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Page 1

Varying COVID-19 Vaccination Dosing Intervals on Vaccines Effectiveness

First published on 07 July 2021 by Boon-how Chew and Hui-Yee Chee, Pandemic Scientific Response team members.

Caution: Summary is a preliminary report of work by Pandemic Scientific Response team. It will be continuously updated in accordance to the unfolding of events and emerging of scientific evidence.

IN BRIEF

- Until today, all COVID-19 vaccines except CanSinoBio (Convidecia) and Johnson & Johnson require double dosing.
- Three vaccines are currently in use in Malaysia, the Pfizer-BioNTech (Comirnaty)[mRNA], the Oxford-AstraZeneca [viral vector], and the Sinovac (CoronaVac)[inactivated virus].
- Pfizer-BioNTech vaccines given at 3 months interval (n=68) elicited 3.5x higher antibody response titre but lesser cellular response (31 vs 60%) at 3 weeks after the second dose (n=89) and then higher 31 vs 15% at 13-14 weeks after the first dose (n= 55), compared to those who were given the standard interval of 3 weeks (n= 79).
- Oxford-AstraZeneca vaccine efficacy after two doses at 6-week interval was 55%, and 81% at 12-week. By estimation, the vaccine efficacy could be about 68% if given at the interval of 9 weeks.
- Vaccine-induced antibodies have a 3-4 months half-life (Moderna mRNA and Oxford-AstraZeneca). The longer-term durability of vaccine-induced protection is currently unknown and we are uncertain whether and when a further booster vaccination is needed.
- Previously infected people need only one dose of vaccine to achieve additional and similar to 2-doses antibody and T cell response immunity.
- Different vaccination strategies in terms of intervals may have immunity implications in short-term but not long-term (> 1 year).
- Effective vaccination campaigns worldwide, swiftest coverage with first dose in highest risk population, followed by booster/s in the most appropriate longest intervals could enhance immunity, with adherence of mask-wearing, physical distancing in-between the doses, would end the pandemic and/or minimising its impact on human life and livings.

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Full Summary

3 GOOD HEALTH AND WELL-BEING

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Newsletter
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July 08, 2021
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Page 2

Mixing COVID-19 Vaccines on Vaccines Effectiveness

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IN BRIEF

- There are at least **10 vaccines** available to fight against SARS-CoV-2 with four different technologies.
- **5 vaccines** are currently available in Malaysia, the Pfizer-BioNTech (Comirnaty)[mRNA], the Oxford-AstraZeneca [viral vector], the Sinovac (CoronaVac)[inactivated virus], the Johnson & Johnson (Ad26.COV2.S) [viral vector] and the CanSinoBio (Convidecia) [viral vector].
- Priming with Oxford-AstraZeneca vaccine and booster with the Pfizer-BioNTech has been tested at 1-, 2- and 3-month. In reverse sequence of priming with the Pfizer-BioNTech vaccine and booster with the Oxford-AstraZeneca has been tested at 2- and 3-month.
- Mix-and-match COVID-19 vaccines, Oxford-AstraZeneca and Pfizer-BioNTech, trigger potent immune response.
- People received mix-and-match vaccines experienced higher rates (20 to 24% rate difference) of vaccine-related systemic side effects such as chills, fatigue, headache, joint pain, malaise, and muscle ache. These resolved **within 48 hours**
- Vaccine-induced antibodies have a **3-4 months half-life** (Moderna mRNA and Oxford-AstraZeneca). If a longer-term vaccine-induced protection is needed, a different vaccine booster has been reported to excite a better immune response.
- Different vaccination strategies in terms of mixing different vaccine types may have immunity implications in short-term but not long-term (> 1 year).
- Effective vaccination campaigns worldwide, swiftest coverage with first dose in highest risk population, followed by booster/s of a different vaccine to enhance immunity, have a surveillance system for emerging variants, would end the pandemic and/or minimising its impact on human life and livings.

