Evidence Summary on COVID-19 mRNA Vaccine (Nucleoside Modified) (COVID-19 Vaccine Moderna) for the prevention of COVID-19

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Background

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to more than three million deaths worldwide, global economic and social disruption, and unprecedented challenges in the health system. As the world continues to face these challenges, several efforts, such as developing and implementing different health technologies that will ultimately lead us to our exit strategy from the crisis, were undertaken. Among these health technologies are vaccines against COVID-19 which are currently in different phases of trials around the world. Similar to other countries, the Philippine government has been exploring all means to access these vaccines and to ensure continuous supply of vaccines.

On 07 May 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for *COVID-19 mRNA Vaccine (Nucleoside Modified) (COVID-19 Vaccine Moderna)*.

To date, 47 countries, the majority of which are high income countries (e.g. US, Canada, Singapore, Qatar, Israel, Switzerland, UK, Japan, and EU countries), have issued an emergency use authorization (EUA) for this product in their respective jurisdictions. The vaccine also has an emergency use authorization from lower middle income countries such as Honduras, Moldova, and the Philippines. Vaccine implementation of *COVID-19 Vaccine Moderna* has already started in most of these countries. The vaccine was also included in the WHO emergency use listing on 30 April 2021.

Basic information on *COVID-19 mRNA Vaccine (Nucleoside Modified) (COVID-19 Vaccine Moderna)* is provided below:

Table 1.1 Characteristics of *COVID-19 Vaccine Moderna*

Trade name	COVID-19 Vaccine Moderna
Other name	mRNA-1273
Manufacturer/s	Moderna Biotech Spain
Vaccine platform	COVID-19 mRNA Vaccine (nucleoside modified)
Dose strength and administration	2 doses, 0.5 mL each, 1 month apart

Route of administration	Suspension for injection, Intramuscular (IM)
Drug delivery system	100 mcg frozen suspension for injection Multi-dose vial (MDV) containing 10 doses per vial
Storage condition	Store between -25°C to -15°C; shelf life: 7 months (once thawed, the vaccine can be stored 30 days at 2 to 8°C, protected from light)
Mechanism of action	The nucleoside-modified mRNA in the COVID-19 Vaccine Moderna is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.
Contraindications	Do not administer the COVID-19 Vaccine Moderna to individuals with a known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the COVID-19 Vaccine Moderna.
PHL EUA status	Released as of 5 May 2021 *https://drive.google.com/file/d/12W3_j5jDZzc8EfMtcZzxqwL4brwQT7XD/view?usp=sharing*
PHL FDA EUA indication	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older
WHO EUL status	Granted as of 30 April 2021 Reference: https://www.who.int/news/item/30-04-2021-who-lists-moderna-vaccine-for-emergency-use

The package insert is available via: https://www.fda.gov/media/144637/download

Pursuant to the role of the Health Technology Assessment Council (HTAC) to develop coverage recommendations particularly in the selection and financing of COVID-19 vaccines using the Evaluation Framework set by the HTAC, this report presents all currently available evidence considered in the assessment of *COVID-19 Vaccine Moderna*. This assessment follows the HTAC evaluation framework to assess COVID-19 vaccines using the following criteria: (1) responsiveness to magnitude and severity; (2) clinical efficacy and safety; (3) affordability and viability; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.

Policy Question

The HTAC aims to answer the policy question:

Should ***COVID-19 Vaccine Moderna*** be recommended for emergency use to reduce COVID-19 cases, severe infection, and deaths?

Recommendation *(as of 28 May 2021)*

The HTAC **recommends the emergency use of *COVID-19 Vaccine Moderna*** to reduce the burden of COVID-19 among the population 18 years of age and older. However, in the future, when supply is no longer a problem, there might be a need to reassess given its relatively high cost compared to other vaccines.

The HTAC considered the following criteria in formulating its recommendation for the vaccine:

Criteria	HTAC Judgment
Can *COVID-19 Vaccine Moderna* significantly reduce the magnitude and severity of COVID-19?	**Yes.** *COVID-19 Vaccine Moderna* has the potential to reduce the disease burden by averting a significant number of symptomatic infections, and likely severe COVID-19, assuming sufficient vaccine coverage.
Is *COVID-19 Vaccine Moderna* efficacious and safe?	Based on interim results of published peer-reviewed Phase III trial on *COVID-19 Vaccine Moderna [cut-off analysis date: 21 November 2021]* (Baden et al., 2021): **Yes**, it is efficacious for preventing symptomatic COVID-19 *(high certainty of evidence).* It is likely that the vaccine also protects against severe COVID-19 *(moderate certainty of evidence*). The duration of protection cannot be assessed given the current data. **Yes**, it is safe in the known short-term safety outcomes, based on high certainty of evidence. Meanwhile, its long term safety outcomes cannot be determined given the short duration of observation at the time of the reports. The WHO interim recommendations for the use of this vaccine noted that a history of anaphylaxis to any component of the vaccine, including polyethylene glycol, is a contraindication to vaccination and that

	should anaphylaxis occur after the first dose, the second dose of the vaccine should not be given.
Is *COVID-19 Vaccine Moderna* affordable and feasible to use in a national immunization program (viability)?	**Yes.** However, the vaccine has a relatively higher budget impact to the government compared to other vaccines. The share of the population to be vaccinated using the said vaccine is disproportionate to the share of the cost of the *COVID-19 Vaccine Moderna* in the total vaccine budget. This would entail utilization of 22.92% of the total national budget for vaccination to cover 9.29% of the target vaccinees for *COVID-19 Vaccine Moderna* for 2021. However, procurement of higher priced vaccines could address issues of low or uncertain supply. When supply is no longer a problem, there might be a need to reassess the vaccine in terms of affordability. **Yes**, it is feasible as there are no significant barriers to vaccine implementation using *COVID-19 Vaccine Moderna* in terms of storage, transport, and handling. Further, there is still a need for training of vaccinators to ensure product integrity across the entire supply chain and close monitoring of adverse events.
Does *COVID-19 Vaccine Moderna* reduce out-of-pocket (OOP) expenses of households due to COVID-19?	**Yes.** Noting its efficacy against symptomatic COVID-19 including severe COVID-19, based on current evidence, *COVID-19 Vaccine Moderna* has the potential to reduce out-of-pocket expenses of Filipino households due to averted treatment and isolation costs for mild, moderate and severe COVID-19.
Does *COVID-19 Vaccine Moderna* possess the characteristics desired by key stakeholders? (Social Impact)	**Yes.** Based on short term outcomes, *COVID-19 Vaccine Moderna* possesses most of the characteristics desired by key stakeholders.
Does *COVID-19 Vaccine Moderna* reduce or not further add to existing inequities in the health system?	**Yes**. The non-stringent logistic requirements (ie., -25 to -15 degrees Celsius) allow it to be utilized widely.

In the development of this recommendation, the HTA Council has appraised the following evidence:

- Interim results of the Phase III clinical trial on *COVID-19 Vaccine Moderna* (Baden et al., 2021, US FDA Briefing Document, WHO SAGE, EMA Public Assessment Report)

- Phase I/II trials conducted in the US for populations 18 years old and above (NCT04813796: Jackson et al., 2020 and Anderson et al., 2020; NCT04405076: Chu et al., 2021).
- Real world evidence on vaccine effectiveness and safety

The HTA Council further emphasizes the need to enforce strict conditions for the emergency use of health products to safeguard against eventualities:

- Transparency and accountability in the processes of allowing emergency use of health products, especially for the public health response;
- Continuous collection of safety and effectiveness data in the context of clinical trials and actual use in the real world;
- Close monitoring of recipients and safeguards for expected and unexpected adverse events that may arise from the use of health products under an EUA;
- National coordination of the emergency use under the Philippine FDA and the DOH;
- Cascading of complete information to vaccinees and healthcare providers on potential risks and benefits, and securing of informed consent with regard to receiving the intervention; and
- Just compensation mechanisms and provisions for medical management of adverse events for patients and vaccinees assured by the national government

Finally, the HTAC recommends the conduct of research to address the current gaps in evidence with regard to the use of the *COVID-19 Vaccine Moderna*:

- Real-world effectiveness in the Philippine context particularly focused on the following knowledge gaps:
    - Effectiveness in reducing COVID-19 cases, hospitalizations and deaths, and preventing outbreaks and transmission of disease across the population
    - Effectiveness in reducing asymptomatic infection
    - Duration of protection
    - Impact of the timing and number of doses received
    - Probable need for booster dosing
    - Differences in the effectiveness of the vaccine among special populations (i.e., elderly, individuals with comorbidities, pregnant and lactating women, immunocompromised patients)

    - Effectiveness of the vaccine against emerging SARS-CoV-2 viral strains
- Continuous safety surveillance and monitoring of all adverse events especially severe allergic reactions, Bell's palsy, serious adverse events such as thrombosis-thrombocytopenia syndrome (TTS), myocarditis and adverse events of special interest (AESI) following vaccination
    - Across the general population
    - In special populations: elderly, patients with comorbidities, pregnant and lactating women, immunocompromised individuals
- Randomized controlled trials should also be done among populations not currently included in clinical trials: children below 18 years of age
- Best practices, challenges, and barriers in implementation across different localities
- Monitoring of unexpected or additional costs associated with vaccine implementation.

Current Evidence on *COVID-19 Vaccine Moderna*

The table below summarizes the appraisal of available evidence on *COVID-19 Vaccine Moderna* based on the HTAC evaluation framework.

In addition, the following appendices are provided for further details:

- Appendix 1. Evidence on evaluation criterion 2 - Clinical Efficacy and Safety
- Appendix 2. Evidence on evaluation criterion 3 - Affordability and Viability
- Appendix 3. References
- Appendix 4. Acknowledgment

Table 1.2 Key Findings in the Current Evidence Considered for the HTAC Evaluation of **COVID-19 Vaccine Moderna**

Evaluation Criteria	Question	Current Evidence	HTAC specification
Responsiveness to magnitude and severity	*Can the COVID-19 Vaccine Moderna significantly reduce the magnitude and severity of COVID-19?*	As of 31 May 2021, the total number of cases has exceeded more than 169 million cases and breached the 3.5 million mark in terms of the total number of deaths globally. In the Philippines, the cumulative number of laboratory-confirmed COVID-19 cases has already exceeded 1,230,301 cases with total deaths reported at 20,966 as of 31 May 2021. Based on the latest DOH-Epidemiology Bureau data (as of 06 May 2021), the young and productive age groups (20-49 years old) have the most exposure and highest prevalence of the disease. However, the most vulnerable are the senior citizens (>60 years) who have the highest case fatality rate (CFR) at 8.1% and comprise around 63.5% of COVID-19 deaths. In addition, individuals with existing comorbidities such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), other pulmonary, cardiovascular and blood diseases are also vulnerable with CFR reported at around 69% to 82%. COVID-19 has led to significant disruptions not only in the delivery of other priority health services (e.g., immunization, maternal and child health, noncommunicable diseases) but also in the social and economic life of the nation by arresting the growth of the economy, displacing migrant and local workers, loss of jobs, and food insecurity (NEDA, 2020; PSA 2020; TESDA, 2020). Social safety nets for the poorest and other vulnerable sectors have not been enough to compensate for these losses (TESDA, 2020). The lockdowns and community quarantines have also been shown to have an impact on the mental health of Filipinos and have affected how common Filipino households adjust under the new normal, unable to visit and freely	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

		enjoy quality time with members of their families, as captured in some focus group discussions conducted by the HTAC and the HTA Unit. Locally-contextualized modelling studies are needed for more accurate projections of the potential impact of vaccination along with other interventions, under different scenarios. These can better inform decision-making. **HTAC Judgment**: *COVID-19 Vaccine Moderna* has the potential to reduce the disease burden by averting a significant number of symptomatic infections including severe COVID-19 assuming sufficient vaccine coverage.	
2. Clinical efficacy and safety	*What is the efficacy of the COVID-19 Vaccine Moderna in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?*	**Efficacy and Effectiveness against COVID-19** ***EVIDENCE ON EFFICACY FROM TRIALS*** There are six ongoing trials using *COVID-19 Vaccine Moderna*, all of which are being conducted in the US: ● NCT04813796: an ongoing Phase I dose-ranging study of mRNA-1283 and mRNA-1273 among healthy adults aged 18-55 years across the United States. This trial was extended to include adults aged >56 years old. Results for the 18-55 years old subgroup were published in Jackson et al., 2020 while the results of the >56 years old subgroup were published in Anderson et al., 2020. ● NCT04405076: a Phase II trial in non-pregnant adults, aged 18 years and older in the US (50 mcg or 100 mcg versus placebo, 2-dose regimen, 28 days apart). Results of this trial were published in Chu et al., 2021. ● NCT04796896 (KidCOVE): an ongoing Phase II/III	The vaccine achieves the following efficacy parameters: **Preferred VE: ≥70% reduction** in the risk of symptomatic infection with vaccination versus no vaccination **Minimum acceptable VE: 50% reduction** in the risk of symptomatic infection with vaccination versus no vaccination

		placebo-controlled trial in children aged 6 months to 11 years old in the US (2-dose regimen, 28 days apart). Currently, there are no interim results published for this trial as it is still in the recruitment phase. ● NCT04649151 (TeenCOVE): a Phase II/III placebo-controlled trial in children aged 12 to 17 years old in the US (2-dose regimen, 28 days apart. The results of this trial are still unpublished. ● **NCT04470427 (COVE):** is an ongoing Phase III study of mRNA-1273 among 30,351 participants aged 18 years and older in 99 centers across the United States (2-dose regimen, 28-days apart). Interim result of this trial was published in Baden et al. 2021. ● NCT04860297: an ongoing Phase IIIb open-label, single arm study in adult transplant recipients and in healthy adults across the United States (2-dose regimen, 28 days apart). Currently, there are no interim results published for this trial as it is still in the recruitment phase. Of these trials, the Coronavirus Efficacy (COVE), a Phase III trial by Baden et al. (2020), was the main evidence used for appraising the safety and efficacy of *COVID-19 Vaccine Moderna*. The authors initially submitted data for its EUA application to the US FDA and EMA with efficacy and safety data cut-offs of 7 November 2020 and 11 November 2020. To meet the regulatory agencies' requirement of median follow-up duration of at least 2 months after completion of the second dose regimen, the authors also submitted data on efficacy and safety with 21 November 2020 and 25 November 2020 data cut-offs, respectively. The US FDA noted that their preliminary assessments of safety and efficacy data and analyses from the second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7,	The following factors were taken into consideration upon setting the minimum acceptability of 50% efficacy: pandemic situation, no standard COVID-19 vaccine, limited production from each manufacturer, and the need for multiple sources of vaccines in the Philippines. Adapted from WHO, US FDA, other stringent regulatory authorities

		2020, and November 11, 2020, respectively. Data for Baden et al. (2020) were used as the source of clinical evidence in the assessment report of WHO SAGE, whose cut-offs on efficacy and safety data were 21 November 2020 and 25 November 2020, respectively. Meanwhile, Trial NCT04813796 and Trial NCT04405076 were considered in the review of Phase I/IIa trials, with the results published as manuscripts (NCT04813796: Jackson et al., 2020 and Anderson et al., 2020; NCT04405076: Chu et al., 2021). The details of Phase I/IIa trials are provided in Appendix 1. ***Phase III trial, N=30,351 (Baden et al. 2020)*** The trial is a randomized, observer-blinded, placebo-controlled trial among adults ≥18 years of age with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection, a high risk of severe COVID-19, or both. Of the 30,351 participants, 15,181 received at least one dose of intramuscular injection of 100 mcg *COVID-19 Vaccine Moderna,* and 15,170 received at least one dose of saline placebo. The interval between doses is 28 days. As of November 25, 2020, the participants had a median follow-up duration of 63 days (range, 0 to 97 days) after the second dose, with 62% of participants having more than 56 days of follow-up. The following efficacy outcomes were considered: ● Symptomatic COVID-19, *with onset at least 14 days after the second dose* (primary endpoint), with subgroup analyses according to: ○ Age (18-64 years of age, 65 years and older) ○ At risk for severe COVID-19	

