BRAVE THE VACCINE!

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I recently received the Pfizer-BioNTech COVID-19 vaccine. After the painless injection, I waited outside the room for 30 minutes in case of any severe allergic reactions. As there were none, I registered to return in three weeks' time to receive my second dose.

Eight hours after the injection, I felt a slight ache in my arm but when I examined the injection site, there was only the red mark of the needle entry and no bruising or swelling. I felt warm but when I checked my temperature, it was 36.8°C. I was otherwise totally asymptomatic. *Phew!*

Three weeks later, I received the second dose. The side effects were identical to the first dose, that is, minimal.

My colleagues who received the vaccine also complained of arm pain. Some had fever, tiredness, headaches, dizziness and chills which lasted for a day or two. Fortunately, nobody I know had any severe allergic reactions.

Early history of the COVID-19 vaccines

Like many kiasu doctors, I did some research on the different vaccines before accepting this vaccine. It is true that the COVID-19 vaccines were achieved in record time, under one year. Some say this was too rushed, and point to some severe reactions.[1] There are two aspects to vaccine development: laboratory research and animal tests, and clinical trials.[2]

The first coronavirus was identified in 1965, but vaccine development did not start until the SARS epidemic in 2003. Unfortunately, research stalled because the outbreak evaporated within a year. The same thing happened again with the MERS outbreak in 2012.[3] Singapore and other countries joined in the vaccine research, but once again the outbreak subsided and research was suspended, never progressing to clinical trials.

Katalin Kariko and Drew Weissman

Groundbreaking research that later emerged to become the foundation of the current messenger RNA (mRNA) vaccine was conducted initially without any connection to the vaccine. Notable is the work of Katalin Kariko and Drew Weissman, who jointly developed the ability to translate mRNA into predetermined proteins and to insert the mRNA into cells. The history of Kariko's work is tantalising.[4] In the 1980s, she joined the University of Pennsylvania and proposed that mRNA could be used not only to fight diseases but also for vaccine development. Sadly, the university consistently rejected her unorthodox ideas and research grant applications, and even demoted her in 1995 from her academic position; at the same time, she was diagnosed with cancer. Luckily, Kariko's colleague Weissman believed in her ideas and collaborated with her. Kariko did not resign from her position, but persevered with their research which was published in 2005. Eventually, her prescient idea of an mRNA vaccine was recognised by others, and later by two pharmaceutical companies – BioNTech and Moderna.

Mechanisms of action of different vaccines[5,6]

mRNA vaccines

A special coded message in the mRNA is presented to the ribosome, which will then translate the message to manufacture the desired protein antigen – in this case, the spike protein found on the COVID-19 virus. Kariko's contributions were crucial. Firstly, she produced a lipid nanoparticle coat that enables the mRNA to penetrate the cell membrane of macrophages and dendritic cells found close to the injection site. Secondly, she discovered exactly how to rewrite the mRNA to give a precise instruction for the cell to produce the immunogenic protein.

mRNA vaccines are advantageous as no virus is used, so one will not come down with COVID-19. The vaccine mRNA does not enter the cell nucleus and therefore cannot affect the genetic material inside the nucleus.

Pfizer-BioNTech and Moderna adopted this vaccination technique, and each completed a Phase 3 double-blind placebo-controlled trial. By December 2020, they confirmed its safety with minimal side effects, and achieved 95% efficacy. The US Food and Drug Administration quickly gave emergency approval. The Pfizer-BioNTech vaccine needs to be stored below -70°C, and the second dose is given three weeks later,[7] while the Moderna vaccine has to be stored at -20°C, with the second dose given four weeks later.[8]

Weakened virus inserted into another viral vector

The use of the adenovirus as a vector to help insert the genetic material of a virus into a cell has previously been employed for measles, Ebola, Zika and HIV vaccines. The adenovirus DNA is first removed, leaving an emptied protein coat or capsid. This is then filled with the intended SARS-CoV-2 virus which has been weakened or inactivated. The adenovirus capsid helps insert the inactivated coronavirus into the cells, thus mimicking a viral infection.[9]

