# Vaccines and Variants:

## *Comparing Apples and Oranges*

Text by Dr Wong Sin Yew and Dr Loh Jiashen

We are now just over 20 months into the COVID-19 pandemic and the amount of scientific data published has been nothing short of overwhelming. The same sets of data have at times been cut and spliced with different interpretations, conclusions and opinions. Clearly, in generating public health policies to move the country forward, it is not just the science that is needed, but political and economic considerations as well. There is no standard playbook to follow and we have already experienced how policies are constantly evolving. So, let us continue to follow the science with a short summary of the current status of vaccines and SARS-CoV-2 variants.

### What's new in COVID-19 vaccines?

In the last six months, national COVID-19 vaccination programmes have demonstrated effectiveness in slowing the rampage of the pandemic. The pandemic's global scale has also resulted in different vaccine developments in different countries, many having diverse modes of action, efficacy and safety data against SARS-CoV-2. The main classes of COVID-19 vaccines are mRNA, viral-vectored DNA, inactivated virus and protein subunit.

The general structure of an mRNA vaccine is an optimised mRNA sequence in a lipid capsule. Delivery occurs via passive fusion of the lipid capsule with the cell membrane and delivery of the spike protein mRNA into the cytosol.

Viral-vectored DNA vaccines, like the Oxford-AstraZeneca, Russian Sputnik V, and Johnson and Johnson (J&J) vaccines, deliver their DNA via the cell entry mechanism intrinsic to the carrier adenovirus. However, since the pathogenic genes are removed and replaced by the DNA of interest, no further viruses may be produced by the host cell, which transcribes and translates the DNA into the protein of interest.

Inactivated virus vaccines, like Sinovac and Sinopharm, deliver an inactivated SARS-CoV-2 virus to the immune system to generate immunity.

A protein subunit vaccine delivers the protein of interest embedded in a lipid capsule and in a form similar to that presented by SARS-CoV-2. An adjuvant has been added to enhance the immunological response for such vaccines. mRNA and protein subunit vaccines present a spike protein molecule in a prefusion configuration to the immune system.

### Vaccine efficacy

The discussion of efficacy of COVID-19 vaccines must be appropriately preluded. Firstly, the efficacy against asymptomatic and symptomatic infections, hospitalisation, severe disease and death should be clearly stated when quoting efficacy. Secondly, heterogeneity in health-seeking behaviour, healthcare access and trial protocols greatly influence the transmission risk of infection in vaccine trials. Thirdly, vaccine trials done in different parts of the world at different times bear the pressure of different virus variants which may again nuance the discussion of efficacy. Lastly, phase III trials describing vaccine efficacy should be distinguished from real world data describing effectiveness. While efficacy is calculated from rigorously conducted randomised placebo-controlled trials, effectiveness reflects real world application of a vaccination programme, with all the attendant compromises of reality such as disrupted cold chain, administrative flaws and reporting of infected cases using active or passive surveillance methodologies.

In phase III trials, the Pfizer-BioNtech, Moderna, AstraZeneca and Sputnik V vaccines quoted 95%,[1] 94%,[2] 90%[3] and 91%[4] efficacy respectively against symptomatic infection in late 2020, prior to the rise of the highly transmissible Delta variant.[5] With the exception of the AstraZeneca vaccine, these trials were not conducted in South Africa, where the resistant Beta variant circulated near the end of 2020. Late to join the pack, the Novavax protein subunit vaccine offered 86.4% efficacy against the Alpha variant and 96.4% against non-Alpha variants. Yet the breakdown of the non-Alpha variants was not detailed in the study nor in the supplementary appendix.[6]

Most vaccines available so far quoted high efficacy in preventing serious illness and death.[1-3, 6-8] The unique single dose J&J vaccine displayed 81.7% efficacy against severe COVID-19 in South Africa, where the resistant Beta strain circulates.[8] Local data at the time of writing showed that 100% of patients fully vaccinated with mRNA vaccines who were infected with COVID-19 in the past 28 days displayed no or mild symptoms, with none requiring oxygen or intensive care.[9] Real world data in Israel which deployed the Pfizer-BioNtech vaccine closely replicated the phase III trial results.