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Full Summary

3 GOOD HEALTH AND WELL-BEING

COVID-19 Vaccination: Dosing Intervals and Mixing Types on Vaccines Effectiveness

First published on 07 July 2021 by Boon-how Chew and Hui-Yee Chee, Pandemic Scientific Response team members

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The Full Summary

There are at least 10 vaccines available for use against the SARS-CoV-2 and COVID-19. They are four different technologies/antigen-vector, slightly different in efficacy and effectiveness, and safety profiles (Table 1)[1]. Three are currently in use in Malaysia, the Pfizer-BioNTech (Comirnaty), the Oxford-AstraZeneca, and the Sinovac (CoronaVac). Two vaccines by the Johnson & Johnson (Ad26.COV2.S) and CanSinoBio (Convidecia) are reported as available in Malaysia. All except require double dosing two, CanSinoBio (Convidecia) and Johnson & Johnson are single dosing.

With probably more than 6 billion eligible global population to vaccinate, and if this is with a 2-dose regimen, we would need 10-11 billion doses to end the pandemic (assuming mostly 2-dose vaccines with minimal defaulters, no new variants that has the vaccine-escape ability). With an estimated global vaccine manufacturing capacity at 2-4 billion doses annually, it will take until 2023-2024 before enough vaccine can be delivered[2]. As of now, Malaysia has succeeded in vaccinating about 20% target population with the 1st dose and 10% completed 2 doses.

COVID-19 vaccines have been shown to be effective against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The protection is observed even after the first dose, and doubled to tripled after the second dose. Among those who were infected (seropositive) due to a prior natural SARS-CoV-2 infection, a single dose vaccine causes a rapid rise in high antibody titers and T Cells response within days that is similar to those who received two injections, but there was no further IgG titer rise after the 2nd dose.

Post vaccination sera from a cohort of 20 volunteers immunized with the mRNA vaccine Moderna or Pfizer-BioNTech showed high binding titres for anti-SARS-CoV-2 spike IgM and IgG with plasma neutralizing activity and antibodies equivalent to those in natural infection3. Furthermore, the memory B cells were found to be equivalent to those of plasma from individuals who had recovered from natural SARS-CoV-2 infection.[3]

However, vaccines equity and availability are great challenges, beside vaccine hesitancy and refusal, to many countries and people in getting the immunity against acute COVID-19 and its long-term sequelae. If high-income or vaccine producing countries exclusively acquire the first 2 billion doses without regard for vaccine equity for resource-poor countries, the number of Covid-19 deaths worldwide could double in 2021 [2].

Covax programme is a collaboration among organisations such as Gavi (the global alliance for vaccines and immunisation), the World Health Organization, the Coalition for Epidemic Preparedness Innovations, UNICEF (United Nations International Children's Emergency Fund), and the World Bank, focused on ensuring that lower income countries can get COVID-19 vaccines.

Dosing intervals and mixing vaccines

Accordingly, some of the reactive and proactive strategies in overcoming vaccines supply shortages and slowness are altering the dosing interval [4] and mixing the vaccination with two different vaccines in the same person. Concern over one particular vaccine has also caused the consideration of mixing of two different vaccines in the same person. Additionally, mixing of vaccines may be unavoidable and would be necessary with the appearance of new SARS-CoV-2 variants. On the other hand, changing the vaccination schedule could risk the public confidence and a waning immunity could lead to subinhibitory levels of antibody favouring the selection of antigenic variants [2,4].

Many vaccines consist of multiple injections. The first triggers an initial immune response to certain proteins of the virus, and the later booster jab excite the immune system's memory cells into action. The latter usually takes weeks for the memory cells to be activated[5]. Over time, the immune response broadens, developing memory cells capable of responding not only to specific proteins, but also to some variants of them. This means that a later booster shot is more effective[5].

Longer dosing intervals

The longer dosing interval approach allows many more people who have not received the vaccination in getting the 1st dose so that they can have some level of immunity, while the longer interval to the second dose should not be too long causing an intermediate subinhibitory immunity exposing the individuals and the virus mutation. More importantly, the second dose is to excite a significant gain of vaccine effectiveness in generating antibodies and plasma memory in the T-cell.

