Evidence Summary on BNT162b2 (*Pfizer-BioNTech COVID-19 Vaccine*) for the prevention of COVID-19

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Prepared by	Health Technology Assessment Council Health Technology Assessment Unit
Contact details	hta@doh.gov.ph

Background

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to more than two 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 national government has been exploring all means to access these vaccines and to prepare the country for its upcoming implementation within the coming months.

On January 14, 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for *Pfizer-BioNTech COVID-19 Vaccine* (BNT162b2). This vaccine is a lipid nanoparticle–formulated, nucleoside-modified RNA (modRNA) encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation. In the US, it has been issued an EUA indication for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

To date, at least 41 countries (US, UK, members of EU, Singapore, among others) have issued an EUA for this product in their respective jurisdictions and have started vaccine implementation. This vaccine has also been listed by the WHO in its Emergency Use Listing and is one of the few COVID-19 vaccines which has already published its Phase III trial interim results.

Basic information on *Pfizer-BioNTech COVID-19 Vaccine* is provided below:

Table 1.1 Characteristics of *Pfizer-BioNTech COVID-19 Vaccine*

International nonproprietary name (INN)	tozinameran
Other name	BNT162b2
Trade name	*Comirnaty*
Manufacturer/s	Pfizer, BioNTech (USA, Germany)
Vaccine platform	mRNA-based vaccine

Dose strength and administration	2 doses, 30 µg vaccine, administered 21 days apart
Route of administration	Intramuscular (IM)
Drug delivery system	Multi-dose vial (MDV) containing 5 doses per vial
Target age group	≥ 16 years old
Storage condition	-80°C to -60°C
Vaccine administration	Must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.
PHL EUA status	Released as of 14 January 2021 *Reference: FDA Press Statement EUA Pfizer-January 14 2021. https://www.fda.gov.ph/wp-content/uploads/2021/01/FDA-Press-Statement-EUA-Pfizer-January-14-2021.pdf*
WHO EUL status	Granted as of 31 December 2020 *Reference: Recommendation for an Emergency Use Listing of COVID-19 mRNA vaccine (Nucleoside modified) Submitted by Pfizer https://extranet.who.int/pqweb/sites/default/files/documents/TAG-EUL_PublicReport_Pfizer_31DEC20.pdf*

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 is produced to present all currently available evidence considered in the assessment of *Pfizer-BioNTech COVID-19 Vaccine*. This assessment follows the HTAC evaluation framework to assess COVID-19 vaccines which consists of 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 Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) *be recommended for emergency use to reduce COVID-19 cases, severe infection, and deaths?*

Recommendation

The HTAC **recommends the emergency use of** *Pfizer-BioNTech COVID-19 Vaccine* (BNT162b2) to reduce the burden of COVID-19 among identified priority groups aged 16 years and older.

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

Criterion	HTAC Judgment
Can *Pfizer-BioNTech COVID-19 Vaccine* significantly reduce the magnitude and severity of COVID-19?	**Yes***. Pfizer-BioNTech COVID-19 vaccine,* with 95% efficacy has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths given sufficient vaccine coverage.
Is *Pfizer-BioNTech COVID-19 Vaccine* safe and efficacious?	**Yes**, it is efficacious for preventing symptomatic COVID-19 based on high certainty of evidence. However, at present, the reported treatment effect of *Pfizer-BioNTech COVID-19 Vaccine* on hospitalized cases due to COVID-19 is still *inconclusive* based on low certainty of evidence. Further, the current evidence on preventing severe cases remains unclear (based on effect size and certainty of evidence) to strongly conclude its benefit for this outcome based on low 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. As with the reported treatment effect of *Pfizer-BioNTech COVID-19 Vaccine,* the long-term safety outcomes are inconclusive based on low to very low certainty of evidence.
Is *Pfizer-BioNTech COVID-19 Vaccine* affordable and feasible to use in a national immunization program (viability)?	**Yes,** it is affordable. The share of the cost to implement the vaccination using the *Pfizer-BioNTech COVID-19 Vaccine* will constitute 31.63% of the total allocated budget for