		○ Age and risk for severe COVID-19 (18 to <65 years old, at risk) ○ Race and ethnic group (Asian) ● Severe COVID-19, *with onset at least 14 days after second dose* ● Severe COVID-19 *with onset at least 14 days after second dose,* resulting in: ○ Hospitalization due to COVID-19 ○ Death Below are the key findings on its efficacy and the rating of evidence: **Critical efficacy outcomes:** The following critical efficacy outcomes were measured at ≥14 days after the second dose. ● Using *COVID-19 Vaccine Moderna* (≥14 days after dose 2)**,** compared to placebo, **reduces the risk for:** ○ **Symptomatic COVID-19** by **94.1% (95% CI: 89.3 to 96.8),** based on high certainty of evidence [Per protocol analysis (PP)] ○ **Symptomatic COVID-19** by **93.6% (95% CI: 88.5 to 96.4),** based on high certainty of evidence [Modified intention-to-treat analysis (mITT)] ● As for its efficacy against **severe COVID-19 (≥14 days after dose 2),** there were zero events in the vaccine group (N=14,134) and 30 events in the placebo group (N=14,073). It is likely that the vaccine also protects against severe COVID-19. ● As for its efficacy against **severe COVID-19 resulting in hospitalization (≥14 days after dose 2),** there were zero events in the vaccine group (N=14,134) and 9 events in the placebo group (N=14,073). Vaccine efficacy against severe COVID-19	

		resulting in hospitalization remains to be demonstrated. **<u>Important efficacy outcomes:</u>** Unless otherwise specified, the following important efficacy outcomes were measured at ≥14 days after the second dose. ● Using *COVID-19 Vaccine Moderna* (≥14 days after dose 2), compared to placebo, **<u>reduces the risk for</u>:** *Subgroup analysis by age* ○ **Symptomatic COVID-19 among participants aged ≥18 to <65 years old** by **95.6% (95% CI: 90.6 to 97.9)**, based on high certainty of evidence ○ **Symptomatic COVID-19 among older adults (≥65 years old)** by **86.4% (95% CI: 61.4 to 95.2)**, based on high certainty of evidence *Subgroup analysis by comorbidity* ○ **Symptomatic COVID-19 among participants with comorbidities** by **90.9% (95% CI: 74.7 to 96.7)**, based on high certainty of evidence *Subgroup analysis by age and risk* ○ **Symptomatic COVID-19 among at risk participants aged 18 to <65 years old** by **94.4% (95% CI: 76.9 to 98.7)**, based on high certainty of evidence ● As for its efficacy against **symptomatic COVID-19 in Asians,** there were zero events in the vaccine group (N=620) and 5 events in the placebo group (N=689). Vaccine efficacy against symptomatic COVID-19 in Asians remains to be demonstrated. ● As for its efficacy against **severe COVID-19 resulting in death,** there were zero events in the vaccine group (N=14,134) and 1 event in the placebo group (N=14,073). Vaccine efficacy against	

		severe COVID-19 resulting in death remains to be demonstrated. ● VEs against **asymptomatic COVID-19** and **new variants** were not reported in the trial. ***REAL WORLD EFFECTIVENESS DATA*** ● The Philippine Living Clinical Practice Guidelines Group conducted a systematic review on the current evidence on the effectiveness and safety of different COVID-19 vaccines which included a review on real world evidence for COVID-19 Vaccine Moderna. Based on their search (last search: 17 April 2021**),** there were five studies, all conducted in the US, which investigated the real world effectiveness of *COVID-19 vaccine Moderna*. These studies were on populations where *COVID-19 Vaccine Moderna* or *Pfizer-BioNTech COVID-19 Vaccine* was used, and did not report effectiveness outcomes separately for each of the vaccines. ○ A test negative case control study by Andrejko et al. (pre-print) (N = 645) showed the real world VE against COVID-19, 15 days after the second dose of an mRNA vaccine, was at **85.7% (95% CI 67.2 to 93.9)**. ○ A cohort study by Thompson et al. (2021) among healthcare workers and frontliners (N = 3,950) reported a higher vaccine efficacy against COVID-19 at least 14 days after the second dose of an mRNA vaccine at **90% (95% CI 68 to 97)**. ○ A matched cohort study by Pawlowski et al. (pre-print) (N = 62,138) demonstrated VE against any PCR-confirmed COVID-19 of **88.7% (95% CI 68.4 to 97.1)** 7 days after the second dose, and **92.5% (95% CI 70.2 to 99.1%)** from 7 to 14 days after the second dose. Two deaths were reported in the study, both in the unvaccinated group.	

		○ Another matched cohort study among health care facility residents (N = 25,378) showed 1.1 to 3.8 fewer hospitalizations and/or deaths per 100 infected persons per day after vaccination with an mRNA vaccine (Mor et al., 2021). ○ Another case study in the US (N = 1,448, 600) did not report vaccine efficacies but reported reduction in daily cases in the younger age group from 0.2% to 0.05% and from 0.1% to 0.01% in the older age group. Death rates also decreased in older adults aged 71 years old and above (Rhogani et al., pre-print). ● Meanwhile, a study by Tenforde, et al. (2021) evaluated the protection provided by full or partial vaccination of *Moderna COVID-19 Vaccine* or Pfizer-*BioNTech COVID-19 Vaccine* against COVID-19–associated hospitalization among adults aged ≥65 years old under real-world conditions. This multi-hospital evaluation set in the US included patients aged ≥ 65 years old who received RT-PCR or antigen testing for SARS-CoV-2 within 10 days of onset of illness and had onset of symptoms 0-14 days before admission. Those who tested positive for SARS-CoV-2 were classified as case-patients and those who tested negative were classified as control. Vaccination status were obtained and were categorized as: (1) unvaccinated (n=287); (2) single-dose vaccinated <14 days before illness (n=49); (3) partially vaccinated (n=62) (i.e. patients who were vaccinated with 1 dose in a 2-dose vaccination series ≥14 days before onset of illness, with the second dose received <14 days before illness onset); and, (4) fully vaccinated (n=19) (i.e., patients who received both doses of a 2-dose vaccination series ≥14 days before illness onset). ○ **Adjusted vaccine effectiveness against COVID-19-associated hospitalization** for **full vaccination (**vs the unvaccinated group): **94% (95% CI: 49 to 99)**	

		○ **Adjusted vaccine effectiveness against COVID-19-associated hospitalization** for **partial vaccination** (vs the unvaccinated group): **64% (95% CI: 28 to 82)**. ○ There was no significant effect for receiving the first dose of a 2-dose COVID-19 vaccine series within 14 days before illness onset. ○ Prevalence of receipt of COVID-19 Vaccine *Moderna* (47%) and *Pfizer-BioNTech* (53%) vaccines across the single-dose vaccinated, partially vaccinated and fully vaccinated groups was comparable. **Evidence of neutralization against COVID-19 new variants of concern** ***Evidence from Wu et al. (2021)*** A letter to the editor by Wu et al. (2021) presented results of serum neutralization assay against pseudoviruses containing spike proteins of different SARS-CoV-2 variants. These were measured using serum samples from Phase I trial (Jackson et al., and Anderson et al.) participants (N = 8) one week after they received their second dose of the *COVD-19 Vaccine Moderna*. Results showed that mutations in the B.1.1.7 variant did not significantly affect neutralization activity elicited by the vaccine. Meanwhile, neutralizing antibody titers against the P.1, B1.427/B.1.429, B1.1.7+E484K and the B1.351 variants were reduced by 2.3 to 6.4 times compared to the original Wuhan-Hu-1 isolate. The highest reduction factor (6.4) was observed in the assay against the B1.351 variant. Despite this reduction, the serum samples were still able to neutralize pseudoviruses carrying the B1.351 spike proteins. From these in vitro results, it can be concluded that *COVID-19*	

		Vaccine Moderna could offer similar protection against the B.1.1.7 variant compared to the Wuhan-Hu-1. Protection conferred by the *COVID-19 Vaccine Moderna* against the P.1, B.1.427/B.1.429, and B1.351 variants remains to be determined. These results highlight the importance of continued viral surveillance and evaluation of vaccine efficacy against new variants and may help to facilitate the establishment of correlates of protection. ***Evidence from a prepublication version of LCPG Review on COVID-19 Effectiveness against Variants of Concern*** The Philippine Living Clinical Practice Guidelines Group conducted a rapid review of clinical evidence to examine the ability of current vaccines (specifically those vaccines which have received authorization and are used in global vaccination programs, or have known preliminary Phase 3 clinical trial results) to provide necessary protection and immunity against emerging SARS-CoV-2 variants. Based on their evidence search (last search: 23 April 2021), there were six studies conducted in the US (3 pre-print, 3 published) which investigated the real world effectiveness of *COVID-19 Vaccine Moderna* against SARS-CoV-2 variants and mutations of concern using immunogenicity data. All the published studies reported vaccine effectiveness as combined immunologic effects of *COVID-19 Vaccine Moderna and Pfizer BioNTech COVID-19 Vaccine* without providing separate outcomes for each. A consistent finding was a reduction in the neutralizing capacity by sera from vaccinated participants but still achieving a level that is effective at neutralizing the variant. One study (Woldemiskel et al., 2021) reported a similar cellular response to the ancestral type and the variants.	

		Details of the results of the immunologic studies on *COVID-19 Vaccine Moderna* are shown in Appendix 1. **HTAC Judgment**: *COVID-19 Vaccine Moderna* passed the preferred VE threshold against symptomatic COVID-19. It is likely that the vaccine also protects against severe COVID-19.	
	What is the duration of protection of the COVID-19 Vaccine Moderna in terms of reducing the incidence and/or severity of COVID-19?	The current interim evidence shows protection against laboratory-confirmed symptomatic COVID-19 based on a minimum median follow up period of two months after receiving two doses. Data on the duration of protection will be assessed as more evidence becomes available. **HTAC Judgment:** Cannot be assessed based on current data	**Minimum acceptable duration of protection:** confers at least 6 months protection **Preferred:** ≥1-year protective immunity *Reference: WHO Target Product Profile for COVID-19 Vaccines, 2020*
	What are the safety issues and incidence of adverse events caused by the COVID-19 Vaccine Moderna?	Both the evidence from trials and real world data were reviewed in assessing the safety of *COVID-19 Vaccine Moderna*. ***EVIDENCE FROM TRIALS*** Findings from Phase I and II trials are detailed in Appendix 1. As for safety outcomes from the Phase III trial, the overall safety set was used in the analysis of unsolicited adverse events, adverse events leading to discontinuation, medically-attended adverse events,	Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine.

		serious adverse events, and deaths while the solicited safety set was used in the analysis of solicited systemic and local adverse reactions. A total of 30,351 participants who received at least one dose were included in the overall safety analysis with 15,185 and 15,166 participants in the vaccine and placebo arm, respectively. The solicited safety set included participants who received at least one dose and reported any solicited adverse reaction. A total of 30,338 participants were included in the solicited safety set, with 15,176 participants in the vaccine arm and 15,162 participants in the placebo arm. Below are the key findings on its safety and the rating of evidence: **<u>Short-term outcomes:</u>** Based on the computed risk ratio (RR), *COVID-19 Vaccine Moderna* shows higher risk of systemic and local reactogenicity when compared to placebo: ● **Systemic reactogenicity [RR: 1.56 (95% CI: 1.54 to 1.59)],** based on high certainty of evidence ● **Local reactogenicity [RR: 3.18 (95% CI: 3.10 to 3.27)]**, based on high certainty of evidence Meanwhile, *COVID-19 Vaccine Moderna,* shows inconclusive safety data on the risk for **severe unsolicited adverse events [RR: 1.16 (95%CI: 0.96 to 1.39)]**, based on moderate certainty of evidence. **<u>Long-term outcomes:</u>** ● In terms of **serious adverse events (SAEs)**, there is inconclusive safety data on the risk associated with the use of *COVID-19 Vaccine Moderna* vs placebo **[RR: 1.04 (95% CI:**	**Short term outcomes** (e.g., reactogenicity and allergic reactions): at least 2 months **Long term outcomes** (e.g., serious AEs): at least 1 year

		0.78 to 1.39), *low certainty of evidence***]**. Among the non-fatal SAEs that were reported in the trial, the investigator considered 7 in the vaccine arm to be related to the study product. Only 3 of these were deemed by the US FDA to be related to the vaccine, namely, one case of intractable nausea and vomiting and 2 cases of facial swelling. For the SAEs of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. One case of Bell's palsy was considered as an SAE occurred in the vaccine arm; however, neither the sponsor or investigator considered the event to be related to the study product. The US FDA assessed that a causal relationship for this event cannot be excluded. ● There is also inconclusive data in terms of **deaths (all-cause mortality) [RR: 0.86 (95% CI: 0.29 to 2.55)** *low certainty of evidence***]**. There were 13 deaths that occurred in the trial; 6 in the vaccine arm and 7 in the placebo arm. The deaths in the vaccine arm were due to cardiopulmonary arrest, myocardial infarction, head trauma, multi-organ failure, suicide, and an unknown cause. The causes of the deaths in the placebo group included myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and an unknown cause. The deaths in the trial represent the rates of death that occur in the general population and specific age groups. ***REAL WORLD DATA*** Real world safety data on *COVID-19 Vaccine Moderna* was taken from the following sources:	

		• Living CPG Group Evidence Review on *COVID-19 Vaccine Moderna* (29 April 2021)
		• Two Global Monthly Safety Report from Zuellig Pharma Corporation (published 15 February and 15 March 2021)
		• EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting highlights (3 to 6 May 2021)
		• US CDC Advisory Committee on Immunization Practices COVID-19 Vaccine Safety Technical (VaST) Work Group presentations on:
		  ▪ Updates on Thrombosis with Thrombocytopenia Syndrome (TTS) (12 May 2021)
		  ▪ Updates on Myocarditis (17 May 2021)
		
		LCPG Report
		The Philippine Living Clinical Practice Guidelines Group conducted a systematic review on the current evidence on the effectiveness and safety of different COVID-19 vaccines which included a review on real world evidence for *COVID-19 Vaccine Moderna*. Based on their evidence search (last search: 17 April 2021), real world safety data were detected from US CDC Safety Monitoring report, Vaccine Adverse Event Reporting System (VAERS) report, US CDC Morbidity and Mortality Weekly reports, WHO Database (Vigibase®), and an international registry-registry based study.
		• The US CDC released a COVID-19 safety monitoring report from December 14 to January 13, 2021 covering the first month after the vaccination rollout using *COVID-19 Vaccine Moderna* and *Pfizer-BioNTech COVID-19 Vaccine*. During this period, 13,794,904 vaccine doses were administered (no breakdown based on vaccine types was provided in the report) and 6,994 adverse event reports were received and processed by the Vaccine Adverse Events Reporting System (VAERS) for both vaccines. Majority (90.8%) were classified as non-serious and	

		9.2% as serious. A total of 113 deaths were reported, 65% of which were among long-term care facility residents. No causal relationship between COVID-19 vaccination and death was established. ● Based on the VAERS report in the US, 258 (18.8%) serious adverse events were noted after the first dose of *COVID-19 Vaccine Moderna*. No information was yet available for the outcomes after the second dose. The most frequently reported adverse events were headache (25.3%), chills (19.0%), nausea (16.7%), fatigue (16.6%) and dizziness (16.6%). There was significant reactogenicity after *COVID-19 Vaccine Moderna* vaccination, with injection site pain being the most common symptom. ● The US CDC Morbidity and Mortality Weekly Report (December 14, 2020 to January 13, 2021) reported 16 cases of anaphylaxis have been confirmed after receipt of the *COVID-19 Vaccine Moderna* vaccine. ● The US CDC Morbidity and Mortality Weekly Report (December 21, 2020 to January 10, 2021) estimated that anaphylaxis rate for *COVID-19 Vaccine Moderna* is at 2.5 cases per million doses administered. ● Out of 32,044 vaccinees who received *Pfizer-BioNTech COVID-19 Vaccine, COVID-19 Vaccine Moderna, and COVID-19 Vaccine (ChAdOx1-S [recombinant (COVID-19 Vaccine AstraZeneca),* data from the WHO database (VigiBase®), which include European, North and South American, and Asian countries, revealed that 78 deaths after *COVID-19 Vaccine Moderna* administration occurred. This represents 1.23% of all adverse event reports after vaccination. ● An international registry-based study (McMahon et al., 2021) on the cutaneous reactions after mRNA vaccination (17% related to *Pfizer-BioNTech COVID-19 Vaccine*, 83% with *COVID-19*	

		Vaccine Moderna) reported delayed large local reaction being the most common among recipients of mRNA vaccines, followed by local injection site reactions, urticarial eruptions and morbilliform eruptions. Additional less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. It was also observed that most patients with first-dose reactions did not have a second dose reaction. The data included in this study were mainly from the US (98% of cutaneous reactions reported). Other countries with reported cutaneous reactions include Canada, Germany, Israel, Italy, UK, Puerto Rico, and Guam. **Global Monthly Safety Data (Zuellig Pharma)** Of the 50,061,700 doses of *COVID-19 Vaccine Moderna* distributed, 39,334,706 of which were administered from December 18, 2020 to February 17, 2021 from different countries including the US, Canada, and several European countries. During the first reporting period covering December 18, 2020 to January 17, 2021, a total of 15,915 adverse events were collected, of which 311 were considered serious. Notable adverse events of special interest (AESI) include anaphylactic reactions (55 cases, 19 of which met the Brighton Collaboration Criteria) and death (12 cases). The second reporting period included events collected from January 18, 2021 to February 17, 2021. A total of 45,294 adverse events were collected, 5,094 of which were considered to be serious adverse events. Notable AESIs collected during this period include:	

		● anaphylactic reaction (225 cases, 94 of which met the Brighton Collaboration Criteria), ● Bell's palsy/ idiopathic peripheral facial nerve palsy (77 events), ● Guillain-Barré syndrome (8 events), and thromboembolism and thrombosis (151 events), and ● death (314 events, 10 of which were sudden deaths). There were no trends or patterns indicating a safety signal identified during this reporting period. **EMA PRAC** ● As a result of the reported unusual blood clots in other COVID-19 vaccines (*AstraZeneca COVID-19 Vaccine* and *Janssen Ad26.COV2.S (COVID-19) Vaccine*), the EMA PRAC has been closely monitoring mRNA vaccines for this adverse event. At the moment, PRAC considers that there is no safety signal for the mRNA vaccines. Extremely low numbers of this adverse event were reported and the frequency is lower than the one occurring in people who have not been vaccinated. ● The EMA PRAC is also closely monitoring myocarditis as an adverse event for mRNA vaccines considering reported cases of myocarditis and pericarditis following vaccination with *Pfizer-BioNTech COVID-19 Vaccine*. Currently, there is no indication that these cases are caused by the vaccine. **US CDC COVID-19 Vaccine Safety Technical (VaST) Work Group** ● ***Update on Thrombosis with Thrombocytopenia Syndrome (TTS)*** ○ As of May 10, 2021, 113 million doses of the *COVID-19 Vaccine Moderna* have been administered in the US. ○ Upon enhanced monitoring and review of data in light of the thrombosis with thrombocytopenia syndrome (TTS) associated with the use of the *Janssen Ad26.COV2.S*	

