# Summary Document

## Topic: Efficacy Endpoints in COVID-19 Vaccine Trials: SARS-CoV-2 Infection

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**Overview:**

This Summary Document discusses the endpoint of SARS-CoV-2 infection in the context of trials assessing vaccine efficacy (VE). During the COVID-19 pandemic, clinical development of COVID-19 vaccines should focus on demonstrating VE against clinically symptomatic COVID-19 in the quickest possible way. Historically, vaccines for respiratory and other mucosal viruses have greater efficacy against severe disease than against mild disease and have greater efficacy against symptomatic disease than against asymptomatic infection.

COVID-19 with signs and symptoms of pneumonia, should be considered for the primary efficacy assessment depending on the background incidence rate. This corresponds with moderate, severe, or critical disease in WHO's COVID-19 severity grading. All clinically symptomatic COVID-19, irrespective of severity grade, may be considered for secondary or primary VE assessment, depending on the incidence rate of SARS-CoV-2 infection. Efficacy against severe disease should be considered as a secondary endpoint. SARS-CoV-2 infection, capturing both symptomatic disease and asymptomatic infection, merits consideration as an additional endpoint. The endpoint of SARS-CoV-2 infection can be assessed by demonstration of virus using RT-PCR or by seroconversion.

Systematic assessment of infection by RT-PCR requires prospective sampling at regular intervals irrespective of symptoms. This will result in a very large numbers of samples. Even with a RT-PCR specificity of 99.9% in a trial setting, false positive tests will result in hundreds of 'cases', outnumbering actual incident SARS-CoV-2 infections and posing a significant challenge. False positive test results are evenly spread between treatment arms, which biases the VE towards the null hypothesis, resulting in a lower VE estimate or failure to demonstrate VE against infection.

Alternatively, infection can be measured by seroconversion using an antibody assay that distinguishes between anti-SARS-CoV-2 antibodies induced by vaccine and natural infection. The sensitivity and usefulness of such assays to substantiate asymptomatic infection remains to be determined.

It is unclear whether COVID-19 vaccines will be able to entirely prevent infection. Early animal challenge data suggest they may not induce sterilizing immunity and prevent infection in the upper respiratory tract despite protecting against SARS-CoV-2 pneumonia. Where sterilizing immunity cannot be elicited, vaccines might still be able to reduce viral load and shorten the duration of viral shedding, thereby preventing or ameliorating subsequent disease.

**COVID-19 Vaccine Efficacy Assessments.**

It is essential that any intervention during the COVID-19 pandemic achieves public health benefit in the quickest possible way. Incident clinically symptomatic COVID-19 represents the main clinical endpoint for vaccine efficacy (VE) trials. COVID-19 with signs and symptoms of pneumonia, classified as moderate to critical disease by WHO [1], should be considered for the primary efficacy assessment depending on the background attack rate of SARS-CoV-2 infection. Alternatively, when the background incidence is very low, all clinically symptomatic COVID-19, irrespective of severity grade, may be considered for the primary VE assessment. The prevention of moderate to critical disease provides individual benefit and is likely to significantly reduce healthcare utilization. From early-stage clinical development, all trials should prospectively collect incident COVID-19 cases irrespective of severity using clearly defined clinical criteria.

**SARS-CoV-2 infection**.

SARS-CoV-2 infection merits consideration as a secondary or exploratory endpoint. The endpoint can be assessed directly by demonstration of virus using RT-PCR, or indirectly by seroconversion. Immune persistence and the performance characteristics of the assay should be considered when ranking the endpoint of SARS-CoV-2 as secondary or exploratory.

The endpoint of SARS-CoV-2 infection aims to capture both symptomatic disease and asymptomatic infection. SARS-CoV-2 infection can remain asymptomatic and remains undetected in most children. Two recent meta-analyses showed estimates of asymptomatic infection in adults to be 45% [2] and 15% [3] of cases respectively. Efficacy against asymptomatic disease may involve reduction of viral shedding and reduce circulation of virus in the community. Complete prevention of infection blocks virus transmission, contributing to herd immunity. However, vaccines against respiratory and other mucosal viruses (e.g. rotavirus) typically have less impact on mild disease and asymptomatic infection. COVID-19 vaccines, like influenza vaccines may reduce the risk of disease with greater impact on severe disease.

It remains unclear whether COVID-19 vaccines will be able to entirely prevent infection in humans. Early animal challenge data suggest they may not induce sterilizing immunity. In at least one SARS-CoV-2 challenge study in rhesus macaques, a reduction in viral shedding from the nose was not observed in animals following vaccination, despite providing protection against SARS-CoV-2 pneumonia [4]. In the same experiment, the vaccine did not prevent all symptoms following viral challenge, but resulted in less frequent, less severe, and shorter lasting respiratory signs in vaccinated animals compared to control animals (‘vaccine-induced disease attenuation'). Results from animal challenge studies, however, should always be interpreted with caution.