	vaccination and will cover 30% of the 70 million target vaccinees for 2021. Yes, it is feasible despite challenges in the implementation because of logistical requirements. In addition, 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 *Pfizer-BioNTech COVID-19 Vaccine* reduce out-of-pocket (OOP) expenses of households due to COVID-19?	Based on current evidence, it is uncertain whether *Pfizer-BioNTech COVID-19 Vaccine* will reduce out-of-pocket expenses of households due to COVID-19.
Does *Pfizer-BioNTech COVID-19 Vaccine* possess the characteristics that are desired by key stakeholders? (Social Impact)	**Yes**. Based on short-term outcomes, *Pfizer-BioNTech COVID-19 Vaccine* generally possesses most of the characteristics desired by key stakeholders except for wide and equitable coverage, given the logistical requirements for this vaccine.
Does *Pfizer-BioNTech COVID-19 Vaccine* reduce or not further add to existing inequities in the health system?	**Yes.** *Pfizer-BioNTech COVID-19 Vaccine* reduces inequities due to personal (e.g., age, race/ethnicity) and clinical characteristics (e.g., presence of comorbidities). However, it does not address inequities related to geographical barriers.

Pfizer-BioNTech COVID-19 Vaccine passed the preferred 70% efficacy threshold, reducing the risk of symptomatic COVID-19 with consistent high efficacy observed across age (including 'at-risk' older adults) and groups with co-morbidities. The vaccine likewise passed specifications for short-term safety outcomes, with few reported moderate local and systemic reactions and no serious adverse events or deaths resulting from vaccination, to date. However, a longer follow-up period is needed to establish concrete evidence on the long-term safety outcomes of *Pfizer-BioNTech COVID-19 Vaccine*, duration of protection, as well as its capacity to reduce the occurrence and/or severity of COVID-19.

Though projected costs show the vaccine to be affordable, more data are needed to establish its cost-effectiveness in terms of preventing COVID-19 mortality, lowering hospitalization, and reducing the incidence of asymptomatic cases. Further, current data remains inconclusive concerning its capacity to reduce out-of-pocket expenses.

Nonetheless, the HTAC emphasizes that, based on best available evidence, the clinical benefits such as decreased symptomatic infection outweigh known short-term risks.

The HTAC 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 on potential risks and benefits, and securing of informed consent with regard to receiving the intervention
- 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 P*fizer-BioNTech COVID-19 vaccine*:

- Real-world effectiveness in the Philippine context particularly focused on the following:
    - Overall effectiveness in reducing COVID-19 cases, hospitalizations and deaths and in 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 and 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 other emerging SARS-CoV2 viral strains
- Continuous safety surveillance and monitoring of all adverse events especially severe allergic reactions, Bell's palsy, serious adverse events 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 16 years of age
- Best practices, challenges and barriers in implementation across different localities

Current Evidence on *Pfizer-BioNTech COVID-19 Vaccine*

The table below summarizes the appraisal of available evidence on *Pfizer-BioNTech COVID-19 Vaccine* against the HTAC evaluation framework.

Further, the following appendices are provided herewith for further details on the evidence considered:

Appendix 1. Evidence for criterion 2 - Clinical Efficacy and safety
Appendix 2. Evidence for criterion 3 - Affordability and Viability
Appendix 3. References
Appendix 4. Acknowledgement

Note that a separate report for further details on the evidence for criteria *Social Impact* and *Responsiveness to Equity* shall be published.

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

Evaluation Criteria	Question	Current Evidence	HTAC specification
1. Responsiveness to magnitude and severity	*Can Pfizer-BioNTech COVID-19 vaccine significantly reduce the magnitude and severity of COVID-19?*	As of 18 January 2021, the total number of cases has exceeded more than 95 million cases and breached the 2 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 500,000 cases with total deaths reported at 10,600 as of 29 January 2021. According to the DOH-Epidemiology Bureau data, the young and productive age groups (20-49 years old) have the highest prevalence of the disease. However, the most vulnerable are the senior citizens (>60 years) who have the highest case fatality rate (CFR) at 9.9% and comprise around 80% 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 25%. 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 in terms of arresting the growth of the economy, displacing migrant and local workers, loss of jobs, food insecurity and inadequacy of social safety nets for the poorest and other vulnerable sectors. The lockdowns and community quarantines	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