		(COVID-19) Vaccine, the VaST Work Group assessed that there are still no safety signals identified for cerebral venous sinus thrombosis (CVST) or TTS for mRNA vaccines as of May 10. ○ As of April 24, 2021, there was a total of 11 cases of CVST identified after administration of 3.3 million doses of *Pfizer-BioNTech COVID-19 Vaccine* and 3 million doses of *COVID-19 Vaccine Moderna* within the Vaccine Safety Datalink (VSD). Of the 11 cases, 3 occurred following *Pfizer-BioNTech* vaccination and 8 occurred after *COVID-19 Vaccine Moderna* vaccination. Of the 11 cases, 5 were ruled out. All remaining 6 potential CVST incident cases did not present thrombocytopenia. As such, there are no confirmed cases of TTS associated with mRNA COVID-19 vaccines in the US as of this writing. ● ***Update on Myocarditis*** ○ As of 17 May 2021, VaST concluded that there are relatively few reports of myocarditis following mRNA vaccination. Most of these cases were considered mild and predominantly occured in adolescents and young adults. Cases were more often reported in males than females, following the second dose than after the first dose, and usually within 4 days after vaccination. ○ Based on the data from the US CDC safety monitoring systems, rates of myocarditis reports in the window following vaccination have not differed from baseline rates. However, VaST deems it necessary to inform healthcare providers on reports of myocarditis. **HTAC Judgment:** Short-term safety of *COVID-19 Vaccine Moderna* is acceptable. However, further follow-up data is needed to establish	

		longer-term safety.	
	Does the COVID-19 Vaccine Moderna provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy?	The current evidence shows that the clinical benefits in terms of decreased occurrence of **symptomatic COVID-19, and likely severe COVID-19,** outweigh the known short-term risks based on data available at the time of evaluation. Likewise, the clinical benefits for older adults (i.e., 65 years and above) and populations with comorbidities in terms of vaccine efficacy against symptomatic COVID-19 outweigh the known short-term risks based on data available at the time of evaluation . Trial evidence on the VEs against severe COVID-19 resulting in hospitalization, severe COVID-19 resulting in death, and symptomatic COVID-19 among Asians are **inconclusive.** Further, VEs against asymptomatic COVID-19 and new variants were not reported in the trial. Thus, the benefit/risk profile specifically for these subgroups cannot be determined. **HTAC Judgment:** PASSED	Favorable benefit/risk profile The benefit of preventing morbidity of at least 50% far outweighs the reported risk of adverse events

3. Affordability and viability	*Is COVID-19 Vaccine Moderna affordable?*	Based on the projected calculations, the total cost of rolling out vaccination with *COVID-19 Vaccine Moderna* for **6.5M Filipinos in 2021** (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) will amount to **Php 18,905,488,006.67.** According to the Department of Finance, the price of *COVID-19 Vaccine Moderna* offered to the Philippine government is within the price range for which *COVID-19 Vaccine Moderna* is available in various markets globally. **HTAC Judgment:** The vaccine has a relatively higher budget impact to the government compared to other vaccines. However, higher priced vaccines could address issues of low or uncertain supply. When supply is no longer a problem, there might be a need to reassess the vaccine in terms of affordability.	Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets. **The vaccine unit cost is comparable with those in other ASEAN countries.*

	What are the budget implications of using the COVID-19 Vaccine Moderna?	Total cost of vaccination per individual, which accounts for other costs such as consumables, logistics, and operations, was computed to be **Php 2,908.54**. According to the Department of Finance, the negotiated price of the vaccine covers end-to-end logistics (i.e., from manufacturing site to inoculation centers). The potential budget impact of the use of *COVID-19 Vaccine Moderna* to the national government to cover 6.5M million Filipinos was calculated at about **Php 18.91B**. With 6.5M Filipinos to be vaccinated, it is estimated that **22.92%** of the total budget of the government will go to **9.29%** of the 70M target vaccinees for 2021. **HTAC Judgment:** The share of the cost of the *COVID-19 Vaccine Moderna* to the total vaccine budget is considered disproportionate to the share of the population to be vaccinated using the said vaccine.	The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be vaccinated using the said vaccine in the total population to be vaccinated.

	Does the COVID-19 Vaccine Moderna represent good value for money in terms of: *a. preventing COVID-19 mortality* *b. lowering hospitalization (moderate, severe and critical cases)* *c. lowering incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases)*	*COVID-19 Vaccine Moderna* represents good value for money in terms of lowering any symptomatic COVID-19 (including older adults aged 65 years and older and individuals with comorbidities). It is likely that the vaccine also protects against severe COVID-19. Whether *COVID-19 Vaccine Moderna* represents good value for money in terms of symptomatic COVID-19 (Asians), severe COVID-19 resulting in hospitalization, severe COVID-19 resulting in death, COVID-19 caused by new variants, and asymptomatic cases (RT-PCR confirmed cases) cannot be fully assessed at the moment. Rough estimates of the vaccination cost per case averted are high. However, HTAC has bases to conclude that these will be offset by averted healthcare costs (i.e., total COVID-19-related PhilHealth claims, out of pocket expenditures), economic gains (i.e., in terms of recovery in GDP), and social gains. **HTAC Judgment:** The HTAC deems that the health, economic, and social benefits of using *COVID-19 Vaccine Moderna* mitigate the negative impacts of COVID-19, such as deaths, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.	The health, economic, and social benefits of the vaccination program outweigh the costs. The vaccine is likely cost-effective. *Note: A full-blown cost-effectiveness analysis is currently not done for rapid reviews under a pandemic situation due to its emergency nature. A full-blown cost-effectiveness analysis that takes on a societal perspective (i.e., including the economic and social impacts) will be performed once sufficient evidence is available and when full market authorization has been granted.*

	Are there significant barriers to vaccine implementation in terms of vaccine storage and transport, handling; adequacy, skills and training of vaccinators; and access of the target population to the health care facility? Are there plans to overcome significant barriers?	The vaccine can be readily stored in a freezer at -25 to -15 degrees Celsius. Given this, it is expected that the *COVID-19 Vaccine Moderna* can be widely distributed to facilities with the said equipment. Like any vaccine implementation, there is still a need for training on vaccine storage and handling to ensure product integrity across the entire supply chain. Trained personnel in handling unreported or rare adverse reactions that could occur following vaccination should also be in place. **HTAC Judgment:** The HTAC notes that there are no significant barriers in vaccine implementation using *COVID-19 Vaccine Moderna* in terms of storage, transport, and handling. Similar to other vaccines, there is still a need for training to: ensure product integrity across the entire supply chain; and, close monitoring of adverse events.	There are no significant barriers and if there are, the plans to address the barriers are clearly reflected in the vaccine roadmap and other relevant documents.
4. Household Financial Impact	*Will the COVID-19 Vaccine Moderna reduce or not add further to the out-of-pocket expenses of Filipino households?*	**For mild COVID-19 pneumonia:** ● PhilHealth has issued the following packages and case rates related to mild COVID-19: - Isolation Package (C19CI): Php 22,499.00 - Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Php 43,997.00 ● Looking at the actual PhilHealth claims as of January 2021, the isolation package amounted to a median cost of **Php 22,499.00,** while claims for mild COVID-19 pneumonia for elderly and those with comorbidities amounted to a median cost of **Php 43,997.00.** ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients for isolation is at **Php 22,499.00** while mild cases among elderly and those with comorbidities is at **Php 60,020.25.** ● From the same dataset, the calculated median out-of-pocket spending for patients with mild COVID-19 pneumonia is at **Php**	The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

		16,023.25. Meanwhile, the median out-of-pocket expense reported for patients availing of an isolation package is Php 0. **<u>For moderate COVID-19 pneumonia:</u>** ● PhilHealth has issued a benefit package C19IP2 for moderate COVID-19 pneumonia with a case rate of Php 143, 267.00. ● Looking at the actual PhilHealth claims for moderate COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 143, 267.00**. ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with moderate COVID-19 is at **Php 234, 925.13**. ● From the same dataset, the calculated median out-of-pocket spending for patients with moderate COVID-19 pneumonia is at **Php 63,371.30**. **<u>For severe COVID-19 pneumonia:</u>** ● PhilHealth has issued a benefit package C19IP3 for severe COVID-19 pneumonia with a case rate of Php 333,519.00. ● Looking at the actual PhilHealth claims for severe COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 333,519.00**. ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with severe COVID-19 pneumonia is at **Php 388,904.20**. ● From the same dataset, the calculated median out-of-pocket spending for patients with severe COVID-19 pneumonia is at **Php 388,903.20**. **HTAC Judgment**: Based on current evidence, *COVID-19 Vaccine Moderna* has the potential to reduce out-of-pocket expenses of Filipino	

		households due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19.	
5. Social Impact	*Does the COVID-19 Vaccine Moderna possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health workers, program managers and/or implementers, patient groups, CSOs, communities, general public)?* ● *Safety* ● *Efficacy* ● *Transparency in the regulatory/approval process and information on the vaccines* ● *Availability* ● *Potential for high and equitable coverage* ● *Ease in logistical and*	Based on the results of the focus group discussions conducted by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the **important and desirable attributes of COVID-19 vaccines** and the corresponding evidences for the *COVID-19 Vaccine Moderna*: 1) **Safe and efficacious** for the general population (aged 18 years and older) and for some vulnerable groups like the older population and individuals with comorbidities. - Evidence: Interim results from the clinical trial show an acceptable safety profile for known short-term risks and efficacy to reduce risk for symptomatic infections and likely, severe COVID-19**.** There is currently no data on the safety and efficacy of the vaccine in special populations such as children below 18 years old, pregnant and lactating women, and immunocompromised individuals. Trials are forthcoming to provide more conclusive evidence on the efficacy and safety for the special populations namely immunocompromised and children. Nevertheless, the WHO has advised that individuals in these special populations who are recommended for vaccination may receive the vaccine. Currently, the EUA issued by the FDA Philippines has recommended its use among individuals aged 18 years and older. 2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the Filipino experience and may impact on implementation strategy

	implementation requirements ● *Cost-efficiency to the government* ● *Public acceptability* ● *Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination* ● *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	- Evidence: *COVID-19 Vaccine Moderna* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA issued an EUA for the vaccine on 07 May 2021. 3) **Potential for high and equitable coverage across the population** - Evidence: *COVID-19 Vaccine Moderna* must be stored at the standard freezer temperature of -25 to -15 degrees Celsius. The vaccine can be made more available since vaccine handling and storage are within the capacity of the RHUs. 4) **Ease in logistics and administration** - Evidence: *COVID-19 Vaccine Moderna* can be stored for 7 months at -25 to -15 degrees Celsius in freezers that are present in most RHUs. According to the EUA fact sheet, the vaccine may also be stored at 2 to 8 degrees Celsius, protected from light for 30 days prior to first use. The vaccine also does not require dilution at the vaccination site which may simplify implementation of the vaccine especially in community settings. 5) **Cost-effective** - Evidence: The health, economic, and social benefits of using *COVID-19 Vaccine Moderna* mitigate the negative impact of COVID-19, such as deaths, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. 6) **Public acceptability** - Evidence: Based on the COVID-19 Vaccine Sectoral surveys conducted by the DOH- Health Promotion Bureau: - 70.54% of participants from the Philippine National Police responded that they are willing to get COVID-19	

		vaccine (February 5-14, 2021). This is an increase from the 56.94% acceptance rate in a similar survey conducted last 29 December 2020 to 8 January 2021. - 68.62% of participants from the Civil Service Commision (excluding DOH, PNP and AFP employees) responded that they are willing to get COVID-19 vaccine (6 February to 3 March 2021). This is an increase from the 44.85% acceptance rate in a similar survey conducted previously (Duration of survey not reported). Based on the national survey conducted by the Social Weather Station from 28 April to 2 May 2021: - 63% of the 1,200 respondents aged 18 years and above picked the United States as one of their preferred country sources of vaccines. This was followed by China which was selected by 19% of the respondents. Meanwhile, 13% of the respondents also opted for the United Kingdom, 12% included Russia, and 3% picked India as one of their preferred country sources of vaccines. - The certainty of the evidence provided by published and real world data that support the favorable recommendation, if appropriately communicated, will increase public acceptability of vaccines. **7) Availability of mechanisms to manage any untoward serious adverse reactions following vaccination** - Evidence: Republic Act 11525 or the COVID-19 Vaccination Program Act of 2021 establishes the COVID-19 National Vaccine Indemnity Fund to provide funds and authorize PhilHealth to pay compensation to any person inoculated through the vaccination program, in the case of death and permanent disability.	

		8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities - Evidence: The interim results from the Phase III clinical trial enrolled individuals 18 years and above. The current evidence for special populations allow it to be used in special at-risk groups such as the older population and patients with comorbidities. Currently, there is limited data from the trial on the use of the vaccine for pregnant and lactating women, children below 18 years old, persons living with HIV, immunocompromised individuals, and persons who have previously received antibody therapy for the treatment of COVID-19. The WHO recommendations (25 January 2021) on the use of the vaccine in the older population, patients with comorbidities, and other special populations are detailed below. *For older populations (24.8% of the trial population):* - According to the WHO interim guidance on the use of this vaccine, the efficacy and safety of the vaccine based on the interim phase III RCT are comparable across all age groups (above the age of 18), hence it is recommended for older persons. *For populations with comorbidities (27.2% of the trial population):* - According to the WHO interim guidance on the use of this vaccine, the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19, based on the results of the interim phase III RCT. The trial included the following comorbidities: chronic lung disease, significant cardiac disease, severe obesity,	

		diabetes, liver disease and human immunodeficiency virus (HIV) infection. Hence, the WHO recommends it for persons with comorbidities. *For extremely frail older persons and persons above the age of 95* - According to the WHO interim guidance on the use of this vaccine, safety and immunogenicity data for older people with and without comorbidities suggest that the benefits of vaccination outweigh the potential risks. Hence, the WHO recommends the vaccine for older persons without a limit to age. For extremely frail older persons with a life expectancy of less than 3 months, the WHO recommended conducting an individual benefit-risk assessment. *For pregnant women* - Evidence for efficacy and safety are insufficient to assess vaccine-associated risks in pregnancy. - The *COVID-19 Vaccine Moderna* is not a live virus vaccine and the mRNA does not enter the nucleus and degrades quickly. - No safety issues were noted from the developmental and reproductive toxicology studies conducted in animals. - The WHO interim recommendation for pregnant women to receive the vaccine remains on the condition that the benefit of protection from COVID-19 outweigh the potential vaccine risks (i.e., pregnant woman is a frontline healthcare worker, with known comorbidities that increase their risk for severe COVID-19.) *For lactating women* - Vaccine efficacy in lactating women is expected to be	

		similar to other adults. - Currently, there is no evidence for safety of the vaccine in lactating women or on the potential effects of the vaccine on breastfed children. - With the current evidence available, the WHO interim recommendations (25 January 2021) for the use of *COVID-19 Vaccine Moderna* state that lactating women who are part of a group recommended for vaccination (e.g., health workers) should be offered vaccination on an equivalent basis. Further, discontinuing breastfeeding after vaccination is not recommended. *For children and adolescents below the age of 18 years* - Currently, no efficacy or safety data for children and adolescents below the age of 18 years are available. Hence, vaccination of individuals aged below 18 years is not yet considered at the moment. *For persons living with HIV* - Based on the current available evidence, no safety concerns were observed in persons with well-controlled HIV who were included in the phase III RCT. However, the current data is insufficient to allow assessment of vaccine efficacy for persons living with HIV that is not well-controlled with therapy. - In the interim, as the vaccine is not a live virus, the WHO noted that persons living with HIV belonging to a group recommended for vaccination may be given the vaccine. Further, counselling and information should be provided to inform individual benefit-risk assessment. *For immunocompromised persons*	

		- Currently, the available data is insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons. - Meanwhile, as the vaccine is not a live virus, the WHO interim recommendations for the use of *COVID-19 Vaccine Moderna* state that immunocompromised persons identified to be in the recommended group for vaccination may be administered with the vaccine. Further, counselling and information should be provided to inform individual benefit-risk assessment. <u>*For persons with autoimmune conditions:*</u> - Persons with autoimmune conditions who have no contraindications may be administered with the vaccine. <u>*For persons who have previously had SARS-CoV-2 infection*</u> - Vaccination should be offered regardless of personal history of SARS-CoV-2 infection. Hence, testing (i.e., viral or serological) for prior infection is not necessary for decision making regarding vaccination. - For vaccines assessed in early 2021, the WHO recommendation was that persons with PCR-confirmed SARS-CoV-2 infection in the last 6 months may choose to delay vaccination given that symptomatic reinfection within 6 months after an initial natural infection is uncommon. While the WHO maintains this recommendation for recently evaluated vaccines in the context of limited supply, they have noted additional recommendations that in settings where variants of concern are circulating, earlier immunization after natural infection may be advisable due to higher risk of symptomatic reinfection.	