Oxford-AstraZeneca chose to use a chimpanzee adenovirus as its vector. In an editorial published in the November 2020 issue of *Cell*, adverse side effects include "fever, pneumonia, diarrhea, transient neutropenia and lymphopenia, fatigue, labored breathing, headaches, liver damage, and fasting hyperglycaemia. Rare adverse reactions include blood clots affecting the abdomen or brain,[10] neuropathies such as Bell's palsy, Guillain-Barré syndrome, gait disturbance, and transverse myelitis." So far, the Oxford-AstraZeneca trial results show 70% efficacy,[11] and the Russian Sputnik V vaccine, which uses the same technique, is said to be 91.4% effective.[12] Both vaccines need to be stored between 2°C to 8°C.

Double strand DNA inserted into adenovirus

Johnson and Johnson's vaccine differs from other vaccines in that it uses DNA and not RNA. A doubled strand of DNA is inserted via an adenovirus vector. The DNA enters the cell's nucleus and carries instructions to manufacture a special non-viral mRNA, which in turn translates the instructions to manufacture the spike protein of the SARS-CoV-2 virus. The other difference of this vaccine is that it only requires a single dose. The vaccine is undergoing Phase 3 clinical trials, and to date the efficacy is between 66% to 72%. It is stored between 2°C to 8°C.

Weakened viruses injected directly

The Salk polio vaccine, most influenza vaccines and the hepatitis A vaccine use the technique of weakening or inactivating the virus which is then injected directly into the subject. This technique has been employed in two of the China-produced vaccines, Sinopharm's BBIBP-CorV and Sinovac's CoronaVac,[13] and India's Bharat Biotech's Covaxin.[14] These "killed" virus vaccines can be stored between 2°C to 8°C. Some commentators are uncertain about the efficacy and side effects of these vaccines.

Subunit vaccines

The Novavax vaccine takes a purified piece of the spike protein of the SARS-CoV-2 virus, and adds an adjuvant which enhances the immunogenicity of the spike protein. Both the spike protein and adjuvant are injected into the subject. So far, the immune response in terms of antibody production as well as increased T-cells have been promising. However, Phase 3 trial data has not been released to date. Novavax can be stored between 2°C to 8°C.[15]

The information above is summarised in Table 1.

Vaccine hesitancy

Many people have a fear of needles stemming from medical injections over the years. Compounded by over-dramatised information, such as anaphylactic shock and deaths following vaccinations, there is a reluctance for some people to voluntarily accept the vaccines. Most of these severe side effects and deaths have been shown to be unrelated to the vaccine.[16]

Severe allergic reactions to the vaccine do occur, but they are very rare and are found in those who have a past history of severe allergic responses.[17,18] Those who have a history of such reactions are advised not to take the vaccine. These severe responses usually occur within 15 minutes of the vaccination, and hence vaccinated subjects are observed for 30 minutes after the injection.

Even in Singapore, a survey conducted on 26 April 2021 showed that 67% are willing to accept the free vaccination offered by the Government.[19] Perhaps Singapore may be a victim of its own success.[20] It has famously flattened the infection curve and reduced the local spread to less than five per day, sometimes with zero cases. The total death rate in the past year reached 32 (as of print), which contrasts with the thousands of daily deaths in most other countries. This has led some Singaporeans to believe that since there are virtually no locally transmitted cases of COVID-19, there is no benefit to getting vaccinated. The Mayo Clinic outlines the benefits.[21]

Dr Lyen receiving his COVID-19 vaccine

While Singapore may be doing well in controlling the spread of coronavirus, the world is still teeming with millions of cases. Travellers to Singapore will inevitably bring some of the virus to our country. There is another potential problem; namely, new mutations.