		have also been shown to have an impact on the mental health of Filipinos and also affected how common Filipino households had to adjust under the new normal, unable to visit and freely enjoy quality time with the members of their families, as captured in some focus group discussions conducted by the HTAC and the HTA Unit. As for the potential impact of the Pfizer-BioNTech COVID-19 vaccine in addressing the current burden of COVID-19 disease: ● A modelling study in the US (Matraj et. al., 2020) showed that a vaccine with at least 95% efficacy can avert approximately 75% of symptomatic infections, and around 75% of deaths at 30% and 20% vaccine coverage, respectively, under an optimal allocation strategy where high-risk groups are prioritized. This model assumed a 20% infection rate and a reproduction number of 3. ● Another simulation study suggests that to extinguish an ongoing epidemic, the vaccine efficacy should be at least 60% for a target coverage of 100% in order to reduce the peak by around 85%. On the other hand, a vaccine with efficacy of at least 80% with a target coverage of 75% may reduce the peak by almost 62%. (Bartsch et al., 2020). ● Locally-contextualized modelling studies are needed for more accurate projection of the potential impact of vaccination along with other interventions under different scenarios that can better inform decision-making.	

		HTAC JUDGMENT: *Pfizer-BioNTech COVID-19 vaccine* has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine coverage.	
2. Clinical efficacy and safety	*What is the efficacy of Pfizer-BioNTech COVID-19 Vaccine in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?*	Currently, there is only one clinical trial (Polack et al., 2020) assessing the efficacy and safety of *Pfizer-BioNTech COVID-19 Vaccine.* This is an ongoing multinational, placebo-controlled, observer-blinded, pivotal phase II/III clinical trial among individuals 16 years of age or older who received 2 doses of *Pfizer-BioNTech COVID-19 Vaccine* or placebo (given 21 days apart). Based on the interim results of this clinical trial: ● For critical efficacy outcomes: ○ Using *Pfizer-BioNTech COVID-19 Vaccine, compared to placebo,* decreases the risk for: - Symptomatic COVID-19 at least 7 days after dose 2 in participants without previous evidence of infection by 95.0% (95% CI: 90.3 to 97.6), [high certainty of evidence] - Symptomatic COVID-19 after at least one dose by 82.0% (95% CI: 75.6 to 86.9), based on high certainty of evidence - Severe COVID-19 after at least one dose exceeding our lower threshold limit (VE: 88.9%, 95% CI: 20.1 to 99.7), [low certainty of evidence]. We note,	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 The following factors were taken into consideration in 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

		the low precision and the lower limit that is below the minimum acceptable vaccine efficacy (50%). ○ *Pfizer-BioNTech COVID-19 Vaccine* shows inconclusive vaccine efficacy against the following: - Hospitalization due to COVID-19 (VE: 100%, 95% CI:-9.9 to 100.0), [low certainty of evidence] - Severe COVID-19 at least 7 days after dose 2 in participants with and without previous evidence of infection (VE: 66.3%, 95% CI: -125.5, 96.3), [low certainty of evidence]. ● For <u>important efficacy outcomes</u>, using ○ *Pfizer-BioNTech COVID-19 Vaccine* decreases the risk for: - Symptomatic COVID-19 at least 7 days after dose 2 in participants without previous evidence of infection <u>among the population with comorbidities</u> by 95.3% (95% CI: 87.7 to 98.8), [high certainty of evidence] - Symptomatic COVID-19 at least 7 days after dose 2 in participants without previous evidence of infection <u>among at-risk older adults (≥</u>65 years old) by 91.7% (95% CI: 44.2 to 99.8), [high certainty of evidence] - Symptomatic COVID-19 after dose 2 <u>among not at-risk older adults</u> (<u>≥</u>65	*Note: Pending legal provision allowing the use of evidence based on Phase III interim results*

		years old, VE: 100%, 95% CI: 29.0 to to 100.0), [moderate certainty of evidence] ● The current trial did not measure the important outcome of efficacy against asymptomatic COVID-19. **HTAC JUDGMENT:** *Pfizer-BioNTech COVID-19 Vaccine* passed the preferred VE threshold against symptomatic COVID-19.	
	What is the duration of protection of Pfizer-BioNTech COVID-19 Vaccine in terms of reducing the incidence and/or severity of COVID-19?	Current interim evidence shows protection against laboratory-confirmed symptomatic COVID-9 infection based on a minimum median follow up period of two months after receiving two doses. Data on the duration of protection will be reassessed as more evidence becomes available. **HTAC JUDGMENT:** Cannot be assessed given the current data.	**Minimum acceptable duration of protection:** confers at least 6 months **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 Pfizer-BioNTech COVID-19 Vaccine?	Based on the same randomized phase II/III clinical trial (Polack et al., 2020) cited above: ● Short-term safety outcomes > Using *Pfizer-BioNTech COVID-19 Vaccine,* compared to placebo, increases the risk for: ● Systemic reactogenicity *(critical outcome)*	Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine.