		- The updated WHO recommendation is consistent with the updated DOH guidelines (Department Memorandum 2021-0175) which states that individuals who have previously had COVID-19 infection may be vaccinated **after recovery or after completion of treatment**, whether for first or second dose, without restarting the vaccine dose schedule. *For persons with current acute COVID-19* - Individuals with acute PCR-confirmed COVID-19 should not be vaccinated until after full recovery from the acute illness and meeting the criteria for discontinuation of isolation. *For persons who previously received passive antibody therapy for COVID-19* - Currently, there are no data on the safety or efficacy of vaccination in individuals who have received monoclonal antibodies or convalescent plasma as treatment for COVID-19. - Vaccination should be deferred for at least 90 days to avoid interference of the antibody therapy with the immune response elicited by vaccination. **HTAC Judgment:** Based on short-term outcomes, *COVID-19 Vaccine Moderna* possesses most of the characteristics desired by key stakeholders.	
6. Responsiveness to equity	*How will the COVID-19 Vaccine Moderna and its use impact pre-COVID-19 and*	*COVID-19 Vaccine Moderna* demonstrated efficacy in preventing symptomatic COVID-19 in older adults aged 65 years and above and individuals with comorbidities. *COVID-19 Vaccine Moderna* can be stored at normal freezing storage	Ideally, health interventions can be fairly adopted and distributed/ implemented for

	COVID-generated health and socioeconomic inequities? *Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the COVID-19 Vaccine Moderna?*	conditions (-25 to -15 degrees Celsius) for 7 months and protected from light. Further, once thawed, the vaccine can be stored at normal cold storage conditions for 30 days and protected from light. With its logistical requirements, this will make vaccine distribution potentially more feasible. **HTAC Judgment:** Its non-stringent logistic requirements (i.e., -25 to -15 degrees Celsius), *COVID-19 Vaccine Moderna* will make the distribution potentially more feasible. The COVE trial has limited data among Asians. Meanwhile, the trial excluded pregnant and breastfeeding women, and persons who were immunocompromised, thus, there is no data for these special populations (Baden et al., 2021 Protocol). Nevertheless, the WHO currently recommends vaccinating these special populations on the condition that they are included in the group recommended for vaccination (e.g., health workers, high risk for COVID). Likewise, the EMA also allows vaccination of these special populations given that the decision is made in close consultation with a healthcare professional after considering the benefits and risk.	eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

Appendix 1. Evidence for criterion 2 - Clinical Efficacy and Safety

Evidence from Phase I to III trials were reviewed on the efficacy. Meanwhile, for the assessment of safety, evidence from both trials and available real world data from published reports, global safety reports, EMA, and US CDC were reviewed. We also reviewed evidence of neutralization against COVID-19 new variants of concern. Appendix 1 is subdivided into the following sections:

- *Evidence from trials*
- *Real world data*
- *Evidence of neutralization against new variants of concern*

EVIDENCE FROM TRIALS

As with evidence from trials, there are six ongoing trials using *COVID-19 Vaccine Moderna*, all of which are being conducted in the US:

- NCT04813796: an ongoing Phase I dose-ranging study of mRNA-1283 and mRNA-1273 among healthy adults aged 18-55 years across the United States. This trial was extended to include adults aged >56 years old. Results for the 18-55 years old subgroup were published in Jackson et al., 2020 while the results of the >56 years old subgroup were published in Anderson et al., 2020.
- NCT04405076: a Phase II trial in non-pregnant adults, aged 18 years and older in the US (50 mcg or 100 mcg versus placebo, 2-dose regimen, 28 days apart). Results of this trial were published in Chu et al., 2021.
- NCT04796896 (KidCOVE): a Phase II/III placebo-controlled trial in children aged 6 months to 11 years old in the US (2-dose regimen, 28 days apart). This is an ongoing trial and no interim results have been published.
- NCT04649151(TeenCOVE): a Phase II/III placebo-controlled trial in children aged 12 to 17 years old in the US (2-dose regimen, 28 days apart. The results of this trial are still unpublished.
- **NCT04470427 (COVE):** is an ongoing Phase III study of mRNA-1273 among 30,351 participants aged 18 years and older in 99 centers across the United States (2-dose regimen, 28-days apart). Interim result of this trial was published in Baden et al. 2021.
- NCT04860297: an ongoing Phase IIIb open-label, single arm study in adult transplant recipients and in healthy adults across the United States (2-dose regimen, 28 days apart). This is an ongoing trial and no interim results have been published.

Of these, there are currently three published manuscripts reporting their trials. Two of these published trials were interim results from the Phase I trials: Jackson et al. (2020) and Anderson et al. (2020). The third document that was reviewed was the published interim results from the Phase III clinical trial by Baden et al. (2020). Meanwhile, evidence from the Phase II clinical trial was taken from the US FDA Briefing Document on *COVID-19 Vaccine Moderna* as results from this trial have not yet been published in a peer-reviewed journal.

PHASE I TRIALS

Study characteristics (Jackson et al., 2020; Anderson et al., 2020)

The Phase I trial was a dose-escalation, open-label trial that evaluated the safety and immunogenicity of *COVID-19 Vaccine Moderna* in participants 18 years and above at

different doses: 25 mcg, 100 mcg, and 250 mcg for participants 18 to 55 years of age; and, 25 mcg and 100 mcg for participants ≥56 years. The results of the trial were published in two separate manuscripts: Jackson et al (2020), which reported the results in participants aged 18 to 55 years old (N=45); and, Anderson et al (2020), which reported the results in older adults aged 56 years and above (N=40). In the Anderson et al. (2020) trial, participants were divided into four subgroups according to age group (56-70 or ≥ 71 years old) and dose (25 or 100 mcg). In both trials, the participants received two doses of the vaccine, 28 days apart.

Data for safety that were collected were solicited local and systemic adverse events 7 days after each vaccination, and unsolicited adverse events collected from the time of each vaccination through 28 days after each vaccination. As for the immunogenicity responses elicited by the vaccine, the trial looked into the (1) SARS-CoV-2 binding antibody responses against SARS-CoV-2 spike-derived ectodomain (S2-P) and the receptor binding domain measured by ELISA; (2) vaccine-induced neutralizing response assessed by pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) and by live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRNT) assay; and, the (3) T-cell responses against the spike protein measured by an intracellular cytokine–staining assay.

Key Findings

Immunogenicity data from participants, 18 to 55 years (Jackson et al., 2020)

For the Phase I trial, 102 individuals were screened for eligibility but only 45 participants were allocated to one of three cohorts: 25 mcg, 100 mcg, or 250 mcg dose vaccine. There were 15 study participants in each cohort, all of whom will be followed for 1 year after the second dose. Results reported in Jackson et al (2020) were obtained from baseline to day 57.

Results from the trial suggest that seroconversion occurred at all doses on day 15 or 14 days after dose 1. Seroconversion was defined by the trial as an increase in antibody titers by a factor of 4 from the baseline geometric mean titer. Seroconversion in all participants in all subgroups was observed by day 15. Generally, SARS-CoV-2 antibody titers peaked at day 43 or 14 days after dose 2 but had a slight decrease when measured at day 57. This occurred for the antibody responses against S-2P and RBD at all doses except for the anti-S-2P at the 250 mcg dose. The same trend can be observed for the neutralizing response as measured by PsVNA where the geometric mean response peaked at day 43 but had a slight drop at day 57. Immunogenicity data of antibody response and neutralizing responses obtained from participants aged 18 to 55 years are found in Table 1.1 and 1.2, respectively.

T-cell responses against the spike protein were also measured but only responses induced by the 25 mcg and 100 mcg dose were reported. Both doses were able to elicit CD4 T-cell responses producing cytokines upon stimulation with SARS-CoV-2 S-peptide pools. Low levels of CD8 T-cell responses to S-2P were detected after the

second vaccination in the 100 mcg dose group. The authors did not describe the results for the 25 mcg dose group.

Table 1.1. Phase I trial data on the SARS-CoV-2 binding antibody response against S-2P and the receptor binding domain as measured by ELISA in participants 18 to 55 years of age.

Days after vaccination	25 mcg dose n = 15	100 mcg dose n = 15	250 mcg dose n = 15
	Geometric Mean Titer (95% CI)	Geometric Mean Titer (95% CI)	Geometric Mean Titer (95% CI)
ELISA anti-S-2P			
Day 1	116 (72 to 187)	131 (65 to 266)	178 (81 to 392)
Day 15	32,261 (18,723 to 55,587)	86,291 (56,403 to 132,016)	163,449 (102,155 to 261, 520)
Day 43	379,764 (281,597 to 512, 152)	811,119 (656,336 to 1,002,404)	994,629 (806,189–1,227,115)
Day 57	299,751 (206,071 to 436,020)	782,719 (619,310 to 989,244)	1,192,154 (924,878–1,536,669)
ELISA anti-receptor-binding domain			
Day 1	55 (44–70)	166 (82–337)	576 (349–949)
Day 15	6567 (3651–11,812)	34,073 (21,688–53,531)	87,480 (51,868–147,544)
Day 43	233,264 (164,756–330,259)	558,905 (462,907–674,810)	644,395 (495,808–837,510)
Day 57	183,652 (122,763–274,741)	371,271 (266,721–516,804)	582,259 (404,019–839,134)

Table 1.2. Phase I trial data on the SARS-CoV-2 neutralization geometric mean response (GMR) as measured by pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) and live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRNT) assay in participants 18 to 55 years of age.

Days after vaccination	25 mcg dose n = 15	100 mcg dose n = 15	250 mcg dose n = 15
	Geometric Mean Response (95% CI)	Geometric Mean Response (95% CI)	Geometric Mean Response (95% CI)
PsVNA ID_{50}			
Day 1	10	10	10
Day 15	14.5 (9.8–21.4)	23.7 (13.3–42.3)	26.1 (14.1–48.3)

Day 43	112.3 (71.2–177.1)	343.8 (261.2–452.7)	332.2 (266.3–414.5)
Day 57	80.7 (51.0–127.6)	231.8 (163.2–329.3)	270.2 (221.0–330.3)
Live virus $PRNT_{80}$			
Day 1	4	4	N/A
Day 43	339.7 (184.0–627.1)	654.3 (460.1–930.5)	N/A

Safety data from participants, 18 to 55 years (Jackson et al., 2020)

As for the safety of the vaccine evaluated in the Phase I trial, no serious adverse events were noted and no trial halting rules were met. Across all doses, reports of mild and moderate systemic adverse events were collected after the first dose. The same is true after the second dose, except in the 250 mcg dose group where 21.4% of participants reported at least one severe adverse event. Participants also reported local adverse events after both doses. Severity of local symptoms reported ranged from mild to severe. Common solicited systemic and local adverse events that were reported by more than half the participants included fatigue, chills, headache, myalgia, and pain. None of the participants reported fever after dose 1. However, after dose 2, moderate and severe fever were reported at all dose levels. Safety data obtained from the Phase I trial are found on Table 1.3.

Table 1.3. Phase I trial data on the percentage of participants aged 18 to 55 years experiencing solicited adverse events by severity and vaccine dose.

Severity of symptoms	25 mcg n = 15		100 mcg n = 15		250 mcg n = 15	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Any systemic symptom (%)						
Mild	20.0	30.8	53.3	20.0	26.7	14.3
Moderate	13.3	23.1	13.3	80.0	26.7	64.3
Severe	0	0	0	0	0	21.4
Any local symptom (%)						
Mild	66.7	69.2	73.3	66.7	60.0	50.0
Moderate	0	7.7	13.3	26.7	33.3	42.9
Severe	0	0	6.7	6.7	6.7	7.1

Immunogenicity data from participants, ≥56 years, N=40 (Anderson et al., 2020)

Potent binding antibody responses and neutralization responses were consistently observed in all the participants 14 days after the second dose of vaccine (on day 43). Tables 1.4 and 1.5 summarizes the antibody responses and neutralization responses, respectively.

As reported in the trial, the vaccine elicited the following responses:

- Strong CD4 cytokine response involving type 1 helper T (Th1) cells across all subgroups except ≥71 years who received the 25-µg dose subgroup.
- Cytokine response was lower among those who were ≥71 years of age or older than among those in the other subgroup.
- Type 2 helper T cells (interleukin-4 and interleukin-13) response was minimal regardless of age or dose.
- CD8 T-cell responses to S-2P were observed only at low levels after the second vaccination among the participants in the two age subgroups who received the 100-µg dose.

Table 1.4. Phase I trial data on the SARS-CoV-2 binding antibody response against S-2P and the receptor binding domain as measured by ELISA in participants ≥56 years of age.

Cumulative days after first dose vaccination	**Subgroup 1** *56-70 years old 25 mcg dose N=10*	**Subgroup 2** *56-70 years old 100 mcg dose N=10*	**Subgroup 3** *≥71 years old 25 mcg dose N=10*	**Subgroup 4** *≥71 years old 100 mcg dose N=10*
	Geometric Mean Titer (95% CI)	Geometric Mean Titer (95% CI)	Geometric Mean Titer (95% CI)	Geometric Mean Titer (95% CI)
SARS-CoV-2 binding antibody response against S-2P (using ELISA)				
Day 1 (First dose)	189 (76 to 466)	655 (270 to 1,591	111 (55 to 222)	953 (493 to 1,842)
Day 15 (14 days after first dose)	10,509 (2,841 to 38,868)	55,532 (40,611 to 75,935)	14,837 (6,925 to 31,787)	84,383 (26,977 to 263,943)
Day 29 (Second dose)	17,684 (5,300 to 59,001)	115,831 (73,288 to 183,069)	57,986 (31,452 to 106,905)	203,365 (97,384 to 424,686)
Day 36 (7 days after second dose)	313,720 (160,451 to 613,395)	5,033,017 (1,113,760 to 22,743,909)*	460,094 (272,951 to 775,548)	2,636,979 (1,072,782 to 6,481,893)
Day 43 (14 days after second dose)	476,136 (263,956, 858,874)	1,305,996 (581,138 to 2,934,971)*	303,630 (167,743 to 549,597)	8,091,439 (2,546,249 to 25,712,881)

Day 57 (28 days after second dose)	323,945 (182,202 to 575,958)	1,183,066 (379,698 to 3,686,201)*	1,128,391 (636,087 to 2,001,717)	3,638,522 (1,316,233 to 10,058,130)
SARS-CoV-2 binding antibody response against the RBD (using ELISA)				
Day 1 (First dose)	204 (114 to 365)	223 (64 to 775)	111 (46 to 270)	503 (174 to 1,455)
Day 15 (14 days after first dose)	2,924 (576 to 14,833)	30,981 (15,901 to 60,362)	4,676 (2,236 to 9,777)	25,670 (12,394 to 53,168)
Day 29 (Second dose)	4,841 (1,531 to 15,304)	45,690 (26,314 to 79,330)	15,338 (7,085 to 33,203)	56,343 (35,052 to 90,567)
Day 36 (7 days after second dose)	198,643 (98,719 to 399,707)	1,471,882 (560,108 to 3,867,893)*	160,591 (82,611 to 312,177)	711,752 (368,657 to 1,374,153)
Day 43 (14 days after second dose)	201,496 (115,918 to 350,251)	1,005,639 (445,521 to 2,269,948)*	295,194 (167,293 to 520,878)	694,471 (465,032 to 1,037,111)
Day 57 (28 days after second dose)	78,045 (42,847 to 142,159)	506,364 (235,654 to 1,088,051)*	218,268 (106,743 to 446,314)	453,506 (255,624 to 804,573)

*N=9 since one participant did not receive a second vaccine dose
Acronyms: **ELISA:** Enzyme-linked immunosorbent assay | **RBD**: receptor binding domain

Table 1.5. Phase I trial data on the SARS-CoV-2 neutralization geometric mean response (GMR) as measured by PsVNA, nLuc HTNA, FRNT-mNG, and PRNT in participants ≥56 years of age.