New mutations

New mutations of the virus have been discovered in the UK, Brazil, South Africa[22] and India.[23] They have been found to be highly infective, probably due to better binding of the virus to the Angiotensin Converting Enzyme 2 receptor, which increases a person's susceptibility to the virus. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases has stated that the British new mutant variant is more deadly than the original virus.[24]

At the moment, the Pfizer-BioNTech and Moderna vaccines seem capable of stimulating a vaccinated person's antibodies to neutralise the invading mutant variants.[25,26]

Prof Ooi Eng Eong of Duke-NUS Medical School told the *Straits Times* that "Singaporeans need not worry about the mutations being reported or the possibility of having to alter the vaccine in the near term."[26]

But we cannot sit on our derrières. Although virologists believe it is unlikely, it is not impossible in the future for a virus to mutate into a new strain which is resistant to the current vaccines.

Who should receive the vaccine?

It is recommended that everybody should seriously consider receiving the vaccine. Those who have had severe allergic reactions in the past, pregnant mothers, children under the age of 12* years and severely immunocompromised people are not recommended to receive the vaccine. Those who have already contracted COVID-19 are recommended to still receive the vaccine.

The Singapore Government promises that all citizens will have access to the full

two doses of vaccines, and even long-term residents will also be eligible.[27] The Islamic Religious Council of Singapore holds the position that a COVID-19 vaccine is permissible for Muslim use. The recommended timing of the second vaccine dose varies slightly according to the vaccine manufacturer.

Final thoughts

At the time of writing, we do not know the effectiveness of the vaccines because clinical trials were only started in the middle of 2020. Our past experiences with other vaccines remind us that no vaccine is 100% protective. We also do not know how effective the vaccines are against the new mutant variants.

The vaccine is probably our best chance of controlling the pandemic. By taking the vaccine, you become immune to the SARS-CoV-2 virus, which means that not only will you be protected, but you will not transmit it to others. If more than 80% if the population is protected, then this is effective herd immunity.

In the meantime, please continue to wear masks, observe social distancing and keep clean. The benefits of the vaccine will trump the side effects. My advice is: "Go for it!" ◆

Table 1: Currently available vaccines arranged according to mechanism of action

MECHANISM	INSERTION	NAME	COUNTRY	APPROVED	EFFICACY	DOSES	STORAGE
mRNA	Lipid nanoparticle	Pfizer-BioNTech	Germany USA	93 countries	95%	2	-70°C
mRNA	Lipid nanoparticle	Moderna	USA	43 countries	95%	2	-20°C
Modified virus	Adenovirus	Oxford-Astra Zeneca	UK Sweden	149 countries	62-90%	2	2° to 8°C
Modified virus	Adenovirus	Gamaleya	Russia	33 countries	92%	2	2° to 8°C
Double strand DNA	Adenovirus	J&J Janssen	USA	17 countries	66-72%	1	2° to 8°C
Weak/ Inactive Virus	Direct	Sinopharm	China	38 countries	79%	2	2° to 8°C
Killed Virus	Direct	Sinovac	China	24 countries	51-91%	2	2° to 8°C
Killed Virus	Direct	Bharat Biotech	India	1 country	81%	2	2° to 8°C
Subunit Spike Protein	Direct	Novavax	USA	-	96%	2	2° to 8°C

Source: https://nyti.ms/3hu5OBl

Information in this article is accurate as of 21 May 2021.
**Singapore has approved the Pfizer-BioNTech vaccines to be given 12 years and above.*

References

1. Torreele E. The rush to create a COVID-19 vaccine may do more harm than good. BMJ 2020; 370:m3209.

2. Li YD, Chi WY, Su JH, et al. Coronoavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci; 27:104 (2020).

3. Su S, Du L, Jiang S. Learning from the past: development of safe and effective COVID-19 vaccines. Nat Rev Microbiol 2020; 19:211-9.