A study in UK among those aged > 80-year-old, with 99 participants received the two Pfizer-BioNTech vaccine doses at 3 weeks apart (the standard interval), and in 73 participants the two doses were given at 11-12 weeks apart (the extended interval)[6]. It had shown that there is no loss in passive immunity but a delayed enhancement in both antibody and cellular immunity. Comparing the antibody and cellular response 2-3 weeks after the respective 2nd doses, it was observed that antibody response titre was about 3.5x higher in those who got 2nd jab after 3 months (n=68) compared to those got it after 3 weeks (n=89). The cellular response was lesser in recipients of delayed 2nd dose (31 vs 60%) at the same 2-3 weeks post-second doses, but at 13-14 weeks after the first dose (the same time point of the second blood drawing), the rates were 31 vs 15%, with higher cellular response in the extended interval[6]. Further follow up is required to assess long term immunity and clinical protection. Another caution is to maintain the SOPs (mask wearing, physical distancing and avoiding crowded or closed setting) in the interval between the two injections. Beside this, there are all positive points implementing this when facing with over-demand of vaccines supply with a wider and faster protection coverage for COVID-19.

In contrast, the CDC liberalized its position to a 6-week interval and World Health Organization (WHO) recommended a wait of no more than six weeks between the first and second doses of the Pfizer vaccine on 8 January 2021 following a policy change in December 2020 in UK, and has advised countries facing a high incidence of COVID-19 with vaccine supply constraints to consider delaying the second dose of the Moderna (mRNA-1273) up to 12 weeks to achieve a higher first dose coverage in high priority populations.

Shorter dosing intervals?

Giving any vaccine booster such as the second dose at a shorter interval will require another if not stronger scientific proof to that has already been established. This is because at a shorter interval to the first dose, the immune system might have generated antibodies that remains too high for the in-coming harmless vector virus in the second/booster dose. If this happen, the vector could be neutralized before it has a chance to deliver its cargo to excite the booster effect. Also, when a booster is given too soon, memory cells are not yet established while the immune system's initial response is still raging[5].

Shorter and different vaccination schedule came from Oxford-AstraZeneca adenovirus vectored vaccine evaluations during phase 3 studies[2]. These studies were initially planned as single-dose studies but were amended to incorporate a second dose after review of insufficient immunogenicity in a phase 1 trial. However, some participants chose not to receive the second dose. Due to vaccine production problems, there were in addition delays in administration of the second dose for a large number of trial participants. These peculiar conditions provided data of the different vaccine schedules effects. A single injection provided protection against primary symptomatic Covid-19 with an efficacy of 76% (the first 90 days). Vaccine efficacy after two standard doses at 6-week interval was 55%, 81% when the two injections were given at 12 weeks apart. If the second dose to be given at 9-week as proposed by the MOSTI's Special Committee on COVID-19 Vaccine Supply (JKJAV: Jawatankuasa Khas Jaminan Akses Bekalan Vaksin COVID-19), the vaccine efficacy could be expected would be about 68%.

Mixing and matching two different vaccines

However, the implementation on the mixing of different COVID-19 vaccines is largely ignored although some evidence of efficacy and safety are available. This is not something new which has been deployed for vaccines against other diseases, such as Ebola. This is known as the *heterologous prime and boost*. However, concern remains of higher rates of side effects from two different vaccines mixed-and-matched.

The CombivacS study[7] gave 431 people the Pfizer-BioNTech's mRNA-based vaccine at least eight weeks after their first dose of the Oxford-AstraZeneca vaccine, which uses a harmless chimpanzee 'adenovirus'. This was compared to a control group of 232 people has not yet received a booster. The antibody response to the Pfizer-BioNTech boost (2nd dose) even stronger than those who received two doses of the Oxford-AstraZeneca vaccine. But it is not clear how those responses compare with those seen in people who receive two doses of mRNA vaccines such as Pfizer-BioNTech's, which tend to trigger a potent antibody response after a second dose too.