Phase III data involving the Sinovac vaccine recently became available. Unpublished vaccine efficacy in earlier trials in Brazil, Indonesia and Turkey quoted 50.7%, 65.3% and 91.3% respectively.[10] A more recent trial of a mass vaccination effort in Chile quoted a vaccine effectiveness of 65.9% against laboratory-confirmed COVID-19 and 86.3% efficacy against death. This is, however, undermined by the similar incidence rate of death between the two-dose vaccinated arm and the unvaccinated arm, casting significant doubt about the 86.3% efficacy against death.[10] Further undermining this data is the phase II finding that vaccinated individuals mounted lower neutralising antibody titres than convalescent patients.[11] As important as efficacy is the longevity of vaccine coverage. This was highlighted by Nicole Doria-Rose et al[12] who found high titres of neutralising antibodies in all 33 healthy study adults, six months after completing the Moderna mRNA vaccine.

### Vaccine side effects

Vaccine safety is a major concern. The principle that the delivery of a therapeutic product in a completely healthy individual should rightfully not cause any harm, though sound in normal settings, could be challenged in a global pandemic of a transmissible lethal disease. It thus follows

that the tolerance for some side effects must be contextualised in the ongoing pandemic. Most local vaccine reactions and mild systemic side effects like fatigue, fever and malaise do not require detailed discussion, and are generally short lasting and of mild to moderate intensity. Three notable adverse effects deserve special mention: the thrombotic thrombocytopenia observed with the AstraZeneca and J&J vaccines, and myocarditis and anaphylaxis with mRNA vaccines in young persons.

The thrombotic thrombocytopenia observed with some of the adenovirus vector vaccines is pathologically synonymous with heparin-induced thrombocytopenia. Both vaccine- and heparin-induced thrombocytopenia are defined by the presence of the platelet factor 4 heparin antibody. In vaccine-induced thrombotic thrombocytopenia, central venous sinus thrombosis (CVST) is the most prominent disease manifestation, with CVST and other thrombotic events occurring in nine out of 11, and 13 out of 23 patients in a German[13] and English[14] cohort respectively, all within five to 24 days of the first dose of the AstraZeneca vaccine. Treatment is strict avoidance of second dose, institution of nonheparin-based anticoagulation and intravenous immunoglobulins. The mortality rate is high – 30% in the English cohort and 54.5% in the German cohort. This side effect is extremely rare and a large Danish and Norwegian study[15] found 11 excess events of venous thrombosis per 100,000 vaccinations with the vaccine. This low rate allowed most countries to continue vaccination with the AstraZeneca vaccine, now made vigilant of this side effect.

Myocarditis has been reported in young men after the second dose of mRNA vaccination. The rate of this rare side effect is difficult to establish but ranges from four in 560,000 persons who have completed the second dose[16] to 23 in 2.8 million doses.[17] Most cases occurred within five days after the second dose,[16,17] and are mild and recover uneventfully after supportive care.

Anaphylaxis mostly occurred within 30 minutes after the first dose of vaccinations. The latest reported rates are 4.7 and 2.5 cases per million doses for the Pfizer-BioNTech and Moderna vaccine respectively. For context, this is still considerably higher than the 0.1 cases per million doses reported for the influenza vaccine. Women and people with prior allergies are more likely to develop anaphylaxis. Most importantly, no deaths after anaphylaxis were reported.[18]

## SARS-CoV-2 variants: Delta everywhere

The Delta variant, previously named B.1.617.2, was first discovered in February 2021. Since then, it has rapidly gained prominence in most regions of the world,[5] including Singapore. A national case-control study by Public Health England (PHE) found the odds of household transmission with the Delta variant to be 1.66 (95% CI 1.26-21.4, p<0.001) compared to the Alpha variant, constituting a 66% increase in transmissibility.[19] Local statistics by the Ministry of Health[9] at the time of writing reported 2.8% of cases ever requiring oxygen and 0.4% of cases ever requiring intensive care among unvaccinated patients. This compares favourably to the 28% of cases requiring oxygen and 16% requiring intensive care in a paper reporting 92 cases of wild-type COVID-19 in Singapore between January and March 2020.[20] Despite this, the increased transmissibility of the Delta variant has resulted in devastating outbreaks, overwhelming the healthcare systems in many countries.