4. Garde D. The story of mRNA: how a once-dismissed idea became a leading technology in the Covid vaccine race. Stat [Internet]. 10 November 2020. Available at: https://bit.ly/3v60bxq.

5. Zimmer C, Corum J, Wee SL. Coronavirus vaccine tracker. The New York Times [Internet]. 8 March 2021. Available at: https://nyti.ms/2O9ZgeR.

6. Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Rev 2021; 27:205-11.

7. Polack FP, Thomas ST, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020; 383:2603-15.

8. 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; 384:403-16.

9. King A. Vector-based vaccines come to the fore in the COVID-19 pandemic. The Scientist [Internet]. 8 September 2020. Available at: https://bit.ly/2MWS6tV.

10. Kupferschmidt K, Vogel G. What's the future of vaccines linked to rare clotting disorders? Science [Internet]. Available at: https://bit.ly/3bnLIor.

11. 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 2020; 397(10269):99-111.

12. Sputnik V. Second Interim Analysis of Clinical Trial Data Showed a 91.4% Efficacy for the Sputnik V Vaccine on Day 28 after the First Dose; Vaccine Efficacy is Over 95% 42 Days after the First Dose [press release]. Available at: https://bit.ly/3rr37Tl.

13. Roxby P. Sinovac: Brazil results show Chinese vaccine 50.4% effective. BBC News [Internet]. 13 January 2021. Available at: https://bbc.in/3qoCs8k.

14. The Wire Science. COVID-19: Bharat Biotech's Covaxin Expected to be 60% Effective, Company says. 23 November 2020. Available at: https://bit.ly/3l1CHVF.

15. Novavax. Novavax Advances Development of Novel COVID-19 Vaccine [press release]. 26 February 2020. Available at: https://bit.ly/3kSz4kZ.

16. Kresge N. Pfizer vaccine safe for elderly despite Norway scare, WHO says. Bloomberg [Internet]. 22 January 2021. Available at: https://bloom.bg/3t2CQe7.

17. Centers for Disease Control and Prevention. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine – United Stated, December 14-23, 2020. Weekly 2021; 70(2):46-51.

18. Walker M. Anaphylaxis cases with Moderna COVID-19 vax follow similar pattern. MedPage Today [Internet]. 22 January 2021. Available at: https://bit.ly/3kVnwxp.

19. Ong J. 67% of S'poreans willing to take COVID-19 vaccine. The Straits Times [Internet]. 26 April 2021. Available at: https://bit.ly/2ReDjNe.

20. Kok X. Coronavirus: could Singapore's vaccine drive become a victim of the city's own success? South China Morning Post [Internet]. 20 January 2021. Available at: https://bit.ly/30mlNrj.

21. Mayo Clinic. COVID-19 Vaccines: Get the facts [Internet]. Available at: https://mayocl.in/30mLKHg.

22. Centers for Disease Control and Prevention. About Variants of the Virus that Causes COVID-19 [Internet]. 12 February 2021. Available at: https://bit.ly/3qskXDQ.

23. National Centre for Infectious Diseases. Researchers in Singapore discover new SARS-CoV-2 variant that causes less severe infections [media release]. 21 August 2020. Available at: https://bit.ly/38ghiTu.

24. Hackethal V. India's COVID-19 Variant. MedPage Today [Internet]. 29 April 2021. Available at: https://bit.ly/3y1JaWR.

25. Mandavilli A. Emerging coronavirus variants may pose challenges to vaccines. The New York Times [Internet]. 20 January 2021. Available at: https://nyti.ms/2OxRyuG.

26. Kurohi R. Vaccines likely still effective against new variants, say experts. The Straits Times [Internet]. 27 January 2021. Available at: https://bit.ly/3ekChZc.

27. Chong C. Covid-19 vaccine and you: what to expect. The Straits Times [Internet]. 9 January 2021. Available at: https://bit.ly/30mqZLP.