

Biological composition, efficacy and primary efficacy endpoint of SARS-CoV-2 vaccines: A special communication

Imran Ishaque¹, Muhammad Muhib², Omer Bin Khalid Jamil³

Abstract

Severe acute respiratory syndrome coronavirus 2 was first reported in Wuhan, China, in late December 2019 and rapidly spread out globally, affecting 130 million individuals and starting a global pandemic. An efficacious vaccine is considered an essential tool to reduce mortality and morbidity rate related to the pandemic. Nine different vaccine candidates announced the efficacy results of their respective phase 3 trial testing up till January 2021. By the end of June 2021, the administration of seven different vaccines started under the supervision of the World Health Organisation. The current article was planned to discuss the biological composition, efficacy and primary efficacy endpoint described in literature, and to identify the factors that could affect vaccine efficacy and vaccine coverage.

Keywords: SARS-CoV-2 vaccine, Efficacy, Vaccine coverage, Efficacy endpoint, Factors.

DOI: <https://doi.org/10.47391/JPM.4640>

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported from Wuhan City, China, in December 2019. The global outbreak affected 130 million individuals and was declared a pandemic.¹ This outbreak resulted in thousands of lives lost, profound increase in the burden on hospitals, a state of paralysing fear amongst individuals, and a resulting decline in the global economy. Efforts to contain and eradicate the virus lead to vaccine development, which would be effective enough to render some resistance to its lethal outcomes.

More than 200 SARS-CoV-2 vaccine candidates are under way in various stages of development and nine different SARS-CoV-2 vaccine candidates announced the interim analysis of the safety and efficacy of their vaccines from phase 3 trial testing till January, 2021.² By the end of June 2021, the World Health Organization (WHO) had approved seven vaccines under Emergency Use Listing (EUL) section

to manage the rapid spread of the pandemic.³ In its target product profile for the SARS-CoV-2 vaccine, the WHO postulated that at least a minimum proportion of 50% efficacy (on the population basis) was required for any acceptable SARS-CoV-2 vaccine.⁴ The development of an effective vaccine encouraged vaccine candidates to utilise several vaccine platforms and methods that aid in attaining the highest possible efficacy.⁵ However, overall vaccine effectiveness does not merely depend on its efficacy as it represents the vaccine's performance in an ideal controlled clinical trial. The overall vaccine effectiveness represents a decrease in the transmission rate of infection among individuals in a vaccinated population at a particular coverage rate compared to those of a non-vaccinated population.⁶ Thus, overall vaccine effectiveness is the product of both efficacy and vaccine coverage. As in the case of the SARS-CoV-2, the computational model study, simulating the spread of SARS-CoV-2 and its vaccination, revealed that a successful vaccine should possess an efficacy of at least 80% with 75% vaccine coverage. Only then other precautionary measures, like social distancing, face mask, etc., can be lifted. If vaccine efficacy is lowered to 60%, the coverage rate had to be at least 100% for eradicating SARS-CoV-2, and vice versa.⁷ Therefore, both these variables have importance in determining the rate of eradication of infection by a particular vaccine in a given population.

The current special communication was planned to discuss and explore biological composition, efficacy and definition of primary efficacy endpoint described in the available literature of the current SARS-CoV-2 vaccines, and to discuss the factors that can influence the efficacy and coverage rate of the available vaccines.

Current SARS-Cov-2 Vaccines

At present, the SARS-COV-2 vaccines can be classified according to their biological composition into four categories: Ribonucleic acid (RNA) vaccine (Pfizer, Moderna), viral vector vaccine (AstraZeneca, Sputnik V, Johnson & Johnson's Janssen), inactivated vaccine (Sinopharm, Sinovac, CanSinoBio vaccine), and the protein-based vaccine (Novavax).⁸ Each of the vaccines possesses different efficacy against SARS-COV-2. All vaccines contain full-length spike glycoprotein of SARS-CoV-2 or its

¹Department of Anatomy, United Medical and Dental College, Jinnah Sindh Medical University, Karachi, Pakistan; ²3rd Year MBBS Student, United Medical and Dental College, Karachi, Pakistan; ³Department of Surgery, United Medical and Dental College, Karachi, Pakistan.