Cumulative days after first dose vaccination	**Subgroup 1** *56-70 years old 25 mcg dose N=10*	**Subgroup 2** *56-70 years old 100 mcg dose N=10*	**Subgroup 3** *≥71 years old 25 mcg dose N=10*	**Subgroup 4** *≥71 years old 100 mcg dose N=10*
	Geometric Mean Response (95% CI)	Geometric Mean Response (95% CI)	Geometric Mean Response (95% CI)	Geometric Mean Response (95% CI)
SARS-CoV-2 neutralization response (PsVNA 614D) ID_{50}				
Day 1 (First dose)	10 (NE)	10 (NE)	10 (NE)	10 (NE)
Day 15 (14 days after first dose)	10 (NE)	11 (9 to 13)	10 (NE)	26 (11 to 60)
Day 29 (Second dose)	10 (NE)	10 (NE)	10 (NE)	16 (10 to 26)

Day 36 (7 days after second dose)	79 (47 to 135)	289 (164 to 507)*	121 (69 to 211)	310 (202 to 475)
Day 43 (14 days after second dose)	116 (66 to 205)	402 (289 to 560)*	112 (67 to 188)	317 (198 to 508)
Day 57 (28 days after second dose)	92 (45 to 188)	324 (212 to 496)*	86 (44 to 171)	242 (147 to 399)
SARS-CoV-2 neutralization response (PsVNA 614G) ID_{50}				
Day 43 (14 days after second dose)	-	1,878 (1,259 to 2,801)*	-	1,456 (895 to 2,368)
SARS-CoV-2 neutralization response (nLuc HTNA) ID_{50}				
Day 1 (First dose)	-	20 (NE)	-	20 (NE)
Day 29 (Second dose)	-	21 (18 to 25)	-	24 (18 to 32)
Day 43 (14 days after second dose)	-	530 (337 to 835)*	-	391 (235 to 649)
SARS-CoV-2 neutralization response (FRNT-mNG) ID_{50}				
Day 1 (First dose)	10 (NE)	10 (NE)	10 (NE)	10 (NE)
Day 29 (Second dose)	19 (11 to 32)	80 (52 to 123)	18 (12 to 29)	39 (18 to 86)
Day 43 (14 days after second dose)	550 (302 to 1,001)	1,425 (980 to 2,072)*	448 (299 to 672)	900 (575 to 1,409)
SARS-CoV-2 neutralization response (PRNT) ID_{80}				
Day 1 (First dose)	-	4 (NE)	-	4 (NE)
Day 43 (14 days after second dose)	-	878 (516 to 1,494)*	-	654 (460 to 930)

*N=9 since one participant did not receive a second vaccine dose
Acronyms: **ID50**: 50% inhibitory dilution | **ID8:** 80% inhibitory dilution | **NE:** not estimable | **PsVNA**: pseudotyped lentivirus reporter neutralization assay | **nLuc HTNA:** Nanoluciferase High-throughput Neutralization Assa**y** | **FRNT-mNG**: focus reduction neutralization test-mNeonGreen | **PRNT:** plaque reduction neutralization test

Safety data from participants, ≥56 years (Anderson et al, 2020)

The authors reported that no serious adverse events were reported, and no prespecified trial-halting rules were met.It was noted that a participant in the 56-70 years age group, 100-mcg subgroup developed paronychia. However, the investigators considered this unrelated to the vaccination.

The authors also noted that local and systemic reactogenicity events occurring after the second dose of the vaccine were predominantly moderate in severity. Details of patients experiencing systemic and local adverse events, reported by age group and severity are presented in Table 1.6.

Table 1.6. Phase I trial data on the percentage of participants aged 56 to 70 and ≥71 years experiencing solicited adverse events by severity and vaccine dose.

Age group	Safety outcome	Percentage of patients experiencing solicited adverse events (95% CI)			
		25 mcg		100 mcg	
		Dose 1	Dose 2	Dose 1	Dose 2
Any systemic symptom					
56-70 yo n = 10	Mild	30 (6.7, 65.2)	50.0 (18.7, 81.3)	30.0 (6.7, 65.2)	33.3 (7.5, 70.1)
	Moderate	20.0 (2.5, 55.6)	10.0 (0.3, 44.5)	0	55.6 (21.2, 86.3)
	Severe	0	10 (0.3, 44.5)	0	0
≥71 yo n = 10	Mild	50.0 (18.7, 81.3)	30.0 (6.7, 65.2)	30.0 (6.7, 65.2)	30.0 (6.7, 65.2)
	Moderate	0	0	0	30.0 (6.7, 65.2)
	Severe	0	0	0	10.0 (0.3, 44.5)
Any local symptom					
56-70 yo n = 10	Mild	50.0 (18.7, 81.3)	40.0 (12.2, 73.8)	80.0 (44.4, 97.5)	66.7 (29.9, 92.5)
	Moderate	0	20.0 (2.5, 55.6)	0	22.2 (2.8, 60)
	Severe	0	0	0	0
≥71 yo n = 10	Mild	60.0 (26.2, 87.8)	50.0 (18.7, 81.3)	80.0 (44.4, 97.5)	60.0 (26.2, 87.8)
	Moderate	0	20.0 (2.5, 55.6)	0	40.0 (12.2, 73.8)

	Severe	0	0	0	0

PHASE II TRIAL *(adults aged 18 years and above, N=600)*

Study characteristics (Chu et al., 2021; US FDA, 2020)

The mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. Of the 600 participants, 300 were 18 to < 55 years old and 300 were 55 years and older. The participants were randomized equally to receive either 2 doses of: 50 mcg of mRNA-1273, 100 mcg of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination. The objectives of the study were to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of binding antibody (bAb) and by neutralizing antibody (nAb) titers at baseline and at various time points after vaccination.

All participants are followed for solicited adverse reactions up to 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Key Findings

Immunogenicity data from participants, ≥18 years and older, N=600

According to the US FDA, the immune response as assessed by bAb and nAb after 2 doses were comparable in the 50 mcg and 100 mcg dose groups. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups. Chu et al., 2021 also noted that both the bAb and nAb were induced by both doses of mRNA-1273 within 28 days after the first vaccination, and rose substantially to peak titers by 14 days after the second vaccination.

Table 1.7 summarizes the bAB response and nAb response of the vaccine at different doses or placebo for the younger age cohort (18 to <55 years). As for the older age cohort (≥55 years), the analysis was further subdivided into three age cutoffs namely ≥55 to <65 years old (i.e, subgroup 2), ≥65 to <75 years old (i.e., subgroup 3), and ≥75 years old age (i.e., subgroup 4). Tables 1.8, 1.9, and 1.10 summarizes the immunogenicity data for these subgroups, respectively.

Table 1.7. Phase II trial data on the SARS-CoV-2 binding antibody response and neutralizing antibody response across ≥18 to <55 years old age group

Cumulative days after first dose vaccination	**Subgroup 1A** *≥18 to <55 years old Placebo*	**Subgroup 1B** *≥18 to <55 years old 50 mcg vaccine*	**Subgroup 1C** *≥18 to <55 years old 100 mcg vaccine*
	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]
SARS-CoV-2 binding antibody response			
Day 1 (First dose)	6.5 (5.9 to 7.1) [n=92]	7.0 (6.3 to 7.8) [n=90]	6.2 (5.7 to 6.7) [n=95]
Day 29 (Second dose)	6.3 (5.7 to 7.0) [n=90]	25.3 (22.5 to 28.4) [n=89]	32.7 (28.8 to 37.1) [n=95]
Day 43 (14 days after second dose)	6.2 (5.6 to 6.8) [n=87]	189 (173-207) [n=84]	239 (221 to 259) [n=94]
Day 57 (28 days after second dose)	6.5 (5.9 to 7.2) [n=84]	146 (132 to 161) [n=84]	181 (164 to 200) [n=87]
SARS-CoV-2 neutralization response, expressed as geometric mean titers			
Day 1 (First dose)	45.6 (NE to NE) [n=92]	46.2 (44.9 to 47.6) [n=90]	45.6 NE-NE [n=95]
Day 29 (Second dose)	47.3 (43.9 to 51.0) [n=90]	184 (148 to 230) [n=89]	273 220-338 [n=94]
Day 43 (14 days after second dose)	45.6 (NE to NE) [n=87]	1733 (1611 to 1865) [n=78]	1909 (1849 to 1971) [n=88]
Day 57 (28 days after second dose)	48.5 (44.4 to 53.0) [n=84]	1613 (1488 to 1747) [n=80]	1692 (1586 to 1805) [n=82]

NE: Not estimable

Table 1.8.Phase II trial data on the SARS-CoV-2 binding antibody response and neutralizing antibody response across ≥55 to <65 years old age group

Cumulative days after first dose vaccination	**Subgroup 2A** *≥55 to <65 years old Placebo*	**Subgroup 2B** *≥55 to <65 years old 50 mcg vaccine*	**Subgroup 2C** *≥55 to <65 years old 100 mcg vaccine*
	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]
SARS-CoV-2 binding antibody response			
Day 1 (First dose)	5.4 (4.8 to 6.0) [n=52]	5.6 (4.9 to 6.4) [n=47]	6.1 (5.2 to 7.2) [n=53]
Day 29 (Second dose)	5.1 (4.5 to 5.8) [n=52]	19.4 (16.4 to 22.9) [n=47]	22.1 (18.0 to 27.3) [n=53]
Day 43 (14 days after second dose)	5.1 (4.5 to 5.8) (n=52)	166 (138 to 200) [n=44]	183 (155 to 216) [n=47]
Day 57 (28 days after second dose)	5.2 (4.6 to 5.9) [n=50]	116 (95.3 to 141) [n=44]	136 (114 to 164) [n=50]
SARS-CoV-2 neutralization response, expressed as geometric mean titers			
Day 1 (First dose)	45.6 (NE to NE) [n=50]	45.6 (NE to NE) [n=44]	45.6 (NE to NE) [n=51]
Day 29 (Second dose)	45.6 (NE to NE) [n=50]	149 (104 to 213) [n=39]	230 [168 to 317] [n=48]
Day 43 (14 days after second dose)	45.6 (NE to NE) [n=50)	1709 (1541 to 1895) [n=27]	1729 (1493 to 2002) [n=34]
Day 57 (28 days after second dose)	45.6 (NE to NE) [n=49]	1557 (1352 to 1793) [n=30]	1701 (1511 to 1914) [n=37]

NE: Not estimable

Table 1.9. Phase II trial data on the SARS-CoV-2 binding antibody response and neutralizing antibody response across ≥65 to <75 years old age group

Cumulative days after first dose vaccination	**Subgroup 3A** *≥65 to <75 years old Placebo*	**Subgroup 3B** *≥65 to <75 years old 50 mcg vaccine*	**Subgroup 3C** *≥65 to <75 years old 100 mcg vaccine*
	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]
SARS-CoV-2 binding antibody response			
Day 1 (First dose)	6.0 (5.2 to 6.9) [n=34]	5.1 (4.4 to 5.9) [n=40]	5.0 (4.3 to 5.8) [n=35]
Day 29 (Second dose)	6.0 (5.1 to 7.0) [n=34]	15.0 (12.5 to 18.0) [n=40]	15.6 (13.1 to 18.6) [n=35]
Day 43 (14 days after second dose)	6.0 (5.0 to 7.1) [n=33]	146 (120 to 177) [n=39]	140 (111 to 177) [n=34]
Day 57 (28 days after second dose)	5.8 (4.9 to 6.9) [n=33]	102 (81.9 to 128) [n=40]	103 (79.7 to 134) [n=34]
SARS-CoV-2 neutralization response, expressed as geometric mean titers			
Day 1 (First dose)	45.6 (NE to NE) [n=31]	45.6 (NE to NE) [n=37]	45.6 (NE to NE) [n=34]
Day 29 (Second dose)	51.0 (40.5 to 64.3) [n=30]	170 (109 to 266) [n=33]	132 (89 to 195) [n=32]
Day 43 (14 days after second dose)	51.0 (40.5 to 64.3) [n=30]	1972 (1900 to 2047) [n=31]	1633 (1367 to 1950) [n=23]
Day 57 (28 days after second dose)	50.3 (41.0 to 61.7) [n=30]	1845 (1737 to 1958) [n=34]	1443 (1177 to 1769) [n=27]

NE: Not estimable

Table 1.10. Phase II trial data on the SARS-CoV-2 binding antibody response and neutralizing antibody response across ≥75 years old age group

Cumulative days after first dose vaccination	**Subgroup 4A** *≥75 years old Placebo*	**Subgroup 4B** *≥75 years old 50 mcg vaccine*	**Subgroup 4C** *≥75 years old 100 mcg vaccine*
	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]	Geometric Mean (95% CI) [n]
SARS-CoV-2 binding antibody response			
Day 1 (First dose)	4.3 (2.7 to 6.9) [n=8]	5.1 (2.9 to 9.1) [n=8]	4.3 (2.3 to 8.3) [n=6]
Day 29 (Second dose)	4.3 (2.7 to 6.8) [n=8]	10.8 (6.5 to 17.9) [n=8]	21.6 (8.0 to 58.1) [n=6]
Day 43 (14 days after second dose)	4.3 (2.7 to 6.9) [n=8]	127 (60.6 to 265) [n=8]	140 (67.6 to 288) [n=6]
Day 57 (28 days after second dose)	4.1 (2.4 to 7.0) [n=8]	84.2 (38.1 to 186) [n=8]	107 (51.7 to 221) [n=6]
SARS-CoV-2 neutralization response, expressed as geometric mean titers			
Day 1 (First dose)	45.6 (NE to NE) [n=8]	45.6 (NE to NE) [n=8]	45.6 (NE to NE) [n=6]
Day 29 (Second dose)	45.6 (NE to NE) [n=8]	173 (47.2 to 635) [n=7]	192 (40.4 to 913) [n=6]
Day 43 (14 days after second dose)	45.6 (NE to NE) [n=8]	1632 (888 to 3000) [n=5]	1650 (1081 to 2520) [n=5]
Day 57 (28 days after second dose)	45.6 (NE to NE) [n=8]	1357 (747 to 2463) [n=6]	1918 (1795-2050) [n=6]

NE: Not estimable

Safety data from participants, ≥18 years and older, N=600

For safety, the US FDA reported the following:

- There were 2 participants in the 100 mcg group who experienced Grade 3 decreases in hemoglobin, but both Grade 3 values were within normal range and not clinically significant.

- As of December 6, 2020, there were 3 severe adverse events (SAEs) reported in the vaccine group:
    - Community acquired pneumonia in a 65-year-old participant 25 days after vaccination,
    - Arrhythmia in a 72-year-old participant after being struck by lightning 28 days after vaccination,
    - Worsening of chronic bradycardia in an 87- year-old participant 45 days after vaccination.

  The US FDA has assessed that none of these SAEs are assessed as related to the vaccine. Further, there were no cases of severe COVID-19 reported in the study.

The authors (Chu et al., 2021) noted that the safety profile of the mRNA-1273 vaccine through 28 days after the last dose was consistent with data previously published for other mRNA vaccines. The vaccine group had more solicited local and systemic symptoms were reported more frequently after mRNA-1273 than placebo, further, were observed to be reported at higher frequencies after the second dose.

PHASE III TRIAL *(adults aged 18 years old and above, N=30,420)*

The trial is a multi-center, randomized, observer-blinded, placebo-controlled phase III trial among adults ≥18 years of age. Of the 30,420 randomized participants, 15,181 received at least one dose of 100 mcg of *COVID-19 Vaccine Moderna* while 15,170 received at least one dose of placebo. Participants included in the safety and efficacy analyses were observed for a median follow-up duration of more than 2 months after the second dose.

Methodology of HTAC Evidence Appraisal

The HTAC's clinical research question elements are as follows:

Population: General and vulnerable population
Intervention: COVID-19 Vaccine Moderna
Comparator: Placebo (Saline) OR Active Control
Outcomes: Vaccine efficacy (VE) and safety (see table below for details)

Table 1.11 Definitions and rating of importance of efficacy outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Vaccine efficacy (VE) against symptomatic COVID-19 after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2: • Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status • Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**CRITICAL** to decision making Subgroup analyses: **IMPORTANT** but not critical to decision-making
VE against Hospitalization due to COVID-19	Hospital admission for the management of COVID-19	**CRITICAL** to decision making
VE against Severe COVID-19 Occurrence after at least dose 1	Symptomatic COVID-19 after dose 1 with the addition of the following clinical manifestations: pneumonia, severe acute respiratory syndrome, multi-organ failure, and death	**CRITICAL** to decision making

	Reference: US FDA	
VE against Severe COVID-19 Occurrence after dose 2	Symptomatic COVID-19 after dose 2 with the addition of the following clinical manifestations: pneumonia, severe acute respiratory syndrome, multi-organ failure, and death *Reference: US FDA*	**CRITICAL** to decision making
VE against symptomatic COVID-19 after at least Dose 1	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 1: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among older adults after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in older adults as defined in the trials: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among population with comorbidities after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in population with comorbidities: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among Asians, after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in Asian population: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against asymptomatic COVID-19	Absence of COVID-19 symptoms but with positive NAAT results	**IMPORTANT** but not critical to decision-making

Table 1.12. Definitions and rating of importance of safety outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Serious adverse events	An adverse event is any undesirable experience associated with the use of a vaccine. The event is serious when the patient outcome is: ● Death ● Life threatening ● Hospitalization (initial or prolonged) ● Disability of permanent damage ● Congenital anomaly/ birth defect ● Required intervention to prevent permanent impairment of damage ● Other serious events which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes *Reference: US FDA*	**CRITICAL** to decision making
Death (All-cause mortality)	Reported deaths regardless of cause	**CRITICAL** to decision making
Systemic reactogenicity (Dose 1)	General systemic reactions to injectable products such as vaccines include nausea/vomiting, diarrhea, headache, fatigue, and myalgia *Reference: US FDA*	**CRITICAL** to decision making
Systemic reactogenicity (Dose 2)		
Local reactogenicity (Dose 1)	Local reaction to injectable products such as vaccines include pain, tenderness, erythema/redness, and induration/ swelling *Reference: US FDA*	**IMPORTANT** but not critical to decision-making
Local reactogenicity (Dose 2)		
Adverse Events, Unsolicited	Any untoward medical occurrence associated with the use of a vaccine in humans, whether or not considered vaccine- related. *Reference: US FDA*	**IMPORTANT** but not critical to decision-making

The risk of bias for each outcome was assessed through Version 1 of the Cochrane risk-of-bias tool for randomized trials (RoB1 tool). Two reviewers independently appraised the risk of bias. Any disagreements between reviewers were resolved through consensus. Quality of evidence was then appraised by two reviewers through the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Approach.

