] WHO 2020: Clinical management of COVID-19; Interim guidance 27 May 2020; available from https://www.who.int/publications/i/item/clinical-management-of-covid-19 (accessed 11 October 2020)