Correspondence: Muhammad Muhib. e-mail: muhibshah19@gmail.com

Table-1: Biological composition of SARS-CoV-2 vaccines.^{3,9-16}

Manufacturing Myriad Pro Cond	Name of the Vaccine	Vaccine platform	TARGET MOLECULE (epitope) OF SARS-CoV-2	Date of approval for emergency use listing
Pfizer/BioNTech	BNT162b2	mRNA (nucleoside-modified RNA)	prefusion stabilized SARS-CoV-2 full-length spike glycoprotein	31-Dec-20
Johnson & Johnson's Janssen vaccines	Ad26.COV2.S	human adenovirus type 26 (Ad26)	prefusion stabilized SARS-CoV-2 full-length spike glycoprotein	2-Mar-21
AstraZeneca & Covishield.	ChAdOx1 nCoV-19	adenoviral vector ChAdOx1	Spike glycoprotein antigen of the SARS-CoV-2	15-Feb-21
Moderna	mRNA-1273	mRNA (nucleoside-modified RNA)	prefusion-stabilized spike covid-19 glycoprotein	30-Apr-21
Gamaleya national center of epidemiology and microbiology	Sputnik v (Gam-COVID-Vac)	recombinant replication-deficient adenovirus type 26 (rAd26) and type 5 (rAd5)	SARS-CoV-2 full-length spike glycoprotein	not approved for EUL
Sinopharm/BIBP	Sinopharm	Vero cell vaccine	contain inactivated SARS-CoV-2 virus	7-May-21
Sinovac	Sinovac (CoronaVac)	Vero cell vaccine	contain inactivated SARS-CoV-2 virus	1-Jun-21
Novavax	NVX-CoV2373	1273 amino acid recombinant protein + matrix M	prefusion stabilized SARS-CoV-2 full-length spike glycoprotein	not approved for EUL

encoding gene (Table-1). Pfizer and Moderna vaccines contain lipid messenger ribonucleic acid nanoparticle-encapsulated (mRNA-LNP) platform encoding with the receptor-binding domain (RBD) of SARS-CoV-2 (antigen). The mRNA vaccine technology emerged as an instantaneous and versatile platform to respond rapidly to this situation because of its ability to stimulate both the robust neutralising antibodies immunoglobulin g (IgG) and a T Helper Cell Type 1 (Th1)-based cellular immune response against SARS-CoV-2.⁵ As a result of mRNA technology, the outcome efficacy of these vaccines (Pfizer and Moderna) is more prominent than the other vaccines.

The platform of AstraZeneca, Sputnik V, Johnson & Johnson vaccines is based on a different strains of recombinant, replication-deficient adenovirus type (rAd) vectors.^{3,9-16} However, AstraZeneca uses the chimpanzee type adenoviral (adCs) vector rather than human type adenovirus (adHus). The study showed that because of non-reactivity of adCs vector to pre-existing adHus-neutralising antibodies, adCs vector vaccines are capable of eliciting a strong immune response in animals preimmune to adHus.¹⁶ Sinovac and Sinopharm traditionally are vero cell vaccine containing inactivated (killed) SARS-CoV-2 virion. Novavax vaccine is a recombinant protein nanoparticle encoded with a genetic sequence of SARS-CoV-2 spike protein accompanied with saponin-based Matrix-M that helps in enhancing immune response and stimulating a high level of antibody titers.¹⁷

Vaccine Efficacy and Efficacy Endpoint

Efficacy of a vaccine is assessed on the basis of the definition of efficacy endpoint, which allows the comparison between vaccine candidates and within differing populations, and to evaluate the frequency of disease between vaccinated participant and control group in randomised control trial (RCT).¹⁸ The primary efficacy endpoint in a clinical trial is defined as an outcome (clinical or laboratory) measured after randomisation to evaluate the hypothesis and to assess whether therapy is effective compared to the control group. The definition of efficacy endpoint proposed by various SARS-CoV-2 vaccine efficacy trials can broadly be classified into two categories: 1) any laboratory-confirmed SARS-CoV-2 symptomatic case regardless of the severity of symptoms; and 2) any laboratory-confirmed SARS-CoV-2 mild-to-severe symptomatic case among seronegative participants (Table-2).¹⁹ According to the definition, the analysis of the primary efficacy endpoint in the second category of efficacy trials has been aligned with the severity grading scale based on the signs and symptoms of mild, moderate and severe SARS-CoV-2 cases.²⁰ A majority of second-category SARS-CoV-2 vaccine efficacy trials use the United States (US) Food and Drug Administration (FDA) recommended severity grading scale to classify symptomatic SARS-CoV-2 cases.⁹⁻¹⁶ However, some studies use self-developed severity grading scales that may cause a slight variation in the grading of symptomatic SARS-CoV-2 cases between the efficacy trials.⁹⁻¹⁶