Efficacy and Safety from the Interim Results of Phase III trial

The following efficacy and safety outcomes were considered in the study:

Table 1.13. HTAC outcomes of interest and the corresponding outcomes reported by **Baden et al., 2021**

HTAC outcome of interest	**Matching reported outcome from the *COVID-19 Vaccine Moderna* trial** (Baden et al., 2021)	**Definition of outcome from the *COVID-19 Vaccine Moderna* trial** (Baden et al., 2020)
Efficacy outcomes		
VE against symptomatic COVID-19 (> 14 days after dose 2), PP/mITT	VE against symptomatic COVID-19 starting 14 days after the second injection	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose: ● Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
VE against severe COVID-19	VE against severe COVID-19 starting 14 days after second injection, adjudicated (*PP)*	To be considered severe COVID-19, the following criteria must be met: ● Confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, AND ● any of the conditions: ○ Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR ○ Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR ○ Significant acute renal, hepatic or neurologic dysfunction, OR ○ Admission to an intensive care unit or death. The date of documented severe COVID-19 will be the later date of: ● Date of documented COVID-19, ● Date of eligible symptom for severe COVID-19, defined as the earliest of the first eligible severe symptom is reported The date of eligible symptoms for severe COVID-19 should be within [-14, +28] days of the positive RT-PCR result used in the confirmation of COVID-19. The time to the first occurrence of severe COVID-19 will be calculated as: Time to the 1st occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of randomization +1

VE against severe COVID-19 resulting in hospitalization	VE against severe COVID-19 which lead to hospitalization 14 days after the second dose, PP	To be considered severe COVID-19, the following criteria must be met: ● Confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, AND ● any of the conditions:: ○ Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR ○ Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR ○ Significant acute renal, hepatic or neurologic dysfunction, OR ○ Admission to an intensive care unit or death ● The date of documented severe COVID-19 will be the later date of: ● Date of documented COVID-19, ● Date of eligible symptom for severe COVID-19, defined as the earliest of the first eligible severe symptom is reported The date of eligible symptoms for severe COVID-19 should be within [-14, +28] days of the positive RT-PCR result used in the confirmation of COVID-19. The time to the first occurrence of severe COVID-19 will be calculated as: Time to the 1st occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of randomization +1 The severe COVID-19 case then resulted in hospitalization.
VE against severe COVID-19 resulting in death	VE against severe COVID-19 which lead to death 14 days after the second dose, PP	To be considered severe COVID-19, the following criteria must be met: ● Confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, AND ● any of the conditions: ○ Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR ○ Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR ○ Significant acute renal, hepatic or neurologic dysfunction, OR ○ Admission to an intensive care unit or death ● The date of documented severe COVID-19 will be the later date of: ● Date of documented COVID-19, ● Date of eligible symptom for severe COVID-19, defined as the earliest of the first eligible severe symptom is reported

		The date of eligible symptoms for severe COVID-19 should be within [-14, +28] days of the positive RT-PCR result used in the confirmation of COVID-19. The time to the first occurrence of severe COVID-19 will be calculated as: Time to the 1st occurrence of severe COVID-19 = Date of documented severe COVID-19 – Date of randomization +1 The severe COVID-19 case then resulted in death
Subgroup analysis, by age		
VE against symptomatic COVID-19 (>14 days after dose 2) ≥18 to <65 years old, PP	VE against symptomatic COVID-19 starting 14 days after the second injection in participants aged ≥18 to <65 years old	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose in participants aged 18 to 65 years old: ● Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
VE against symptomatic COVID-19 (>14 days after dose 2) among older adults (≥65 years old), PP	VE against symptomatic COVID-19 starting 14 days after the second injection in participants aged ≥65 years old	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose in participants 65 years and older: ● Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
Subgroup analysis by comorbidity		
VE against symptomatic COVID-19 (>14 days after dose 2) in population with comorbidities, PP	VE against symptomatic COVID-19 starting 14 days after the second injection in participants at risk for severe COVID-19	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose in participants at risk for severe COVID-19: ● Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
Subgroup analysis by age and risk		
VE against symptomatic COVID-19 (>14 days after dose 2), >18 to <65, at risk, P	VE against symptomatic COVID-19 starting 14 days after the second injection in participants aged ≥18 to <65 years old who are at risk for severe COVID-19	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose in participants aged 18 to 65 years old who are at risk for severe COVID-19: ● Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Subgroup analysis by race and ethnicity		
VE against symptomatic COVID-19 (>14 days after dose 2), Asians, PP	VE against symptomatic COVID-19 starting 14 days after the second injection in Asians	The case definition for a confirmed COVID-19 case was defined as: At least TWO of the following systemic symptoms, at least 14 days after the second dose in Asians: ● Fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** ● At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographic evidence of pneumonia; **AND** ● NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR
VE against asymptomatic COVID-19	Not reported	Not reported
Safety outcomes		
Serious adverse events	Serious adverse events	An adverse event (including adverse reaction) is considered serious if, in the view of either the investigator or sponsor it results in any of the following outcomes: ● **Death** - a death that occurs during the study or that comes to the attention of either the investigator during the protocol-defined follow-up period, whether or not it is considered related to the investigational product. ● **Is life-threatening** - AE for which its occurrence places the participant at immediate risk of death. It does not ● include an AE that, had it occurred in a more severe form, might have caused death. ● **Inpatient hospitalization or prolongation of existing hospitalization** - admission to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE. ● **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**- does not include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. ● **Congenital anomaly of birth defect** ● **Medically important event -** important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. (i.e. allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or

		convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
Death (all-cause mortality)	Deaths	A death that occurs during the study or that comes to the attention of either the investigator during the protocol-defined follow-up period, whether or not it is considered related to the investigational product.
Systemic reactogenicity	Solicited systemic adverse reactions	Any of the following events, experienced on the day of each injection and for the 6 days after the day of dosing: ● Headache ● Fatigue ● Myalgia ● Arthralgia ● Nausea/vomiting ● Chills ● Fever
Local reactogenicity	Solicited local adverse reactions	Any of the following events, experienced on the day of each injection and for the 6 days after the day of dosing: ● Injection site pain ● Injection site erythema (redness) ● Injection site swelling/ induration (hardness) ● Axillary (underarm) swelling or tenderness ipsilateral to the side of injection
Severe Adverse events	Severe unsolicited adverse events	Any unsolicited adverse event that prevents the participant's daily activity and requires intensive therapeutic intervention.

Below are the details of the analysis sets used in the Phase III interim analysis as reported in the US FDA report (2021).

Table 1.14 Analysis Set definitions used in the report by US FDA, 2021

Analysis Set	Population
Randomized	All participants who are randomized, regardless of the treatment status during the study.
Full analysis set (FAS)	All participants who received at least one dose of mRNA-1273 or placebo
Modified intention-to-treat (mITT) set	All participants in the FAS who has no immunologic/virologic evidence of SARS-CoV2 infection at day 1, before dose 1
Per-protocol (PP) set	All participants in mITT who received 2 doses
Immunogenicity Subset	All participants in the FAS who had a valid immunogenicity test result prior to the first dose of IP and at least 1 valid result after the first dose.
Solicited Safety Set	All randomized participants who received at least one dose and contributed any solicited AR data.

Safety subset (SS)	All Participants who received at least one dose of mRNA-1273 or placebo

COVID-19 Vaccine Moderna demonstrated vaccine efficacy of 94.1% (95% CI: 89.3 to 96.8) using per-protocol analysis and 93.6% (95% CI: 88.5 to 96.4) using modified intention-to-treat analysis, based on high certainty of evidence. Subgroup analysis by age showed that *COVID-19 Vaccine Moderna* provides adequate protection against symptomatic COVID-19 in participants aged 18 to 65 years old, and ≥65 years old and above, based on high certainty of evidence. Subgroup analysis by comorbidity showed that *COVID-19 Vaccine Moderna* is protective against symptomatic COVID-19 in participants with comorbidity, based on high certainty of evidence. In terms of combined age and risk, the vaccine also showed benefit in preventing symptomatic COVID-19 in participants aged ≥18 to <65 years old who are at risk for severe COVID-19, based on high certainty of evidence.

There were zero events in the vaccine group (N=620) and 5 events in the placebo group (N=689) in Asian participants. Thus, vaccine efficacy for this subpopulation remains to be demonstrated. Additionally, vaccine efficacy after the first dose, before the second dose [VE: **69.5%** (95% CI: 43.5 to 84.5)] is observed to be lower than after the second dose [**94.1%** (95% CI: 89.3 to 96.8)]. Thus, it is advised to complete the intended dosage regimen for *COVID-19 Vaccine Moderna*.

Meanwhile, for its efficacy against severe COVID-19, there were zero events in the vaccine group (N= 14,134) and 30 events in the placebo group (N= 14,073). For severe cases of COVID-19 resulting in hospitalization, there were zero events in the vaccine group (N=14,134) and 9 events in the placebo group (N=14,073). As for severe COVID-19 resulting in ICU admission, there were zero events in the vaccine group (N=14,134) and 2 events in the placebo group (N=14,073). Lastly, for severe COVID-19 resulting in death there were zero events in the vaccine group (N=13,134) and 1 event in the placebo group (N=14,073). Vaccine efficacy against these outcomes therefore, remains to be demonstrated.

As for the safety of *COVID-19 Vaccine Moderna*, relative risks were calculated based on the reported number of participants that experienced adverse events. The relative risk is inconclusive for long term safety outcomes such as solicited serious adverse event [RR: 1.04 (95% CI: 0.78 to 1.39)] , and death / all-cause mortality [RR: 0.86 (95% CI: 0.29 to 2.55)] both based on low certainty of evidence. Further, data on serious adverse events related to study vaccination [RR: 1.50 (95 CI: 0.42 to 5.31)] and withdrawals due to adverse events [RR: 0.62 (95% CI: 0.44 to 0.89)] were also inconclusive.

Meanwhile, for systemic reactogenicity after any vaccination, based on high certainty of evidence, the relative risk in the vaccine group is 1.56 times higher (95% CI: 1.54 to 1.59) than those in the placebo group. In terms of local reactogenicity after any vaccination, based on high certainty of evidence, the relative risk is 3.18

times higher (95% CI: 3.10 to 3.27) in the vaccine group compared to the placebo group. Relative risk for unsolicited severe adverse events is inconclusive [RR: 1.16 times higher (95% CI: 0.96 to 1.39)] based on moderate certainty of evidence.

Overall, the rates of unsolicited adverse events, severe adverse events, withdrawals due to adverse events, serious adverse events, and deaths were generally balanced across treatment groups. As of the safety cutoff date, there were 7 serious adverse events in the vaccine arm and 5 in the placebo arm that were assessed by the study investigator to be related to the study product. Of these, the US FDA considered 3 to be likely related to the vaccine, namely, one case of intractable nausea and vomiting and two cases of facial swelling. Both cases of facial swelling had a history of cosmetic filler injections hence it was possible that the inflammation may have occurred due to the interaction between the immune response and the dermal filler. The US FDA could not exclude the possibility that the vaccine contributed to the other SAEs assessed by the investigator as related such as rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction. There were 3 reports of Bell's palsy in the vaccine arm and 1 report in the placebo arm, with one of the reports in the vaccine arm being a serious adverse event. Both the study investigator and sponsor did not consider this SAE to be related to the study product; however, the US FDA assessed that a causal relationship cannot be excluded.

As of December 3, 2020, a total of 13 deaths were reported in the trial (6 in the vaccine arm and 7 in the placebo arm). The deaths in the vaccine arm were due to cardiopulmonary arrest, myocardial infarction, head trauma, multi-organ failure, suicide, and an unknown cause. The participants who died of cardiopulmonary arrest and of myocardial infarction both were older than 75 years of age and had pre-existing cardiac disease. The cause of the deaths in the placebo group included myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and an unknown cause. According to the FDA, the deaths in the trial represent the rates of death that occur in the general population and specific age groups.

Table 1.15. Summary of findings for efficacy outcomes

EFFICACY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moderna n/N**	**Placebo n/N**	**Effect Size (95% CI)**		
1. Symptomatic COVID-19										
1.1 VE against symptomatic COVID-19 (≥ 14 days after dose 2), PP	Not serious	N/A	Not serious	Not serious	None	11/14,134 (0.08%)	185/14,073 (1.31%)	**VE: 94.1%** (89.3 to 96.8)	⊕⊕⊕⊕ **HIGH**	CRITICAL
Subgroup by age										
1.1.A.1 VE against symptomatic COVID-19 (≥14 days after dose 2) ≥18 to <65 years old, PP	Not serious	N/A	Not serious	Not serious	None	7/10,551 (0.07%)	156/10,521 (1.48%)	**VE: 95.6%** (90.6 to 97.9)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
1.1.A.2 VE against symptomatic COVID-19 (≥14 days after dose 2) among older adults (>65 years old), PP	Not serious	N/A	Not serious	Not serious	None	4/3583 (0.1%)	29/3552 (0.8%)	**VE: 86.4%** (61.4 to 95.2)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
Subgroup by comorbidity										
1.1.B. VE against symptomatic COVID-19 (≥14 days after dose 2) in population with	Not serious	N/A	Not serious	Not serious	None	4/3206 (0.1%)	43/3167 (1.4%)	**VE: 90.9%** (74.7 to 96.7)	⊕⊕⊕⊕ **HIGH**	IMPORTANT

comorbidities, PP										
Subgroup by age and risk										
1.1.C. VE against symptomatic COVID-19 (≥14 days after dose 2), >18 to <65, at risk, PP	Not serious	N/A	Not serious	Not serious	None	2/2155 (0.09%)	35/2118 (1.65%)	**VE: 94.4%** (76.9 to 98.7)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
Subgroup by race and ethnicity										
1.1.D VE against symptomatic COVID-19 (≥14 days after dose 2), Asians, PP	Not Serious	N/A	Serious (P not well represented)	Serious (CI not estimable)	None	0/620 (0%)	5/689 (0.7%)	**VE: 100%** (not estimable)	⊕⊕◯◯ **LOW**	IMPORTANT
1.2 VE against symptomatic COVID-19 (≥ 14 days after dose 2) (Primary Definition), mITT	Not serious	N/A	Not serious	Not serious	None	12/14550 (<0.1%)	185/14413 (1.3%)	**VE: 93.6** (88.5 to 96.4)	⊕⊕⊕⊕ **HIGH**	CRITICAL
2. Severe COVID-19										
2. VE against severe COVID-19 (≥ 14 days after dose 2), PP	Not serious	N/A	Serious (needs longer follow-up)	Serious (CI not estimable)	None	0/14,134 (0%)	30/14,073 (0.2%)	VE: 100% (not estimable)	⊕⊕⊕◯ **MODERATE**	CRITICAL
3. Severe COVID-19 resulting in Hospitalization due to COVID-19										
3. VE against severe COVID-19 resulting in hospitalization due to COVID-19 (≥ 14 days after dose 2), PP	Not Serious	N/A	Serious (needs longer follow-up)	Serious (CI not estimable)	None	0/14,134 (0%)	9/14,073 (<0.1%)	**VE: 100%** (not estimable)	⊕⊕◯◯ **LOW**	CRITICAL

4. Severe COVID-19 Resulting in Death										
5. VE against severe COVID-19 resulting in death (≥14 days after dose 2), PP	Not serious	N/A	Serious (needs longer follow-up)	Serious (CI not estimable)	None	0/14,134 (0%)	1/14,073 (<0.1%)	**VE: 100%** (not estimable)	⊕⊕◯◯ **LOW**	IMPORTANT
5. Asymptomatic COVID-19										
6. VE against asymptomatic COVID-19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

Table 1.16. Summary of findings for safety outcomes

SAFETY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moderna n/N**	**Placebo n/N**	**Effect Size (95% CI)**		
1. Serious adverse events	Not serious	N/A	Serious (needs longer follow-up)	Serious (wide CI)	None	93/15185 (0.6%)	89/15166 (0.6%)	**RR: 1.04** (0.78 to 1.39)	⊕⊕◯◯ **LOW**	CRITICAL
2. Death (All-cause mortality)	Not serious	N/A	Serious (needs longer follow-up)	Serious (wide CI)	None	6/15185 (<0.1)	7/15166 (<0.1)	**RR: 0.86** (0.29 to 2.55)	⊕⊕◯◯ **LOW**	CRITICAL
3. Systemic reactogenicity	Not serious	N/A	Not serious	Not serious	None	12553/15176 (82.7%)	8032/15162 (53.0%)	**RR: 1.56** (1.54 to 1.59)	⊕⊕⊕⊕ **HIGH**	CRITICAL
4. Local reactogenicity	Not serious	N/A	Not serious	Not serious	None	13962/15176 (92%)	4381/15162 (28.0%)	**RR: 3.18** (3.10 to 3.27)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
5. Severe adverse event	Not serious	N/A	Not serious	Serious (wide CI)	None	234/15185 (1.5%)	202/15166 (1.3%)	**RR: 1.16** (0.96 to 1.39)	⊕⊕⊕◯ **MODERATE**	IMPORTANT

Notes:
NA- not applicable, cannot be assessed at the moment

REAL WORLD DATA

Real World Effectiveness against COVID-19

According to a systematic review conducted by the LCPG Group on the current evidence on different COVID-19 vaccines which included *COVID-19 Vaccine Moderna* with the last search for evidence on **17 April 2021,** five studies, all done in the USA, provided real world effectiveness data for *COVID-19 Vaccine Moderna*. These studies were on populations where *COVID-19 Vaccine Moderna or Pfizer-BioNTech COVID-19 Vaccine* was used, and did not report efficacy outcomes separately for each of the vaccine.