Locally, the Delta variant is the predominant COVID-19 variant. Vaccine efficacy against the Delta variant remains an important question that may be answered in the form of non-peer reviewed reports and preprint. An important starting point is the data from the UK demonstrating Pfizer-BioNtech's 87.9% two-dose efficacy against the Delta variant compared to AstraZeneca's 66.1%. Importantly, the efficacy after one dose of Pfizer-BioNtech and AstraZeneca vaccine was only 33% against the Delta variant.[21] This strongly undermined the delayed second dose strategy employed in many countries earlier this year. PHE also released a preprint demonstrating Pfizer-BioNtech's 96% two-dose efficacy against hospitalisation compared to AstraZeneca's 92%.[22] A local paper reported two-dose mRNA vaccination to be only 69% effective against infection[23] by the Delta variant. Do note that the earlier data by PHE examined symptomatic infection while the local data examined infection as the main outcome. This figure is concerning because a 69% vaccine efficacy raises the proportion of vaccinated population required to achieve herd immunity to 95%, assuming an R0 of 3. Since children younger than 12 years are currently not eligible for vaccination, herd immunity is now mathematically impossible. This also means that vaccination for prevention of infection can no longer be the principal objective. The focus of the national vaccination programme must be for the prevention of severe illness and death.

## Endless variants or convergent evolution

The appearance of COVID-19 variants is a direct consequence of its rampant spread.[24] So binding is the relationship between viral load and new mutations that even in a single person with persistent viremia, accelerated viral evolution may be observed.[25] Mutations are random, but retained mutations are not. Retained mutations provide viruses with new characteristics aimed at overcoming selective pressures. The greatest selection pressure faced by a virus is its inability to transmit more efficiently than before. Most mutations are also deleterious for the virus. Within each host, mutations may only occur during viral replication. In the case of SARS-CoV-2, each infected case can only afford relatively few replication cycles as the disease is acute and short-lasting.[26]

Convergent evolution describes the phenomenon where different independent lineages of viruses develop analogous mutations, resulting in lineages that are increasingly alike. Various lines of evidence support convergent evolution. After passaging a patient-isolated virus in a mouse adaptation model for 36 passages, two mutations that arose, K417N and N501Y,[27] were also found in the beta and gamma variants that arose on opposite sides of the Atlantic Ocean. E484K mutations have also arisen independently in beta and gamma variants and confers decreased viral susceptibility to vaccine-induced antibodies.[28] Whether such evolutionary pressures are created by post-infection seropositivity, vaccine-induced antibodies or simply a natural process to become more adapted to human hosts is currently unclear. The fact that the same mutations are arising independently in different parts of the world to increase viral fitness and survival is the strongest evidence of convergent evolution. The clear implication is that convergent evolution could potentially decrease the variability in the spike protein, allowing subsequent vaccine candidates to be more precise and retain longer or even permanent relevance.

## Other considerations

There are many other areas of interest not elaborated on and these include:

1. Coupling of community vaccination rates with reopening of the economy. We are looking closely at the UK "Freedom Day" which started on 19 July 2021.
2. Heterologous vaccination schedule. There is increasing interest in determining if using different COVID-19 vaccines may produce a more robust humoral and cellular immune response.
3. Booster doses. The role of "third" doses of mRNA vaccines in immunocompromised patients are actively being pursued and we are likely to see more clarity on this issue in the coming months.
4. What will future versions of vaccines look like? Changing the mRNA or protein subunit to deal with variants will not be technically difficult in the current platform. Other considerations include adding influenza into the mix to induce immunity against both SARS-CoV-2 and influenza with the same shot.