To date, no phase 3 trial conducted on CanSinoBio vaccine

Table-2: Efficacy testing in phase 3 trial of SARS-CoV-2 vaccines available for administration.⁹⁻¹⁶

Name of the Vaccine	Efficacy against SARS-CoV-2 (95% CI) [†]	Timing of assessment of Efficacy	Primary Efficacy endpoint	Criteria for primary endpoint analysis
BNT162b2	94.6 (89.9-97.3)	7 days after second dose	any covid-19 disease diagnosed in seronegative participants	Acc to FDA criteria of mild covid-19: fever; cough; sore throat; dyspnoea; loss taste and smell; diarrhoea.
Ad26.COV2.S	66.9% (52.3- 77.3)	14 days after single dose	any moderate to severe covid-19 case diagnosed in seronegative participants	Any two symptoms. Moderate case: fever; heart rate ≥ 90 BPM; rigors; loss taste; cough; sore throat; headache; abnormal SpO ₂ $\geq 93\%$; dyspnoea. Severe critical case: heart rate > 125 BPM; respiratory failure; hepatic neurological and renal failure.
ChAdOx1 nCoV-19	70.4% (54.8 - 80.6)	14 days after the second dose	NAAT-confirmed Covid-19 case among seronegative participants	NAAT-Positive swab + Symptom: fever $\geq 37.8^{\circ}\text{C}$; cough, shortness of breath; anosmia or ageusia.
mRNA-1273	94.1% (89.3 - 96.8)	14 days after single dose	any covid-19 disease diagnosed in seronegative participant	swab test covid-19 confirmed+ Symptoms: fever $\geq 37.8^{\circ}\text{C}$; chills; myalgia; headache; sore throat; olfactory or taste disorder; cough; shortness of breath; evidence of pneumonia.
Sputnik v (Gam-COVID -Vac)	91.6% (85.6-95.2)	21 days after the first dose of vaccine (day on 2nd dose)	any covid-19 disease diagnosed in seronegative participant	any laboratory test confirmed participant before second dose given.
Sinopharm	72&78% (58.1- 82.4 & 64.8 86.3)	14 days after the second dose	laboratory-confirmed symptomatic COVID-19 cases	RT-PCR TEST conformation + symptoms: fever; dry cough; fatigue; sore throat; myalgia or diarrhoea, sputum; lower respiratory tract secretions.
Sinovac (CoronaVac)	83.5% (65.4-92.1)	14 days after the second dose	laboratory-confirmed symptomatic COVID-19 cases	RT-qPCR TEST conformation + at least one symptom: fever; cough; sore throat, loss of smell and taste; dyspnoea; fatigue; rhinorrhoea; vomiting; diarrhoea.
NVX-CoV2373	90% (80.2 - 94.6)	7 days after second dose	PCR- confirmed any mild to severe covid-19 disease diagnosed in seronegative participants	Any two symptoms acc to FDA criteria. Mild case: fever; cough; headache; loss of taste or smell; sore throat; fatigue. Moderate case: fever; shortness of breath; tachypnoea 20 to 29 RR; SpO ₂ 94 to 95%. Severe case: tachypnoea ≥ 30 RR; heart rate ≥ 125 BPM, SpO ₂ : $\geq 93\%$; acute respiratory syndrome; multi organ failure.

has been published that may provide information about its primary efficacy endpoint.

Factors that Affect the Efficacy of SARS-Cov-2 Vaccines

Factors such as characteristic of population, altered virus variants, presence of difference medical co-morbidities and other social determinants of health may affect and contribute to differences in the efficacy of a vaccine.

Genomic sequencing of SARS-CoV-2 mutates with the evolutionary rate of roughly 1×10^{-3} nucleotide substitutions per year, which causes it to produce its distinct evolving variants.²¹ To date, six SARS-CoV-2 current variants of concerns and majority of other variants have been identified in various countries around the world.²² The vaccines will likely function differently against a heterogeneous variant of SARS-CoV-2. The efficacy yielded by the designed trial of Ad26.COV2.S (Johnson & Johnson) vaccine performed on South African moderate-to-severe critical cases was 52% after 14 days of vaccine single dosage(10). During the trial, B.351 (20H/501Y.V2) variant was found predominantly in South African SARS-CoV-2