**SARS-CoV-2 infection as measured by RT-PCR**

Viral shedding for less than 9 days has been reported among mildly symptomatic patients [1,5]. Therefore, frequent sampling, ideally on a weekly basis, will be needed to capture most infections. Weekly sampling may also enable an assessment of whether there is a difference in duration of viral shedding between treatment arms. The need for a very large number of tests, however may require use of home sampling kits for self-administered nasopharyngeal swabs. This requires repeated training and may be associated with operational challenges.

The performance characteristics of RT-PCR kits, in particular sensitivity and specificity, must be carefully considered. It is important to note that kit performance characteristics included in package inserts are obtained under ideal laboratory conditions. The performance characteristics in the clinical trial setting may be lower [6,7]. RT-PCR assays covering at least two gene targets, should be considered to overcome potential mutations.

When large number of tests are conducted, the assay's specificity will be the crucial consideration. Even the slightest reduction in specificity biases the VE estimate towards the null hypothesis. False positivity is non-differential, spreading 'cases' equally between treatment arms thereby lowering VE. Whereas a specificity of 96% or higher might be justifiable for surveillance purposes and to confirm clinically suspected disease, even the slightest decrease in specificity will pose a major challenge when assessing infection endpoints in asymptomatic trial subjects in a very large number of samples.

For example: an RT-PCR test with 99.9% specificity, obtained weekly from 4,000 volunteers over a 52-week period (208,000 tests) would result in 208 false positive test results, vastly outnumbering actual SARS-CoV-2 infections. Evenly spread between treatment arms, these 'cases' lower the VE point estimate and might result in failure to demonstrate efficacy against infection, irrespective of the true efficacy of the vaccine.

In contrast, RT-PCR assays with poor sensitivity may not reliably pick up mild or asymptomatic infections with low viral load. This might lead to an underestimating of the number of infections. False negative results, however, do not bias results towards the null hypothesis. The assay's sensitivity relates to its lower limit of detection (LLOD). When selecting an RT-PCR assay the LLOD must be considered in addition its sensitivity.

**SARS-CoV-2 infection as measured by seroconversion**

Infection can also be measured indirectly through seroconversion against an antigen not included in the vaccine, e.g. anti-nucleoside-protein antibodies (anti-N-ab). Seroconversion is of limited use for real-time assessment of infection because samples must be drawn at protocol scheduled visits. Far fewer samples will be required compared to RT-PCR, as in theory, samples may only need to be taken at baseline, 4 weeks after the last dose, and then for example at months 3, 6, and 12 following vaccination, or less frequently if deemed appropriate within the design of the trial.

For seroconversion, an IgG/IgM combo assay should be considered. Both the sensitivity and specificity of the antibody assay will be key considerations. To date, few data exist on the sensitivity of anti-N-ab assays and their performance in asymptomatic individuals is unknown. Furthermore, it remains unclear whether seroconversion occurs after all infections, as a correlation between disease severity and antibody levels has been suggested [8]. Data on immune persistence beyond six months are lacking altogether. The anti-N-ab seroconversion endpoint might be useful when reliable assays are available and the antibody response to natural infection is better characterized.

**Additional Resources:**


1. Clinical Management of COVID-19 (WHO interim guidance): https:// www.who.int/publications/i/item/clinical-management-of-covid-19.
2. Oran D, Topol E. Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review. Ann Intern Med. 2020 Jun 3.
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4. Van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. https://doi.org/10.1101/2020.05.13.093195. Available at: https://www.biorxiv.org/content/ 10.1101/2020.05.13.093195v1#disqus_thread.
5. Liu Y, Yan L, Wan L, Xiang T, Le A, Liu J et al. Viral dynamics in mild & severe cases of COVID-19. Lancet. 01 June 2020. 20(6):656-7.
6. SARS-CoV-2 Molecular assay evaluation: Results. Available at: https://www.finddx.org/covid-19/sarscov2-eval-molecular/molecular-eval-results/ (Accessed on: 10 June 2020).
7. van Kasteren, van der Veer, van den Brink, Wijsman, de Jonge, van den Brandt et al. Comparison of seven commercial RT-PCR diagnostic kits for COVID-19. Journal of Clinical Virology 128 (2020) 104412.
8. Tan W, Lu Y, Zhang J, Wang J, Dan Y, Tan Z. Viral Kinetics and Antibody Responses in Patients with COVID-19. https://doi.org/10.1101/2020.03.24.20042382. Available at: https://www.medrxiv.org/content/10.1101/2020.03.24.20042382v1.