COVID-19 Vaccines FAQs

1) Has safety been compromised for speed, and why is it that the vaccines can be developed so quickly this time?

Prof Teo Yik Ying: The research and development of the vaccines have certainly not compromised any elements on safety. The three phases of clinical trials have their own safety benchmarks, and these continued to be adhered to strictly and rigorously, especially as the data generated from the clinical trials by each company must be inspected and considered by regional and national regulatory agencies, including the US Food and Drug Administration, European Medicine Agency, and of course Singapore's Health Sciences Authority. What has allowed the development to happen much faster this time around is because of the following three factors:

(i) Traditionally, the three phases of the clinical trials run in series: so the design and recruitment of Phase 2 only starts when Phase 1 is concluded and the results analysed, and when the pharmaceutical company is convinced that there is commercial and financial interest to progress to the next phase; and Phase 3 only starts when Phase 2 concludes. However, given the global scale of the outbreak, phases of the clinical trials take place concurrently, where there has been substantial overlap in rolling out Phase 1 and Phase 2, and overlap in rolling out Phase 2 and Phase 3. This parallel approach significantly shortened the time taken for the clinical trials. However, at the end of each phase, the results are still evaluated for safety and efficacy, so no corners were cut for the few key vaccine candidates that we have heard about being approved by the key regulators in the US and Europe.

(ii) At the same time, the actual large-scale production of the vaccines happened even before the clinical trials were concluded. This meant there were substantial financial risks, where many of the candidate vaccines were already in production even before the safety and efficacy results were available. These risks were underwritten by a number of governments and philanthropic organisations, with the explicit understanding that some of these produced vaccines may have to be destroyed should the results on safety and efficacy not turn out to be positive. By underwriting the risks involved in large-scale vaccine production, this has enabled the production to happen much quicker than the traditional approach of waiting for confirmatory results from the clinical trials before production even starts.

(iii) The third reason is due to the very high number of infections, which meant that it was much easier to recruit the right people into the clinical trials than traditional drug and vaccine development. Clinical trials require the identification and recruitment of suitable patients into the trials, and for most drugs and vaccines, this can be the one that takes the most time – to accrue the number of subjects into the clinical trials. However, for COVID-19, the speed, scale and spread of the global outbreak meant it was much easier and quicker to recruit people into the clinical trials.

So in summary, the speed of COVID-19 vaccine development certainly did not come at the expense of compromising safety.

2) What are the differences between the three vaccines from Pfizer, Moderna and Sinovac, in terms of effectiveness, risk of side effects, and the group of people that can receive them?

Prof Ooi Eng Eong: The COVID-19 vaccines from Pfizer/BioNTech and Moderna are both RNA vaccines whereas that from Sinovac is an inactivated virus vaccine.

RNA vaccines are messenger RNA (mRNA) that bear the genetic code of the spike protein of SARS-CoV-2 and packaged in lipid nanoparticles to protect the RNA from degradation. When injected into our body, the muscle and immune cells at the site of injection would take up the lipid nanoparticle containing RNA, which would then allow the RNA to get into the cytoplasm of our cells to be read and converted into SARS-CoV-2 spike proteins. This spike protein would then be presented to a variety of

immune cells, which would then result in the development of antibody-producing B cells and killer T cells. Memory B and killer T cells would then be able to rapidly expand in numbers and function when we encounter the SARS-CoV-2 and thus prevent us from getting ill from infection.

Side effects of RNA vaccines are very similar to that of many other forms of vaccine. Commonly reported side effects are pain at the injection site, headache and tiredness. There are rare side effects, such as severe allergic reaction or anaphylaxis.

RNA vaccines do not persist in our cells. RNA is processed by our cells in a number of different ways, all of which lead to a very transient presence in our cells. There is no concern with the persistence of these RNA vaccines in our bodies. RNA cannot be converted to DNA and integrated into our genome. Although RNA vaccines are a relatively new form of vaccine, we have had thousands of years to learn from viruses with positive-strand RNA genomes. Positive-strand RNA genomes are functionally mRNA. Such viruses include dengue and the common cold virus (rhinovirus). Despite the fact that most if not all of us have had the common cold, sequencing of the human genome has not found integration of rhinovirus or any other virus with positive-strand RNA genomes into our DNA. An RNA virus that can integrate its genome into ours is HIV. This process requires two key enzymes: reverse transcriptase and integrase. Without either enzyme, HIV would not be able to convert its RNA into DNA and integrate itself into our DNA. RNA vaccines have neither reverse transcriptase nor integrase. We can thus be confident from the thousands of years of living with RNA viruses that RNA vaccines will not persist in our cells or integrate into our DNA.

The inactivated virus vaccine is made up of chemically inactivated SARS-CoV-2. The inactivated virus is unable to enter our cells to cause infection. Our immune system is thus able to "see" this inactivated virus and develop antibodies against it. It should be noted, however, that although there will be some level of killer T cell response to this form of vaccine, it will not be as good as those forms of vaccines where the spike protein is made inside our bodies.

3) Is there a higher risk in taking the mRNA COVID-19 vaccines, compared to the inactivated virus vaccines?