cases. In contrast, the ChAdOx1nCoV-19 (AstraZeneca & Covishield) vaccine did not have significant efficacy (21%) in providing protection against the B.1.351 SARS-CoV-2 variant.²³ In comparison, the ChAdOx1nCoV-19 vaccine provides 70% efficacy against B.1.1.17 variant that was common in the United Kingdom (UK).²⁴ The variation in efficacy of an individual vaccine against different SARS-CoV-2 variants is due to the particular sequence mutation to the RBD of SARS-CoV-2 variants.²⁵ Because of that, there is reduced but detectable binding of vaccine-elicited antibodies to mutant RBD protein of SARS-CoV-2 variants.²⁵ Nevertheless, most RBD mutant variants easily escape from vaccine-induced neutralisation and lead to a decreased efficacy of vaccines.²⁵ Another kind of mutation represented by B.1.1.17 variant arises under selection pressure on the virus, which facilitates it to infect human cells more effectively and maximise the replication of its genome.²⁶ However, B.1.1.17 is not a neutralisation escape variant and is not more concerning than the B.1.351 and P.1 variants that exhibit RBD mutation.^{25,26} The time duration of assessment of efficacy after vaccination also impacts the

efficacy result.^{18,19} As the efficacy assessment of SARS-CoV-2 vaccines merely lies in the current transmission of SARS-CoV-2, the early follow-up of the participants in the efficacy trial will decrease the exposure phase of SARS-CoV-2, and, hence, ultimately lead to less accurate higher efficacy results. The inclusion of asymptomatic SARS-CoV-2 infection in the efficacy endpoint inversely affects the efficacy outcome.¹⁹ If a vaccine illustrates an impressive reduction in SARS-CoV-2 symptomatic infection, as a net result, there will be an increase in asymptomatic SARS-CoV-2 cases in a pool. In such a scenario, the vaccine would likely meet success criteria if the efficacy endpoint is based on the detection of symptomatic SARS-CoV-2 cases.¹⁹ However, a modest efficacy outcome would be observed in the same vaccine if the endpoint includes asymptomatic SARS-CoV-2 infection.¹⁹

The characteristics of a population, such as age, gender and race, may also impact the effectiveness of SARS-CoV-2 vaccines. However, the effect is less profound and not significant in contrast to heterogeneous virus variant factor.⁹ Moreover, it has been suggested by previous studies that expanding sleep duration after vaccination causes additional increases in efficacy by boosting up the person's immune response against the respective vaccine.²⁷ Antibody titers are found to carry less than half deficit in individuals with sleep deprivation than individuals with average sleep duration after four consecutive nights of vaccination.²⁷ Patients with immunocompromised disease will not respond competently to vaccination, and the presence of immunosuppressed disease within the population could lead to lower immunogenicity and lower efficacy overall.²⁸

Factors that may Impede Vaccination Coverage

An increase in misinformation susceptibility regarding SARS-CoV-2 and its vaccines could mislead people's beliefs and knowledge about it. Such misinformation negatively impacts people's self-compliance with SARS-CoV-2 precautionary measures and the willingness to get vaccinated against SARS-CoV-2 themselves or their family and friends.²⁹ The acceptance rate of SARS-CoV-2 vaccines in a general population of different countries around the globe is $\geq 70\%$. However, the SARS-CoV-2 vaccine acceptance level is reported further low in middle and low-income countries.³⁰ Another impeding factor is waiting for the availability of vaccines with higher efficacy. When an initial vaccine is available with low efficacy early in a pandemic, waiting until the higher efficacy vaccine is available could cause the pandemic to progress and decrease vaccine coverage rate. Furthermore, the additional rising cases offset the potential gain of higher efficacy vaccines.³¹

The production cost of vaccines could be an indirect factor that can impede the vaccination process. An estimated expense of around \$2.8-3.7 billion is reported for a single vaccine development and its progression through to the end of phase 2 trial.³² To increase vaccine coverage, vaccination against SARS-CoV-2, despite its expensive production, should be expedited at no or low cost, especially for lower-income countries. Due to their insufficiency of resources, middle and low-income countries depend on the assistance of world superpowers and global institutions, such as the WHO, to advance the campaign against SARS-CoV-2 outbreak. However, sometimes the priorities of major donors may align with self-interest rather than global wellbeing, and, as a result, necessitous and vulnerable may be left to endure.³³ Another problem is a deficiency of governance and scrutiny systems for coronavirus diseases-2019 (COVID-19) prevention and vaccination progression in lower and middle-income countries worldwide, like lack of epidemiological data, surveillance system to monitor vaccinated and non-vaccinated individuals, diagnostic screening of SARS-CoV-2 and effective platform that provide intervention in communities about SARS-CoV-2 and its vaccine. It often takes years, and sometimes decades, for such countries to attain the same frequency of vaccination process in their population as in high-income countries.³⁴