- A test negative case control study by Andrejko et al. (pre-print) among the population of California (N = 645) showed the real world vaccine efficacy against COVID-19 15 days after the second dose of an mRNA vaccine to be at 85.7% (95%CI 67.2, 93.9).
- Another prospective cohort study by Thompson et al. (2021) among healthcare workers and frontliners (N = 3,950) reported a higher vaccine efficacy against COVID-19 after at least 14 days after the second dose of an mRNA vaccine at 90% (95%CI 68-97).
- A propensity matched cohort study by Pawlowski et al. (pre-print) (N = 62,138) used data from an electronic health record database in the US reported outcomes of vaccination with *Pfizer-BioNTech COVID-19 Vaccine* and *COVID-19 Vaccine Moderna*. The study did not report the outcomes of each vaccine separately. It demonstrated VE against any PCR-confirmed COVID-19 of 75% (95%CI 67.4 to 81.1) from Day 15 onwards after the first dose; 88.7% (95%CI 68.4 to 97.1) 7 days after the second dose; and, 92.5% (95%CI 70.2 to 99.1%) from 7 to 14 days after the second dose. The VEs against hospital admission (VE = 60% (95%CI 14 to 79) and ICU admission (VE = 18%, 95%CI −140 to 72) could be derived from this study based on the reported relative risks assessed at least 14 days after dose 1. Two deaths were reported in the study, both in the unvaccinated group.
- Another matched cohort study among health care facility residents (N = 25,378) showed 1.1 to 3.8 fewer hospitalization and/or deaths per 100 infected persons per day after vaccination with an mRNA vaccine (Mor et al., 2021).
- Another case study in the United States (N = 1,448, 600) did not report vaccine efficacies but reported that daily cases in the younger age group from 0.2% to 0.05% and from 0.1% to 0.01% in the older age group. Death rates also decreased in older adults aged 71 years old and above (Rhogani et al., 2021).

Meanwhile, a study by Tenforde, et. al evaluated vaccine effectiveness of *Moderna COVID-19 Vaccine* or Pfizer-*BioNTech COVID-19 Vaccine* against COVID-19-associated hospitalization. This multi-hospital evaluation set in the US included patients aged ≥ 65 years old who received RT-PCR or antigen testing for SARS-CoV-2 within 10 days of onset of illness and had onset of symptoms 0-14 days before admission. Those who tested positive for SARS-CoV-2 were classified as

case-patients and those who tested negative were classified as control. Vaccination status were obtained and were categorized as: (1) unvaccinated, (2) single-dose vaccinated <14 days before illness, (3) partially vaccinated , and (4) fully vaccinated.

The prevalence of receipt of *Moderna* (47%) and *Pfizer-BioNTech* (53%) vaccines across the single-dose vaccinated, partially vaccinated and fully vaccinated groups were comparable. The authors noted that receipt of an authorized COVID-19 vaccine was associated with significant protection against COVID-19 hospitalization. Adjusted vaccine effectiveness against COVID-19- associated hospitalization for full vaccination (vs the unvaccinated group) was 94% (95% CI: 49 to 99) and adjusted vaccine effectiveness against COVID-19- associated hospitalization for partial vaccination (vs the unvaccinated group) was 64% (95% CI: 28-82). There was no significant effect for receiving the first dose of a 2-dose COVID-19 vaccine series within 14 days before illness onset (i.e., single-dose vaccinated group). Table 1.17 summarizes the adjusted vaccine effectiveness of included patients per vaccination status category.

Table1.17. Vaccine efficacy among hospitalized adults aged aged ≥65 years old as a function of vaccination status

Vaccination status category of patient (N=417)	**Definition**	**Adjusted vaccine effectiveness among hospitalized adults aged ≥65 years old (vs the unvaccinated group)**
Unvaccinated (n=287)	no receipt of any SARS CoV-2 vaccine before illness onset	
Single-dose vaccinated <14 days before illness (n=49)	Receipt of the first vaccine dose <14 days before COVID-19–like illness onset	3% (95% CI: −94% to 51%)
Partially vaccinated (n=62)	Receipt of 1 dose of a 2-dose vaccination series (Pfizer-BioNTech or Moderna vaccines) ≥14 days before illness onset or 2 doses, with the second dose received <14 days before illness onset**	64% (95% CI: 28% to 82%)
Fully vaccinated (n=19)	Receipt of both doses of a 2-dose vaccine series, with the second dose received ≥14 days before illness onset	94% (95% CI: 49%–99%)

Finally, the authors presented the following limitations of their study:

- Confidence intervals of vaccine efficacy (VE) estimates were wide due to small sample size
- The report is an interim analysis

- Confounding and selection bias cannot be excluded
- Hospitalized adults not geographically representative of the United States
- The design of the study (i.e., case-control) infers protection based on associations between disease outcome and previous vaccination but cannot establish causation
- Duration of adjusted vaccine effectiveness and adjusted vaccine effectiveness for non-hospitalized COVID-19 patients was not assessed.

Real World Safety

Real world safety data on *COVID-19 Vaccine Moderna* was taken from the following sources:

- Living CPG Group Evidence Review on *COVID-19 Vaccine Moderna* (prepublication version, 9 May 2021)
- Two Global Monthly Safety Report from Zuellig Pharma Corporation as the local EUA holder of *COVID-19 Vaccine Moderna* (published 15 February and 15 March 2021)
- EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting highlights (3-6 May 2021)
- US CDC Advisory Committee on Immunization Practices COVID-19 Vaccine Safety Technical (VaST) Work Group presentation on:
  - Thrombosis with Thrombocytopenia Syndrome (TTS) (12 May 2021)
  - Myocarditis (17 May 2021)

LCPG Report

According to a systematic review conducted by the LCPG group on the real world evidence on the effectiveness and safety of the different COVID-19 vaccines which included *COVID-19 vaccine Moderna* with last search on 17 April 2021, real world safety data were detected from US CDC Safety Monitoring report, Vaccine Adverse Event Reporting System (VAERS) report, US CDC Morbidity and Mortality Weekly reports, WHO Database (Vigibase®), and an international registry-registry based study.

- The US CDC released a COVID-19 safety monitoring report covering December 14 to January 13, 2021 covering the first month after the vaccination roll out using Pfizer-BioNTech COVID-19 Vaccine and mRNA-1273. During this period, 13,794,904 vaccine doses were administered (no breakdown based on vaccine types was provided in the report) and 6,994 adverse event reports were received and processed by the Vaccine Adverse Events Reporting System (VAERS) for both vaccines. Majority (90.8%) was classified as non-serious and 9.2% as serious. A total of 113 deaths were reported, 65% of which were among long-term care facility residents. No causal relationship between COVID-19 vaccination and death was established.

- Based on the VAERS report in the US, 258 (18.8%) serious adverse events were noted after the first dose of mRNA-1273. No information was yet available for the outcomes after the second dose. The most frequently reported adverse events were headache (25.3%), chills (19.0%), nausea (16.7%), fatigue (16.6%) and dizziness (16.6%). There was significant reactogenicity after mRNA-1273 vaccination, with injection site pain being the most common symptom.
- The US CDC Morbidity and Mortality Weekly Report (December 14, 2020 to January 13, 2021) reported sixteen cases of anaphylaxis have been confirmed after receipt of the *COVID-19 Vaccine Moderna*.
- The US CDC Morbidity and Mortality Weekly Report (December 21, 2020 to January 10, 2021) estimated that anaphylaxis rate for *COVID-19 Vaccine Moderna* is at 2.5 cases per million doses administered.
- Out of 32,044 vaccinees who received *Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, and COVID-19 Vaccine (ChAdOx1-S [recombinant (COVID-19 Vaccine AstraZeneca),* data from the WHO database (VigiBase®), which includes European, North and South American, and Asian countries, revealed 78 deaths after mRNA-1273 administration, representing 1.23% of all adverse event reports after mRNA-1273.
- An international registry based study (McMahon et al., 2021) on the cutaneous reactions after mRNA vaccination (17% related to Pfizer-BioNTech COVID-19 Vaccine, 83% with mRNA-1273) reported delayed large local reaction being the most common among recipients of mRNA vaccines, followed by local injection site reactions, urticarial eruptions and morbilliform eruptions. Additional less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. It was also observed that most patients with first-dose reactions did not have a second dose reaction. The data included in this study were mainly from the US (98% of cutaneous reactions reported). Other countries with reported cutaneous reactions include Canada, Germany, Israel, Italy, UK, Puerto Rico, and Guam.

Global monthly safety data (Zuellig Pharma Corporation)

Of the 50,061,700 doses of *COVID-19 Vaccine Moderna* distributed, 39,334,706 of which were administered from December 18, 2020 to February 17, 2021 from different countries including the United States and several European countries. The proponent provided two reports - the February 2021 report covering the events/ cases that had occurred for the period December 18, 2020 - January 17, 2021; and, the March 2021 report covering the events/ cases that had occurred for the period January 18, 2020 - February 17, 2021. Table 1.19 summarizes the classification of reported adverse events per data cutoff according to medical confirmation.

Table 1.19. Number of medically and non-medically confirmed adverse events reported per data cutoff.

Parameter	NUMBER OF EVENTS	
	December 18, 2020 - January 17, 2021 *February 15, 2021 report*	**January 18, 2021 - February 17, 2021** *March 15, 2021 report*
Regardless if medically confirmed or non-medically confirmed		
serious adverse events	311	5,094
non-serious adverse events	15,604	40,200
Medically confirmed		
serious adverse events	Not disaggregated	4,615
non-serious adverse events	Not disaggregated	14,268
Non-medically confirmed		
seriou s adverse events	Not disaggregated	479
non-serious adverse events	Not disaggregated	25,932

As shown in Table 1.20, it summarizes the events/ cases based on populations of interest. We note that the two reports had used different age group cutoffs for the elderly. The February 2021 report uses above 65 years old cutoff while the March 2021 report uses the 65 years old and above cutoff.

Table 1.20. Number of events reported per population of interest

Parameter by population of interest	NUMBER OF EVENTS	
	December 18, 2020 - January 17, 2021 *February 15, 2021 report*	**January 18, 2020 - February 17, 2021** *March 15, 2021 report*
Age		
Children	74 (< 18 years old)	172 (< 18 years old)
Elderly	2,633 (> 65 years old)	6,452 (≥ 65 years old)
Frail elderly	-	5,215 (≥ 85 years old)
Pregnant	231*	467

*reported as number of cases

According to the report, no trends or patterns were noted in terms of age, country or in special populations indicating a safety signal. The following narrates the key findings per population of interest:

- **Among children <18 years old:**
  - March 2021 report: There were 172 events in 124 cases. Two cases were tagged as serious:
    - Case 1: A 2-month old was exposed to the vaccine from breast milk and developed hematemesis and coffee ground stool on day 2. Endoscopy revealed stomach ulcers and was treated accordingly. Outcome of the event is unknown as of writing.
    - Case 2: A case of a misclassified patient (i.e., 61-year old).

    The top three frequent events (in terms of MedDRA Preferred Terms) for children < 18 years old were products administered to patients of inappropriate age (111 events), pyrexia (5 events), dizziness, vaccine site reactions and exposure via pregnancy (3 events each).
  - Feb 2021 report: There were 74 events in 60 cases reports of exposure to the vaccine in the population <18 years old. All events were non-serious. Among the 60 cases of exposure to the vaccine, 49 did not report any adverse events.
- **Among the elderly:**
  - March 2021 report: Among the elderly aged ≥ 65 years old, there were 6,452 events in 1,994 case reports. Of these, 1,417 events (22%) were reported as serious representing 473 serious case reports. The top three frequent events (in terms of MedDRA Preferred Terms) for the elderly aged ≥ 65 years old were pyrexia (263 events), pain in extremity (202 events), and fatigue (193 events). If considering only serious adverse events, death (116 events) is the most frequent serious event (in terms of MedDRA Preferred Terms).
  - Feb 2021 report: Among the elderly older than 65 years, there were 2,633 events, 87 of which were considered serious. The three most frequently reported events (in terms of MedDRA Preferred Terms) were headache (138 events), fatigue (117 events) and pyrexia (111 events). If considering only serious adverse events, death (6 events) is the most frequent serious event (in terms of MedDRA Preferred Terms).
- **Among the frail elderly population ≥ 85 years old:**
  - March 2021 report: There were 5,215 events in 1,200 case reports. Of these, 2,566 events in 693 cases were serious. The top three events (in terms of MedDRA preferred terms) reported in this population were death (116 events), dyspnea (93 events), and pyrexia (69 events).
  - Feb 2021 report: Population not reported
- **Among the pregnant population:**
  - March 2021 report: There were 467 events in 436 case reports of which 28 events in 13 cases were tagged serious. Serious case reports included foetal death, bleeding, loss of fetal heartbeat, spontaneous abortion, amniorrhea,

hydrops fetalis and premature labor. Nine of the serious cases related to pregnancy are detailed below.

Table 1.21. Serious pregnancy cases as reported in March 2021 document

Case ID	Time to onset	Gestational Age	Remarks
MOD-2021-018045	Unknown	Unknown	Syndactyly and spine malformations
MOD-2021-011921	Unknown	Unknown	Hypertrophic cardiomyopathy
MOD-2021-021 2855	2 days	Unknown	27-year old experienced malaise and foetal death. Unclear if patient received Moderna or Pfizer vaccine
MOD-2021-006202	Unknown	Early pregnancy	Bleeding started prior to the vaccine. Had history of miscarriage.
MOD-2021-010831	23 days	15 weeks	Loss of fetal heartbeat. History unknown.
MOD-2021-012949	12 days	Unknown	34 year old female with history of miscarriage experienced spontaneous abortion
MOD-2021-016584	Unknown	34 weeks	Amniorrhea (leakage of amniotic fluid)
MOD-2021-011729	24 days	Unknown	Fetal heart rate abnormal-no fetal heartbeat
MOD-2021-007934	1 day	26 weeks	Hydrops fetalis and Premature labour, one day after vaccination

- Feb 2021 report: All events collected from the pregnant population were non-serious and no adverse pregnancy outcomes were reported in any of the cases.

The report also tabulated the events/ cases based on adverse events of special interest (AESI). Of the AESIs, we note the following:

- **Anaphylactic reaction:**
  - March 2021 report: There were 225 cases with reported anaphylactic reaction, 94 of which met the Brighton Collaboration Criteria.
  - Feb 2021 report: There were 55 cases with reported anaphylactic reaction, 19 of which met the Brighton Collaboration Criteria.

  According to the March 2021 report, Moderna will continue to monitor possible allergic reactions and/or anaphylaxis reports as part of its ongoing safety and risk management activities.
- **Bell's palsy/ idiopathic peripheral facial nerve palsy**
  - March 2021 report: During the reporting period, there were a total of 77 events in 76 cases of facial paralysis, 52 of such cases were medically confirmed.
  - Feb 2021 report: Not reported

  As of writing, there is no information yet whether the events were associated with the administration of the vaccine.
- **Guillain-Barré syndrome**
  - March 2021 report: During the reporting period, there were a total of 8 medically-confirmed cases of Guillain-Barré Syndrome.
  - Feb 2021 report: Not reported

  As of writing, there is no information yet whether the events were associated with the administration of the vaccine.
- **Thromboembolism and thrombosis**
  - March 2021 report: During the reporting period, there were 151 events in 131 thromboembolism and thrombosis cases of which 109 were medically confirmed. The top three events were cerebrovascular accident (43 events), pulmonary embolism (27 events), and myocardial infarction (20 events).
  - Feb 2021 report: Not reported

  As of writing, there is no information yet whether the events were associated with the administration of the vaccine.

Table 1.22 Number of cases reported per adverse event of special interest

Parameter by adverse event of special interest (AESI)	**NUMBER OF CASES**	
	December 18, 2020 - January 17, 2021 *February 15, 2021 report*	**January 18, 2020 - February 17, 2021** *March 15, 2021 report*
Acute disseminated encephalomyelitis	-	1 (medically confirmed)
Acute kidney injury	1	24 (including medically and non medically confirmed)
Acute respiratory distress syndrome	-	7 (medically confirmed)

Ageusia and anosmia	40 (including medically and non medically confirmed)	138 (including medically and non medically confirmed)
Appendicitis	-	16 (including medically and non medically confirmed)
Acute aseptic arthritis	114 (arthritis) (including medically and non medically confirmed)	96 (including medically and non medically confirmed)
Aseptic meningitis	-	6 (including medically and non medically confirmed)
Bell's palsy/ idiopathic peripheral facial nerve palsy	-	76 (including medically and non medically confirmed)
Thromboembolism and thrombosis	2 (coagulation disorders) (including medically and non medically confirmed)	131 (including medically and non medically confirmed)
Encephalitis	-	4 (medically confirmed)
Encephalomyelitis	-	13 (medically confirmed)
Fibromyalgia	-	3 (medically confirmed)
Convulsion	-	43 (including medically and non medically confirmed)
Guillain-Barré syndrome	-	8 (medically confirmed)
Acute liver injury	-	2 (medically confirmed)
Multisystem inflammatory syndrome	-	3 (including medically and non medically confirmed)
Myelitis transverse	-	2 (medically confirmed)
Pericarditis / Myocarditis	4 (including medically and non medically confirmed)	21 (including medically and non medically confirmed)
Myocardial infarction	-	34 (including medically and non medically confirmed)
Narcolepsy	-	34 (including medically and non medically confirmed)

Acute pancreatitis	1	8 (medically confirmed)
Postural orthostatic tachycardia syndrome (POTS)	-	2 (medically confirmed)
Pulmonary embolism	1 (medically confirmed)	27 (including medically and non medically confirmed)
Rhabdomyolysis	-	1 (medically confirmed)
Stroke	2 (including medically and non medically confirmed)	82 (including medically and non medically confirmed)
Cutaneous vasculitis	-	4 (including medically and non medically confirmed)
Dermatological events		12 (including medically and non medically confirmed)
Anaphylactic reaction	55 (19 met the Brighton Collaboration Criteria)	225 (94 met the Brighton Collaboration Criteria)

Fatal outcomes were also included in the report. Of the 314 fatal cases, 187 (59.6%) of which occurred in those over 75 years of age, while 64 cases (20.4%) in age 65-74, and 53 (16.9%) in adults under the age of 65. Age was unknown in 10 cases (23.2%). The following narrates the key findings of reported fatal outcomes:

- **Death**
  - March 2021 report: There were 314 cases with fatal outcomes during the reporting period. Of these, 64 deaths were in the 65-74 age group and 187 were in the individuals 75 years old and above. Across all ages, the observed reporting rate of deaths is lower than the calculated expected deaths. Of the 10 cases of sudden deaths, 9 of which were from the elderly group and 7 of those 9 that died had comorbidities.