The Com-COV study[8] in UK (Oxford-AstraZeneca and Pfizer-BioNTech both at 28-day and 84-day prime-boost intervals, participants are ⩾ 50 years with no or mild-to-moderate, well controlled comorbidity) reported that people in the mix-and-match groups experienced higher rates (20 to 24% rate difference) of common vaccine-related side effects, such as fever, than did people who received two doses of the same vaccine[8] Similar increases were observed for chills, fatigue, headache, joint pain, malaise, and muscle ache. There were no hospitalisations due to solicited symptoms, and most of this increase in reactogenicity was observed in the 48 h after immunisation and short lived.

Vaccination strategies best for target outcomes?

US scientists developed a computer model exploring different vaccination strategies, which accounted for country-specific age structure, age-contact structure, infection fatality rates and seroprevalence and different transmission rates (R values)[2]. Three possible strategies for different goals of vaccination could consider:

1. To minimise cumulative incidence
The model recommends to prioritize adults 20-49 for vaccination if infection-minimizing strategies are targeted and not mortality.

2. To minimise mortality
The model showed that across countries those aged 60 and older should be prioritized to minimize deaths. However, the model identified three situations in which prioritizing adults aged 20-49 would provide greater mortality benefits than prioritizing older adults when:
(i) infection is well controlled the R value ⩽ 1.15,
(ii) a vaccine displaying 80% or higher effectiveness; or
(iii) if vaccine effectiveness is substantially lower in older than younger people.

3. To minimise years of lost life and quality of life lost
Social values such as returning to school, to work and social life are important consideration with the respective target population-vaccinees. Priority setting for vaccination strategies thus depends on factors beside the dynamic of the pandemic, but also the political and societal priorities.

Children below 12 years old and their needs of the vaccination with SARS-CoV-2 would require more robust data about its safety and efficacy before a roll-out can be considered.

Emerging data show that Moderna mRNA had a half-life of 50 to 100 days for ELISA antibodies, and 70 to 200 days for neutralizing antibodies in the sera of vaccinees. The anti-SARS-CoV-2 spike IgG to a single dose of Oxford-AstraZeneca vaccine decayed log-linearly over a 6-month period, antibodies showed a decrease of 34% by day 90 and a decrease of 64% by day 180, compared to that at day 28[2]. The longer-term durability of vaccine-induced protection is currently unknown and we are uncertain whether and when a further booster vaccination is needed.

Vaccines update?

As new variants with unforeseen combinations of mutations continue to emerge, it is important to quantify the phenotypic impacts of specific mutations present in variants, both individually and in combination with other mutations. Such knowledge on the SARS-CoV-2 spike mutations and other aspects of virus biology, their possible effects on antigenicity will facilitate detection of potential variants of concern before they begin to spread widely. Tracking and flagging the emergence mutated viruses as potential significant variants will help to alert and guide control measures and more importantly for the preparation of updated vaccines to tailor maximally to be cross-reactive against all circulating variants.

Combining various variants gene in one vaccine will be another possible approach like dengue vaccine

Conclusion

We have early evidence of different dosing intervals for the Pfizer-BioNTech vaccine at 3 months beside the proven 3 weeks, and the mixing of Oxford-AstraZeneca and Pfizer-BioNTech vaccines at 1 month, 2 months and 3 months intervals. The data suggest that longer intervals improved immune response. However, there is no an absolute winner of which is the best interval for the Pfizer-BioNTech vaccine. Factors to consider include equal and fast access to protection to the most people, adherence behaviours of the people to recommended SOPs, vaccine hesitancy and refusal, assurance and consistency in the vaccine supply and delivery. Shorten any vaccine interval such as from 12 weeks to 9 weeks for the Oxford-AstraZeneca has to be taken with careful consideration of the factors. Based on the reported data, the vaccine efficacy could only be about 68% if given at 9 weeks interval..