Prof Ooi: Although inactivated virus vaccines have been around for longer and are thought by many to be safe, they have a chequered history. While this form of vaccine has worked well for diseases such as polio, the immunity conferred by such vaccines can be short-lived. Moreover, this form of vaccine can exacerbate lung disease caused by respiratory syncytial virus (RSV) infection. RSV infection is common in children and a clinical trial of inactivated RSV vaccine was terminated when vaccinated children developed more severe chest infection compared to unvaccinated children when infected with RSV. Thus, while inactivated virus vaccines may be theoretically safe, their safety and efficacy cannot be assumed and would have to be robustly tested in clinical trials.

4) Is vaccination safe for people with autoimmune diseases, or on long-term immunosuppressants?

Prof Ooi: People on immunosuppressants should consider getting vaccinated to prevent infection by any of the vaccine-preventable diseases. This is because the ability to fend off infection would be weaker than those with a normal functioning immune system. The only form of vaccine that should be avoided is the live attenuated vaccine. Live attenuated viral vaccines are viruses that have been weakened because of mutations in their respective genomes. They stimulate our immune system by causing an infection that does not result in disease (asymptomatic infection). People who are immunosuppressed should generally avoid such vaccines as the weakened immune system may not be able to control even attenuated viruses. RNA vaccines can be safely used in those who are on immunosuppressant therapy.

5) Is the COVID-19 vaccine 'halal'?

Prof Ooi: RNA vaccines are made chemically, without the use of cells, let alone animal cells. The Islamic Religious Council of Singapore (MUIS) has reviewed this issue and deemed that RNA vaccines against COVID-19 can be used by Muslims (https://www.channelnewsasia.com/news/singapore/covid-19-vaccine-muis-permissible-for-muslim-use-halal-13762806).

6) How do we know that the vaccines we are taking will not have any long-term side effects, since there is no long-term data at the moment? What about something like Bell's palsy?

Prof Dale Fisher: Side effects usually are limited to the first few days. In some vaccines, there were problems, e.g. live vaccines causing the disease itself in the immune-suppressed. These vaccines are not alive. Any unusual events such as Guillain-Barré would occur in the first two months, and none have been described. Now, many millions of vaccines have been administered. Other fears around autism and other things are not substantiated but are promoted by anti-vaccine groups.

7) If I am allergic to some seafood/peanuts and I get a range of reactions from mild rash to difficulty breathing, is vaccination going to be safe for me? If I have some drug allergies such as to Panadol and aspirin, is it safe for me to get the vaccine?

Prof Fisher: It seems the rate of severe anaphylaxis is around 1 in 100,000 for the Pfizer vaccine. This was based on a review of nearly 2 million first doses and describes 21 people. Seven had a history of anaphylaxis and 10 others had a history of allergy. So four had no past history. To counter this in Singapore, we are advising against vaccination for now to anyone with prior anaphylaxis or severe drug allergy (difficulty breathing, face/throat/eye/lip swelling etc.). To ensure the safety of the small number with no prior history, we will be providing medical supervision and 30 minutes' observation as this is when virtually all severe reactions will occur.

8) If a person does not have any side effects from the usual annual flu jab, can we infer that it is likely to be the same for the COVID-19 vaccine?

Prof Fisher: Almost! If one has no past history of allergy, then the risk is extremely low. You will be observed for 30 minutes afterwards nonetheless.

9) Is the risk of a severe anaphylactic reaction to the vaccine higher in chronic asthma patients?

Prof Fisher: Everyone is different. There are different types and severities of asthma. It should also not be forgotten that if you get COVID (or influenza for that matter) then your disease will possibly be more severe. I would suggest you speak with your doctor. It could be that severe and brittle atopic asthma may warrant a cautious approach whereas most asthma would not be a problem. Irrespective, you will be monitored afterwards and any asthma flare, if it did occur, could be managed immediately.

10) I heard that the vaccines are only shown to reduce disease severity and mortality and not yet shown to protect from infection. Is that true? If so, then why should we take the vaccination since we may still be infected and can infect others?

Assoc Prof Alex Cook: We don't know right now if it is true or not. Why not? The trials follow tens of thousands of people. When someone falls ill, they are to report for testing, and then the researchers test to see if they are actually ill with COVID-19 or something else. This means if those getting the vaccine were being infected, but not developing disease, we wouldn't know. If they were getting infected and spreading it, but not developing disease themselves, we wouldn't know: because the trial wasn't designed to investigate that as it would cost too much. Some countries like Israel, the US or UK are launching mass vaccinations and suffering large outbreaks so we should start to see whether those who are not vaccinated get any protection from their vaccinated contacts soon. But lack of evidence of secondary protection should not be a reason to avoid vaccination, since it *does* provide primary protection and *may* provide secondary protection.

11) Is there a rationale for not making vaccination mandatory?

Assoc Prof Cook: Yes. Actually, only two vaccines are mandatory in Singapore: diphtheria and measles. All the other vaccines are optional, despite several of them being very effective in preventing disease and death. If we have enough vaccines to allow anyone who wants it to get it, then for the most part, those who decide not to be vaccinated are only putting themselves at risk. (Caveat: some people may not be able to be vaccinated, and yes, they are put at risk by their contacts declining to be vaccinated.)

12) Why are people younger than 16 excluded from the vaccination programme? With the B117 variant, young children are easily susceptible.

Assoc Prof Cook: The participants in the trials have all been adults, and as yet there is not enough data about safety in children to justify vaccinating them, especially since COVID-19 infection is usually mild for children. I understand both Pfizer-BioNTech and Moderna are now testing the safety of their vaccines in teenagers so potentially at some point we may see older children being vaccinated.