  - Feb 2021 report: There were 12 cases of fatality during the reporting period, 6 of which occurred in individuals over 65 years old while the rest were unknown. The observed reporting rate of deaths is much lower than the background incidence death rates.

As of writing, there is no information yet whether the events were associated with the administration of the vaccine.

Table 1.23. Number of cases of fatal outcomes reported

	NUMBER OF CASES

Parameter	December 18, 2020 - January 17, 2021 *February 15, 2021 report*	January 18, 2020 - February 17, 2021 *March 15, 2021 report*
Death	12	314
Sudden death	No data	10

EMA PRAC

As a result of the reported unusual blood clots in other COVID-19 vaccines (*AstraZeneca COVID-19 Vaccine* and *Janssen Ad26.COV2.S (COVID-19) Vaccine*), the EMA PRAC has been closely monitoring mRNA vaccines for this adverse event. At the moment, PRAC considers that there is no safety signal for the mRNA vaccines. Extremely low numbers of this adverse event were reported and the frequency is lower than the one occurring in people who have not been vaccinated.

The EMA PRAC is also closely monitoring myocarditis as an adverse event for mRNA vaccines considering reported cases of myocarditis and pericarditis following vaccination with Pfizer-BioNTech COVID-19 Vaccine. Currently, there is no indication that these cases are caused by the vaccine.

US CDC

Thrombosis with Thrombocytopenia Syndrome (12 May 2021)

On May 12, 2021, the US CDC Advisory Committee on Immunization Practices convened to review new scientific data on COVID-19 vaccines and evaluate post-authorization COVID-19 vaccine safety data. From the most recent update of the COVID-19 Vaccine Safety Technical (VaST) Work Group as of May 10, 113 million doses of the *COVID-19 Vaccine Moderna* have been administered in the United States. Upon enhanced monitoring and review of data by the Vaccine Safety Technical (VaST) Work Group in light of the TTS associated with the use of the *Janssen Ad26.COV2.S (COVID-19) Vaccine*, the group assessed that there are still no safety signals identified for cerebral venous sinus thrombosis (CVST) or thrombosis with thrombocytopenia syndrome (TTS) for mRNA vaccines as of May 10. In particular, there have been no confirmed cases of TTS associated with the use of mRNA vaccines. Further, data from the Vaccine Safety Datalink (VSD), a collaboration between the US CDC and nine integrated healthcare organizations, up to April 24, 2021 were also presented. After administration of 3.3 million doses of the *Pfizer-BioNTech COVID-19 Vaccine* and 3.0 million doses of COVID-19 Vaccine Moderna within the VSD, a total of 11 cases of CVST diagnoses were identified; 3 following *Pfizer-BioNTech* vaccination and 8 following *COVID-19 Vaccine Moderna*. Of the 11 cases, 5 were ruled out and the 6 potential CVST incident cases did not present thrombocytopenia. There were no confirmed cases of CVST with thrombocytopenia following mRNA vaccines administered in the VSD and it was assessed that TTS does not appear to be associated with mRNA COVID-19 vaccines.

Myocarditis (17 May 2021)

In a Vaccine Safety Technical (VaST) Work Group session held last 17 May 2021, presentations from the Department of Defense, the Vaccine Adverse Event Reporting System (VAERS), and the Vaccine Safety Datalink (VSD) has presentations on myocarditis following mRNA vaccination. The Veteran's Administration and Clinical Immunization Safety Assessment (CISA) groups also presented their plans for investigation of myocarditis. In the session, VaST concluded that there are relatively few reports of myocarditis following mRNA vaccination. Most of these cases were considered mild and predominantly occur in adolescents and young adults. Cases were more often reported in males than females, following the second dose than after the first dose, and usually within 4 days after vaccination. Based on the data from the US CDC safety monitoring systems, rates of myocarditis reports in the window following vaccination have not differed from baseline rates. However, VaST deems it necessary to inform healthcare providers on reports of myocarditis.

EVIDENCE OF NEUTRALIZATION AGAINST COVID-19 NEW VARIANTS OF CONCERN

Wu et al, 2021

A correspondence to the editor by Wu et al. 2021 presented serum neutralizing activity elicited *COVID-19 vaccine Moderna* against pseudoviruses bearing spike proteins of the original Wuhan-Hu-1 isolate, D614G variant, the B1.1.7, B1.351, P.1, B.1.427/B1.429, B1.1.7+E484K, the 20E [EU1], 20A.EU2, N439K-D614G, and the mink cluster 5 variant. The assay used serum samples collected in eight participants from the phase 1 trial (Jackson et al., and Anderson et al.) 1 week after receiving the second dose .

Results showed that mutations in the B.1.1.7 variant did not significantly affect neutralization activity elicited by the vaccine. Meanwhile, neutralizing antibody titers against the P.1, B1.427/B.1.429, B1.1.7+E484K and the B.1351 variant was reduced by 2.3 to 6.4 times compared to the original Wuhan-Hu-1 isolate. The highest reduction factor (6.4) was observed in the assay against the B1.351 variant. Despite this reduction, the serum samples were still able to neutralize pseudoviruses carrying the B1.351 spike proteins.

With this, it can be concluded that COVID-19 Vaccine Moderna offers similar protection to the B.1.1.7 variant compared to the Wuhan-Hu-1. Protection conferred by the *COVID-19 Vaccine Moderna* against the P.1, B.1.427/B.1.429, and B1.351 variants remains to be determined. These results highlight the importance of continued viral surveillance and evaluation of vaccine efficacy against new variants and may help to facilitate the establishment of correlates of protection.

LCPG Rapid review

According to the LCPG rapid review report dated 02 May 2021 with last search for evidence last 17 April 2021, six studies investigated the efficacy of *COVID-19 Vaccine Moderna* against SARS-CoV-2 variants and mutations of concern. All reported immunogenicity data. No clinical outcomes were available. Three of these studies provided the combined immunologic effects of *Pfizer BioNTech COVID-19 Vaccine* and *COVID-19 Vaccine Moderna* without providing separate outcomes for each. A consistent finding was a reduction in the neutralizing capacity by sera from vaccinated participants but still achieving a level that is effective at neutralizing the variant. One study reported a similar cellular response to the ancestral type and the variants.

Details of the results of the immunologic studies on *COVID-19 Vaccine Moderna* are shown in Table 1.18.

Table 1.18. Results of immunologic studies on *COVID-19 Vaccine Moderna* versus SARS-CoV-2 variants and mutations of concern

Study	Population	Test Used	Results (change in neutralizing capacity versus variant/mutation compared to reference strain)	Other observations	Interpretation of results by Authors
B.1.1.7					
Garcia-Beltran [pre-print]	I: 99 participants C: 1220 pre-pandemic samples	Lentiviral pseudovirus neutralization	2.3-fold reduction		
Woldemiskel [published] (results for combined Pfizer-BioNTech COVID-19 Vaccine and mRNA-1273)	I: 30 participants C: Not reported	Cellular response (CD8+ T-cell depleted PBMC	No significant difference in SFUs/million median titers between ancestral strain and B.1.1.7		T cell responses elicited or enhanced by mRNA vaccines may be able to control variants
Wu [pre-print]	I: 8 participants C: Not reported	VSV based pseudovirus neutralization assay	1.2-fold reduction	decreased titers but still with levels able to neutralize (1/290)	reduced but still significant neutralization against variants
B1.351					
Edara [pre-print]	I: 19 participants C: Not reported	IgG binding GMT	3.8 fold reduction in titers		

		variant neutralization titer (GMT)			
Garcia-Beltran [pre-print] (* 3 variations of the B1.351 studied)	I: 99 participants C: 1220 pre-pandemic samples	Lentiviral pseudovirus neutralization	v1 : 27.1 fold reduction v2 : 20.8-fold reduction v3: 10.2-fold reduction	41.9% had no detectable neutralization of at least 1 version of the B1.351 after 2 doses	
Stomatatos [published] (results for combined Pfizer-BioNTech COVID-19 Vaccine and mRNA-1273)	15 previously infected donors who received 1 or 2 doses of vaccine OR 13 uninfected donors who received 2 doses of vaccine	HIV-1 derived pseudoviral neutralization assay	B1.351 : 3-fold reduction B1.351 242-243 : 10-fold reduction	only 8/13 vaccinated were able to achieve 80% neutralization of the 242-243 strain	significantly lower titers for both strains of the B1.351 compared to Wuhan but still above the set thresholds
Woldemiskel [published] (results for combined Pfizer-BioNTech COVID-19 Vaccine and mRNA-1273)	I: 30 participants C: Not reported	Cellular response (CD8+ T-cell depleted PBMC	No significant difference in SFUs/million median titers between ancestral strain and B1.351		T cell responses elicited or enhanced by mRNA vaccines may be able to control variants
Wu [pre-print]	I: 8 participants C: Not reported	VSV based pseudovirus neutralization assay	6.4-fold reduction	decreased titers but still with levels able to neutralize (1/290)	reduced but still significant neutralization against variants
P.1					
Garcia-Beltran [pre-print]	I: 99 participants C: 1220 pre-pandemic samples	Lentiviral pseudovirus neutralization	4.5- fold reduction		
P.2					
Garcia-Beltran [pre-print]	I: 99 participants C: 1220 pre-pandemic samples	Lentiviral pseudovirus neutralization	2.9- fold reduction		

B.1.429					
Garcia-Beltran [pre-print]	I: 99 participants C: 1220 pre-pandemic samples	Lentiviral pseudovirus neutralization	2.0 fold reduction		
Triple RBD Mutation (E484K+K417N+N501Y)					
Wang [published] (results for combined Pfizer-BioNTech COVID-19 Vaccine and mRNA-1273)	I: 20 participants C: Not reported	HIV-1 pseudotyped neutralization assay	1-3 fold decreased activity	but all titers above the 102 NT50 threshold	

Appendix 2. Evidence for Criteria 3 - Affordability and viability

Cost of Implementing *COVID-19 Vaccine Moderna*

The following cost items were identified in calculating for the total resource requirement in implementing *COVID-19 Vaccine Moderna* to the Philippine government: the *COVID-19 Vaccine Moderna* and vaccine consumables; and operations (recruitment and training of vaccinators). No logistics cost shall be incurred by DOH as end-to-end logistics cost is already included in the unit price per dose of *COVID-19 Vaccine Moderna*. The source of these costs was derived from the DOH - Disease Prevention and Control Bureau's (DPCB) overall vaccine budget plan and the Department of Finance (DOF). Overall, the projected cost of vaccine and consumables, logistics and operations based on the data is Php 18,905,488,006.67. The paragraphs below covered the costing calculation for cost components.

Vaccine and Consumables

The total cost of vaccines and consumables for 6.5M million Filipinos will amount to Php 18,472,154,566.67. This amount takes into account 5% estimated wastage of vaccines and cost of two doses of *COVID-19 Vaccine Moderna*. Vaccine consumables include personal protective equipment (PPE) of the vaccination team and injection devices at 10% estimated wastage.

Logistics

No logistics cost shall be incurred by DOH as end-to-end logistics cost is already included in the unit price per dose of *COVID-19 Vaccine Moderna*.

Operations

Operations cost includes mobilization and hiring costs for vaccine implementation. Since it is projected that 6.5M Filipinos will receive *COVID-19 Vaccine Moderna*, it is assumed that 27,083 vaccinators will be needed for the rollout. Further, the number of supervisors needed is estimated at 9,028, with the assumption that one supervisor is assigned per three vaccinators. The duration of the activity provided by DPCB was 24 days. With a mobilization allowance of Php 500 per day for 24 days, the cost of mobilization of these individuals is estimated to be Php 433,333,440.00. Additional staff may be hired depending on demand, but are charged to augmentation/contingency funds of DOH regional offices at Php 18, 786,556 and are not considered in this costing. Trainings will be conducted through online platforms; hence, it will not incur costs to the government. In total, the operations cost is computed at Php 433,333,440.00. Excluded in the operations cost are the cost of conducting routine RT-PCR tests among vaccination teams, as well as their transportation or any other costs necessary for mobilization, additional hiring of staff, and service delivery.

Table 2.1 presents the resource requirement costs and assumptions in the roll-out of the *COVID-19 Vaccine Moderna* for 6.5 million Filipinos in 2021.

Table 2.1 Resource requirement costs in the roll-out of *COVID-19 Vaccine Moderna* in the Philippines in 2021 (for 6.5M Filipinos)

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	**Php18,472,154,566.67**	For two doses including end-to-end logistics cost, with 5% wastage; consumables include syringes, personal protective equipment *(estimated costs for vaccinating 6,500,000 Filipinos based on identified target vaccinees for this brand)*	DOF DPCB
Logistics	**-**	No logistics cost shall be incurred by DOH as end-to-end logistics cost is already included in the unit price per dose of *COVID-19 Vaccine Moderna*.	DOF
Operations	**Php 433,333,440.00**	This does not include yet cost of their testing, transportation of vaccinators, or any other costs necessary for mobilization and service delivery. Note that the duration of activity provided by DPCB was 24 days. Cost of hiring additional staff (depending on demand) is not considered in this costing. *(estimated costs for vaccinating 6,500,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
TOTAL COST	**Php 18,905,488,006.67**		
TOTAL VACCINATION COST PER INDIVIDUAL	**Php 2,908.54**		

Acronym: **DPCB:** Disease Prevention and Control Bureau | **DOF:** Department of Finance

Based on the projected calculations, the total cost of rolling out vaccination with *COVID-19 Vaccine Moderna* for 6,500,000 Filipinos would amount to Php 18,905,488,006.6 (which translates to Php 2,908.54 per individual). This would entail utilization of 22.92% of the total allocated budget for vaccination to cover 9.29% of the target vaccinees for *COVID-19 Vaccine Moderna* for 2021.

Deployment and Feasibility

The COVID-19 Vaccine Deployment Plan outlines the prioritization of eligible populations in receiving the COVID-19 vaccine which includes *COVID-19 Vaccine Moderna*. For Stage 1 of the Vaccine Deployment Plan of COVID-19 vaccines, 22.8% (24,668,128) of the Philippine population is targeted to receive the vaccine under Priority Eligible Population A. This group includes frontline health workers (1.6% or 1,762,994), indigent senior citizens (3.5% or 3,789,874), senior citizens (5.3% or 5,678,544), indigent populations (12.0% or 12,911,193), and uniformed personnel (0.5% or 525,523). On the other hand, Stage 2 of the Vaccine Deployment Plan will increase coverage to 32.95% of the population that will include teachers and social workers (0.95% or 1,179,097), other government workers (1.66% or 1,728,641), other essential workers (1.63% or 1,690,206), other socio-demographic groups with a significantly higher risk (1.72% or 1,785,000), overseas Filipino workers or OFWs (1.66% or 1,728,641), and other remaining members of the workforce (1.25% or 1,298,729) will be inoculated with the vaccine. Finally, in Stage 3 of the Vaccine Deployment Plan, the remaining Filipinos (67.05% or 73,888,198) will be vaccinated. In terms of the priority areas for the deployment of the COVID-19 vaccine, regions determined to have a higher prevalence would be prioritized for the vaccine rollout (i.e., NCR and Region III – Central Luzon).

In the rollout of the vaccine deployment plan, the logistics involved must be taken into consideration. The required storage temperature for the *COVID-19 Vaccine Moderna* is at -15 to -25 degrees Celsius protected from light. This temperature requirement can be addressed by use of freezers. It is expected that the *COVID-19 Vaccine Moderna* can be widely distributed to facilities with the said equipment; examples of which include tertiary hospitals, Rural Health Units, Municipal Health Offices, and City Health Offices. *COVID-19 Vaccine Moderna* can be accessible at the rural level.

Even though there is anticipated easier and wider distribution brought about by the storage temperature requirements, there is still a need for training on vaccine storage and handling to ensure product integrity across the entire supply chain, and a need to ensure the availability of trained personnel in handling unreported or rare adverse reactions that could occur following vaccination.

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