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SYNOPSIS

Review of "Sustained T cell immunity, protection and boosting using extended dosing intervals of BNT162b2 mRNA vaccine"

08/13/21

Article citation: Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S, et al. Sustained T cell immunity, protection and boosting using extended dosing intervals of BNT162b2 mRNA vaccine. Cell [Preprint]. 2021 July 23 [cited 2021 July 26]. Available from: https://www.pitch-study.org/PITCH_Dosing_Interval_23072021.pdf

One-minute summary

- The authors examined differences in immunogenicity for conventional ("short", 2-5 weeks) and extended ("long", 6-14 weeks) dosing interval regimens between the two doses for BNT162b2 (Pfizer-BioNTech vaccine).

- The PITCH (Protective Immunity from T Cells in Health Care Workers) study which is a subset of SIREN (UK SARS-CoV-2 Immunity & REinfection EvaluatioN), included 503 healthcare workers (HCW; median age 43 years, IQR 33-52) from five UK National Health Service (NHS) Hospital centres who received two doses of the Pfizer-BioNTech vaccine between December 9, 2020 and May 23, 2021. Within the study population, 56% HCWs were SARS-CoV-2 naïve (n=280) and 44% were previously infected (n=223) based on documented PCR, serology results, or Mesoscale Discovery (MSD) assay spike antibody results. Approximately 15% of individuals were in the conventional interval group (n=75, median 24 days, IQR 21-26) and 85% were in the extended interval group (n=428, median 70 days, IQR 63-77). Data on overall vaccine effectiveness against COVID-19 infection was obtained from a larger cohort of HCWs as part of the SIREN study (n=25,066).[1]

- The PITCH study of HCWs found that following the first vaccine there was a marked decline in SARSCoV-2 neutralizing antibody (NAb) levels; however, in contrast, there was a sustained T cell response to spike protein. This difference among immune responses was accompanied by protection from COVID-19 infection from the circulating alpha (B.1.1.7) variant, prevalent in UK during this period.

- For the **extended interval** group of SARS-CoV-2 naïve participants, there was waning of antibody titres (SARS-CoV-2 neutralizing antibody, NAb) but maintenance of spike-specific T cell responses between the first and second dose of vaccine. After the second dose of vaccine, there was also a higher level of NAb for the extended interval group compared with the conventional interval group. These findings correspond to a high level of vaccine effectiveness (VE) over this

period of time; VE against symptomatic infection was 72% 21 days after the first dose and 86% 7 days after the second dose.[1]

- In the SARS-CoV-2 naïve participant group using the **extended dosing interval**, there was limited detection of NAb against virus variants Beta (B.1.351) and Delta (B.1.167.2) after the first dose. Titres against the Gamma (P.1) variant was similar to the Victoria strain but slightly reduced. Increased NAb levels were seen for all variants after the second dose. The Alpha variant was not tested in this study since Alpha was the dominant variant in the UK during this time; however, similar results had previously been seen where there was reported limited protection after the first dose and boosted levels of NAb following the second dose.[2]

- This study illustrated that two doses of the Pfizer-BioNTech vaccine are highly immunogenic for antibody and T cell responses for both the conventional/short and extended/long dosing intervals between dose one and dose two.

- This study reveals a distinction between the NAb and T cell response, related to the impact of a second dose and extension of the dosing interval. There was a clear decline in circulating antibodies over a three month period, with strong maintenance of the T cell response.

- The serologic antibody response to one or two doses of Pfizer-BioNTech vaccine falls over time, and is higher after an extended dosing interval compared with the three to four week dosing interval that was tested in the clinical trials. In contrast, the T cell response is well maintained after one then two doses, and is of a marginally lower magnitude after the longer dosing interval.

- The data provided from the larger clinical study in SIREN showed clear evidence of VE from a single dose of vaccine over an extended period.

- Although these observations were limited by the numbers studied and balance of the cohort, differences based on sex and ethnicity were not detected using simple comparative or multivariate analyses; however, older age was found to be associated with lower neutralizing antibody levels in naive HCWs.

Additional Information

There was sustained protection against infection after a single dose of the Pfizer-BioNTech vaccine over an extended dosing interval:

- In the larger SIREN cohort of HCWs (n=25 066), VE against asymptomatic and symptomatic infection reached 72% by week three following the first vaccine dose and was maintained beyond this time point up to 95 days.

In the extended dosing interval group, NAb levels against SARS-CoV-2 and viral variants dropped significantly between doses:

- There was a significant reduction in anti-spike binding antibodies between weeks 4 and 10 after the first dose in both naïve and previously infected HCWs. Four weeks after the second vaccine dose, antibody levels were higher than those following dose one in naïve HCW group but not in the previously infected group.

- A NAb response against the vaccine strain virus is induced by a single dose of vaccine across the cohort but was not well maintained – in contrast to the clinical protection that was observed against the alpha variant. NAb against the delta variant were poorly induced after a single dose, and not maintained at all during the interval before the second dose. This is despite a degree of protection against delta variant that is described following a single dose.