Despite their high efficacy rate and cost-effectiveness, mRNA vaccines need to be stored at temperatures varying from about -20°C to -70°C for a duration between 2 weeks and 6 months, respectively. Therefore, the problem may arise in the practical implementation of these vaccines in most locations because of supply challenges.³⁴ On the other hand, vero cell vaccines with their moderate efficacy rate (80-60%) are feasible for using in middle and low-income countries and could help alleviate the burden induced by COVID-19, but, still, such vaccines require a high coverage rate of around 100-75%.⁷

Conclusion

The diversity in vaccine platforms and technology results in variations in efficacy endpoint. Due to the novelty of SARS-CoV-2 and understanding of its clinical spectrum, this heterogeneity in efficacy endpoint analysis can be appreciated. However, it is essential to adopt a single standard set of clinical efficacy endpoints across all vaccine efficacy trials to provide a uniform evaluation of different SARS-CoV-2 vaccines. Also, the application of a single set of clinical efficacy endpoints will assist in comparing the efficacy of SARS-CoV-2 vaccines to select an effective vaccine for the community. Efficacy determination is a complicated process, especially for COVID-19, as its vaccine

efficacy evaluation relies on current SARS-CoV-2 transmission and biological make-up. Nonclinical public health interventions to reduce infection rates may lead to nonconformity in exact efficacy. Maintenance of cold chain for mRNA vaccine requires resources, which for larger population segment is challenging and may not be feasible. The problem has risen regarding the mutation rates of SARS-CoV-2. The presence of distinct variants in a population could diminish the vaccine's strength and lead to immune evasion. The stakeholders and healthcare providers should ensure the selection of vaccines for the community, according to representative efficacy against the virus variant prevailing in that region.

The involvement of major vaccine manufacturers from middle and low-income countries in primary vaccine development will increase the production rate and fulfill the rapidly evolving demand for vaccines across the globe during pandemics. Furthermore, it may reduce the shortage and supply cost of vaccines in LMICs. Productive vaccine administration scrutiny and surveillance system could aid in the assessment of vaccine coverage rates.