Mixing the Oxford-AstraZeneca and Pfizer-BioNTech vaccines is a viable approach if systemic side effects are tolerable and do not increase hospitalization at the time when the healthcare facilities are stretched in managing the acute COVID-19.

Vaccination strategies and approaches could be dynamic to the changing situations of the pandemic, new variants, vaccine supply, target-change in either minimising incidences, deaths or quality of life lost. Sound long-term evidence is needed to better inform about the effectiveness of the different vaccination schedules and strategies, and delivery at the individual level. Past evidence of other vaccines if applied to COVID-19 vaccines would support similar long-term (< 1 year) humoral and cellular immunity levels irrespective of the interval between the two injections.

New vaccine candidates are encouraged to be properly tested in phase 3 trials because one that might be more effective against circulating variants, generate longer-lasting immunity, work better in certain subpopulations, provide greater protection against severe disease, prevent infection transmission better or will be cheaper, could be found and produced.

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Table 1: Main vaccines that have been approved or rolled out for emergency use

No.	Manufacturers (vaccine name)	Technology used	Doses/ interval	Efficacy*	Safety profile (from phase III trials)	Efficacy against variants	Effectiveness**
1.	Pfizer and BioNTech (Comirnaty)	mRNA	2 / 3 weeks	95%. Approved for 12-year-old and above. Trial ongoing in 6-month-old to 11-year-old. Working on 3rd dose as a booster.	Safe, also in pregnant and lactating women. Transient site pain. Serious adverse events were rare. Extremely rare cases of myocarditis and pericarditis in the young men < 30-year-old, in the first week after vaccination.	Yes to the Alpha, Beta andDelta, low to Gamma	Reduced symptomatic cases by 94%, and severe COVID-19 by 92% (in Israel). Reduced hospitalisation by 87%.
2.	Sinovac (CoronaVac)	Inactivated virus	2 /4 weeks	50.4%	Safe. Details TBC.	TBC	Reduced symptomatic disease by 66%, hospitalization 85%, and death 80% (Chile). Reduced hospitalization by >90% (Indonesia). 10 fully vaccinated Indonesian doctors died from COVID-19 (new variant?)
3.	Oxford-AstraZeneca (ChAdOx1-S)	Viral vector	2 / 12 weeks	63-82.4% (12 weeks between doses)	Safe. Extreme rare cases of thrombosis occurring with thrombocytopenia, more within 3 weeks post-vaccination in those < 40-year-old.	92% to the Delta against hospitalization. 74.6% to the Alpha. Low (10%) to the Beta and Gamma.	Reduced risk of hospitalization by up to 94% (4 weeks after 1st doses in Scotland).
4.	Johnson & Johnson (Ad26.COV2.S)	Viral vector	1	67-72%	Acceptable	57% to the Beta, yes to Delta.	TBC
5.	CanSinoBio (Convidecia)	Viral vector	1	65.7% Trial ongoing in 12- to 17-year-old.	Acceptable	TBC	TBC
6.	Moderna and NIH (mRNA-1273)	mRNA	2 / 4 weeks	94.5% Early data safe for 12-year-old and above. Trial ongoing in 6-month-old to 11-year-old.	Safe. Transient adverse events at the injection site. Serious adverse events were rare.	Yes to the Alpha, Beta and Delta	TBC
7.	Gamaleya (Sputnik V)	Viral vector	2	91.6%	Safe	TBC	TBC
8.	Novavax (NVX-CoV2373)	Protein	2	95.6%	Acceptable. Details TBC.	85.6% to the Alpha and 60% to the Beta	TBC
9.	Sinopharm (BBIBP-CorV)	Inactivated virus	2	79.3%	TBC	TBC	TBC. Reduced hospitalization by >90% (United Arab Emirates).
10.	Bharat Biotech (Covaxin)	Inactivated virus	2	TBC	TBC	TBC	TBC

* Early testing or smaller clinical trials

** Mass population/community roll-out

TBC= to be confirmed

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