## Conclusion

The onslaught of new variants worldwide threatens the efficacy of our vaccines, especially in acquisition of "new" infections. In discussions on comparative efficacy, we need to ensure that we are not comparing apples and oranges. As in all other communicable diseases, we maintain that widespread vaccination with its beneficial effect in reducing severe disease and death remains as the principal public health strategy against the COVID-19 pandemic. ◆


Dr Wong is an infectious disease physician in private practice for the past 20 years. He helps to manage the Infectious Disease Specialists Group and its main focus is on enhancing patient care and safety. He contributes regularly to *SMA News* on contemporary issues relating to infectious diseases and patient safety.

Dr Loh is an infectious disease physician in private practice. He graduated from NUS Yong Loo Lin School of Medicine in 2007, completed his specialty training in Tan Tock Seng Hospital in 2016, and served in various clinical and leadership positions in Seng Kang General Hospital before entering private practice in January 2021.



***References***

*1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med 2020; 383(27):2603-15.*

*2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384(5):403-16.*

*3. Voysey M, Clemens SAC, Madhi SA, 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.*

*4. Logunov DY, Dolzhikova IV, Shcheblyakov DV, 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.*

*5. GISIAD. hCov19 Variants. Available at: https://bit.ly/3iUUIV9.*

*6. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 COVID-19 Vaccine. N Engl J Med 2021. [Epub ahead of print]. Available at: https://bit.ly/3yafp5M.*

*7. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021; 384(15):1412-23.*

*8. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single dose Ad26.COV2.S Vaccine against COVID-19. N Engl J Med 2021; 384(23):2187-201.*

*9. Ministry of Health. Updates on COVID-19 (Coronavirus Disease 2019) Local Situation. Available at: https://bit.ly/3xauwee.*

*10. Jara A, Undurraga EA, Gonzalez C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021. [Epub ahead of print]. Available at: https://bit.ly/3xbmzoS.*

*11. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in heathy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021; 21(2):181-92.*

*12. Doria-Rose N, Suthar MS, Makowski M, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for COVID-19. N Engl J Med 2021; 384(23):80-2.*

*13. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021; 384(22):2092-101.*

*14. Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021; 384(23):2202-11.*

*15. Pottegard A, Lund LC, Karlstad O, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021; 373:n1114.*

*16. Kim HW, Jenista ER, Wendell DC, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 2021. [Epub ahead of print]. Available at: https://bit.ly/3rCvcrH.*

*17. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol 2021. [Epub ahead of print]. Available at: https://bit.ly/3BPezO4.*

*18. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US–December 14, 2020-18 January 18, 2021. JAMA 2021; 325(11): 1101-2.*

*19. Allen H, Vusirikala A, Flannagan J, et al. Increased household transmission of COVID-19 cases associated with SARS-CoV-2 Variant of Concern B.1.617.2: a national case-control study. Public Health England. Available at: https://bit.ly/3rEpJAm.*

*20. Young BE, Fong SW, Chan YH, et al. Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study. Lancet 2020; 396:603-11.*

*21. Bernal JL, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. medRxiv 2021. [Epub ahead of print]. Available at: https://bit.ly/3BSlg1J.*

*22. Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England. [Epub ahead of print]. Available at: https://bit.ly/2TFJBqt.*

*23. Yong M. Full COVID-19 vaccination provides 69% protection against infection by Delta variant: Singapore study. Channel NewsAsia [Internet]. Available at: https://bit.ly/3iT9kEw.*

*24. Martin DP, Weaver S, Tegally H, et al. The emergence and ongoing convergent evolution of the N501Y lineages coincides with a major global shift in the SARS-CoV-2 selective landscape. medRxiv. 25 July 2021. [Epub ahead of print]. Available at: https://bit.ly/3g5VIoJ.*

*25. Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SAR-CoV-2 in an immunocompromised host. N Engl J Med 2020; 383(23):2291-3.*

*26. Cobey S, Larremore DB, Grad YH, Lipsitch M. Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination. Nat Rev Immunol 21; 330-5.*

*27. Sun S, Gu H, Cao L, et al. Characterization and structural basis of a lethal mouse-adapted SARS-CoV-2. bioRxiv. 11 November 2020. [Epub ahead of print]. Available at: https://bit.ly/3yQWP2Z.*

*28. Centers for Disease Control and Prevention. SARS-CoV-2 Variant classification and Definitions. Available at: https://bit.ly/3s7P6e4.*