Deliverance of Community-level public health intervention regarding COVID-19 can aid in reducing vaccine hesitancy and increasing coverage rate.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Worldometer. Covid-19 Corona Virus Pandemic. [Online] 2021 [cited 2021 May 25]. Available from URL: https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1
2. Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. *Nat Med* 2021;27:205-11. doi: 10.1038/s41591-021-01230-y.
3. World Health Organization (WHO). Coronavirus disease (COVID-19): Vaccines. News Release. The WHO Media Centre. [Online] 2020 [Cited 2021 June 21]. Available from URL: [https://www.who.int/news-room/q-a-detail/coronavirus-disease-\(covid-19\)-vaccines?topicsurvey](https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines?topicsurvey)
4. World Health Organization (WHO). WHO Target Product Profiles for COVID-19 Vaccines. [Online] 2020 [Cited 2021 June 20]. Available from URL: <https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf>
5. Zhang NN, Li XF, Deng YQ, Zhao H, Huang YJ, Yang G, et al. A Thermostable mRNA Vaccine against COVID-19. *Cell* 2020;182:1271-83.e1216. doi: 10.1016/j.cell.2020.07.024
6. Halloran ME, Longini IM Jr, Struchiner CJ. Assessing Indirect, Total, and Overall Effects. In: Gail M, Tsiatis A, Krickeberg K, Wong W, Samet J, eds. *Design and Analysis of Vaccine Studies*, 1st ed. New York, USA: Springer Science+Business Media, 2010; pp. 271-312.
7. Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U, et al. Vaccine Efficacy Needed for a COVID-19 Coronavirus Vaccine to Prevent or Stop an Epidemic as the Sole Intervention. *Am J Prev Med* 2020;59:493-503. doi: 10.1016/j.amepre.2020.06.011.
8. Brüssow H. Efforts towards a COVID-19 vaccine. *Environ Microbiol* 2020;22:4071-84. doi: 10.1111/1462-2920.15225.
9. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;383:2603-15. doi: 10.1056/NEJMoa2034577.
10. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* 2021;384:2187-201. doi: 10.1056/NEJMoa2101544.
11. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111. doi: 10.1016/S0140-6736(20)32661-1.
12. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021;384:403-16. doi: 10.1056/NEJMoa2035389.
13. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397:671-81. doi: 10.1016/S0140-6736(21)00234-8.
14. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA* 2021;326:35-45. doi: 10.1001/jama.2021.8565.
15. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021;398:213-22. doi: 10.1016/S0140-6736(21)01429-X.
16. Fitzgerald JC, Gao GP, Reyes-Sandoval A, Pavlakis GN, Xiang ZQ, et al. A simian replication-defective adenoviral recombinant vaccine to HIV-1 gag. *J Immunol* 2003;170:1416-22. doi: 10.4049/jimmunol.170.3.1416.
17. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med* 2021;385:1172-83. doi: 10.1056/NEJMoa2107659.
18. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* 2021;21:e26-35. doi: 10.1016/S1473-3099(20)30773-8.
19. Mehrotra DV, Janes HE, Fleming TR, Annunziato PW, Neuzil KM, Carpp LN, et al. Clinical Endpoints for Evaluating Efficacy in COVID-19 Vaccine Trials. *Ann Intern Med* 2021;174:221-8. doi: 10.7326/M20-6169.
20. COVID-19 Clinical Working Group. COVID-19 Efficacy Endpoints in Interventional Trials: What Constitutes an Incident Clinical Disease Case and What Triggers Diagnostic Work-Up. [Online] 2020 [Cited 2021 June 25]. Available from URL: https://media.tghn.org/articles/COVID-19_Clinical_Endpoint_Case_Definition_V2.0_25_June_20_RETIRED.pdf
21. Duchene S, Featherstone L, Haritopoulou-Sinanidou M, Rambaut A, Lemey P, Baele G. Temporal signal and the phylodynamic threshold of SARS-CoV-2. *Virus Evol* 2020;6:veaa061. doi: 10.1093/ve/veaa061.
22. World Health Organization (WHO). Tracking SARS-CoV-2 variants. [Online] 2022 [Cited 2022 April 20]. Available from URL: <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
23. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021;384:1885-98. doi: 10.1056/NEJMoa2102214.

24. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021;397:1351-62. doi: 10.1016/S0140-6736(21)00628-0.
25. Garcia-Beltran WF, Lam EC, St Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell* 2021;184:2372-83.e9. doi: 10.1016/j.cell.2021.03.013.
26. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. *Cell Host Microbe* 2021;29:529-39.e3. doi: 10.1016/j.chom.2021.03.002.
27. Benedict C, Cedernaes J. Could a good night's sleep improve COVID-19 vaccine efficacy? *Lancet Respir Med* 2021;9:447-8. doi: 10.1016/S2213-2600(21)00126-0.
28. Experts Discuss COVID-19—Variants and Vaccine Efficacy, Immunosuppressed Patients, and More. *JAMA* 2021. doi: 10.1001/jama.2021.5938 [ahead of print]
29. Roozenbeek J, Schneider CR, Dryhurst S, Kerr J, Freeman ALJ, Recchia G, et al. Susceptibility to misinformation about COVID-19 around the world. *R Soc Open Sci* 2020;7:e201199. doi: 10.1098/rsos.201199.
30. Sallam M. COVID-19 Vaccine Hesitancy Worldwide: A Concise Systematic Review of Vaccine Acceptance Rates. *Vaccines (Basel)* 2021;9:160. doi: 10.3390/vaccines9020160.
31. Bartsch SM, O'Shea KJ, Wedlock PT, Strych U, Ferguson MC, Bottazzi ME, et al. The Benefits of Vaccinating With the First Available COVID-19 Coronavirus Vaccine. *Am J Prev Med* 2021;60:605-13. doi: 10.1016/j.amepre.2021.01.001.
32. Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *Lancet Glob Health* 2018;6:e1386-96. doi: 10.1016/S2214-109X(18)30346-2.
33. Wadoun REG, Clarke A. How prepared is Africa to face COVID-19? *Pan Afr Med J* 2020;35(Suppl 2):e1. doi: 10.11604/pamj.supp.2020.35.2.22665.
34. Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force Members. Operation Warp Speed: implications for global vaccine security. *Lancet Glob Health* 2021;9:e1017-21. doi: 10.1016/S2214-109X(21)00140-6.