In the extended dosing interval group, anti-spike T cell responses were induced and maintained:

- Between 4 and 10 weeks after the first dose of vaccine, spike specific T cell response was maintained in both naïve and previously infected HCWs. There was no significant reduction in anti-spike T cell response observed in either cohort after adjusting for age and sex.

- T cells in the naive group were further boosted by the second dose, although no further statistically significant boosting effect was seen for the previously infected group.

- A significant increase in anti-spike T cell response four weeks following the first dose and four weeks following the second dose was seen in both naive and previously infected HCWs.

In the extended dosing interval group, there was an increase in peak NAb levels but not T cell response:

- NAb levels were 2-4 fold higher (depending on virus variant) in those vaccinated at four weeks following the second dose of both regimens (previous infection, naïve) with extended intervals. While those in the naïve group had a significantly higher anti-spike binding antibody level four weeks after the second dose, this increase was not seen in the previously infected group. Increasing age was modestly associated with decreased antibiotic levels in naïve HCWs; no impact of ethnicity was observed.

- There was a significant difference between anti-spike responses in naïve HCWs between dose intervals of 4 versus 10 or 12 weeks but no differences between other intervals for previously infected HCWs.

- An extended dosing interval did not result in greater induction of T cell response after the second dose. For naïve HCWs there was a moderately decreased T cell response weeks after the second dose in the extended interval group compared with the conventional standard interval group. While the anti-spike T cell response was significantly higher in the previously infected HCW group four weeks following the second dose, this was modestly reduced by an extended dosing interval.

The dynamics of immune response are similar after first and second dose of vaccine:

- In the naïve HCW group, NAb response peaked one week after the second dose. Following this point there was a clear decline in NAb titers at week four and week 13 against the Victoria and virus variants (Beta, Gamma, Delta). For the Victoria strain, there was a 4-fold decrease between weeks one and four, a 3-fold decrease between weeks four and 13, and 12-fold decrease over the 3-month period. In contrast, T cell levels were maintained over this same time period.

- This study demonstrates that there is a decline in circulating antibodies over a three month period but maintenance of a T cell response, during a period when protection following dose two was observed during the clinical trials.[3] In January 2021, those in the conventional dosing

interval group that received a second dose of the vaccine at 3-4 weeks had NAb levels that were substantially higher against the Victoria and other virus variants than those in the extended dosing interval who had received a first dose only four weeks earlier. However, the reverse was true when NAb levels were examined at week 13 when HCWs in the extended interval group (four weeks after second dose) were found to have significantly higher NAb titers than those in the conventional dosing interval (13 weeks after second dose).

PHO reviewer's comments

- This study provides detailed information about the immune response to the Pfizer-BioNTech vaccine in a healthy, working age population to help better understand the impact of dosing intervals on vaccine effectiveness in naïve and previously infected individuals.

- This study used several different assays to ascertain NAb levels and T cell response. Laboratory thresholds used to examine NAb levels may not accurately reflect immunity on re-exposure to spike proteins.

- Vaccine effectiveness was not directly measured in the study population and was obtained from the larger SIREN study cohort; therefore it is not possible to calculate immune correlates of protection. In addition, over the study duration, a reduction in the number of unvaccinated individuals resulted in a wide confidence interval for VE estimates.

- The immunogenicity of an extended dosing interval appears robust, and antibody levels improved over the conventional 3-4 week regimen. It was demonstrated that T cells are induced and sustained during the longer period between doses in an extended dosing regimen.

- After the first dose, participants were followed up to 16 weeks. A longer follow-up timeframe is required to better understand the sustained durability of the immune response, both antibody and T-cell.

- The findings of these study are best applied to a population compared to the individual level. This is due to the heterogeneity of the NAb and T cell responses using an extended dosing interval.

- The results of this study are consistent with Ontario data on the effectiveness of mRNA vaccines given over extended intervals which demonstrated VE of 66-71% against symptomatic infections after the first dose for younger adults (i.e., < 70 years of age) and VE of 69% for individuals with no comorbidities.[4]

- Study participants were mostly female and white. The authors examined these variables in their analysis and did not identify them as significant co-variables.

- The population included in this study were healthy individuals of working age and therefore, this study does not provide information on the impact of extended dose intervals in special populations such as those who may have a suboptimal immune response and are at increased risk of severe outcomes from COVID-19 infection.[5]

- The extended dosing interval appears optimal for immunogenicity given current relatively low circulating levels of virus but this needs to be considered in the context of the more immediate benefits of two doses versus only one in a two dose vaccine schedule.

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Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of "Sustained T cell immunity, protection and boosting using extended dosing intervals of BNT162b2 mRNA vaccine". Toronto, ON: Queen's Printer for Ontario; 2021.

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