		- by 1.26 times more (95% CI: 1.21 to 1.31) after dose 1, [high certainty of evidence] - by 2.07 times more (95% CI: 1.97 to 2.17) after dose 2, [high certainty of evidence] ● Local reactogenicity *(important outcome)* - by 6.12 times (95% CI: 5.64 to 6.64) after dose 1, [high certainty of evidence] - by 6.92 times (95% CI: 6.29 to 7.61) after dose 2, [high certainty of evidence] > No hospitalization due to reactogenicity was reported in the clinical trial. ● <u>Long-term safety outcomes</u> > Using *Pfizer-BioNTech COVID-19 Vaccine, compared to placebo shows inconclusive risk for:* ● Serious adverse events (SAEs) after at least one dose [RR: 1.14 (95%: 0.88-1.47)], [low certainty of evidence]. Three SAEs were reported in the vaccine group and were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. Upon review of the US FDA, it was noted that two of these events (i.e., shoulder injury, lymphadenopathy) were considered as possibly related to the Pfizer-BioNTech COVID-19 Vaccine.	**Short term outcomes** (e.g., reactogenicity and allergic reactions): at least 2 months **Long term outcomes** (e.g., serious AEs): at least 1 year *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*

		● Death (all-cause mortality) in participants who received at least one dose (RR: 0.50, 95% CI: 0.09-2.73), [low certainty of evidence]. According to the WHO interim recommendation, a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine is a contraindication to vaccination. In particular, *Pfizer-BioNTech COVID-19 Vaccine* should not be administered to individuals with a known history of severe allergic reaction to polyethylene glycol (PEG) or related molecules as PEG is a component of the vaccine. The US CDC also included those with severe allergic reactions (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine in the list of contraindications. Based on real world data: ● Countries that started the implementation of *Pfizer-BioNTech COVID-19 Vaccine* reported several AEs that were consistent with the clinical trial's interim results. Currently, no deaths reported can be directly linked to the vaccine. ● Records of Vaccine Adverse Events Reporting System (VAERS) of the US CDC showed that after the implementation of *Pfizer-BioNTech COVID-19 Vaccine*, 21 patients experienced severe allergic reactions which led to hospitalization or emergency department visits. **HTAC JUDGMENT:** Short-term safety of Pfizer BioNTech COVID-19 vaccine is acceptable. However,	

		further follow-up data is needed to establish longer-term safety.	
	Does *Pfizer-BioNTech COVID-19 Vaccine* provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy?	The current evidence shows that likely clinical benefits such as the decreased occurrence of symptomatic COVID-19 by 95% outweigh the known short term risks based on data available at the time of evaluation. Evidence on serious adverse events and all-cause mortality is still inconclusive; thus, we cannot determine the benefit/risk profile in terms of long-term safety outcomes. **HTAC JUDGMENT:** PASSED	Favorable benefit/risk profile The benefit of preventing morbidity of at least 50% reduction in the risk of COVID-19 infection far outweighs the reported risk of adverse events *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*
3. Affordability and viability	*Is Pfizer BioNTech COVID-19 Vaccine affordable?*	Based on the projected calculations, the total cost of rolling out vaccination with *Pfizer-BioNTech COVID-19 Vaccine* for 21 M Filipinos in 2021 (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) would amount to about Php 26.09 B. **HTAC Judgment: Yes.** The vaccine is affordable since the budget for the purchase and use of *Pfizer-BioNTech COVID-19 Vaccine* for the target number of vaccinees has been allocated.	Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets

	What are the budget implications of using Pfizer-BioNTech COVID-19 Vaccine?	The total cost of vaccination per individual, which accounts for the unit cost of the vaccine and other costs such as consumables, hauling and storage, and operations, was computed at Php 1,242.41 (DOF, DOH). The potential budget impact of the use of *Pfizer-BioNTech COVID-19 Vaccine* to the national government to cover 21 million Filipinos was calculated at about Php 26.09 billion. It is estimated that 31.63% of the total allocated budget for vaccination will go to 30% of the 70 million total target vaccinees for 2021. **HTAC JUDGMENT:** While the share of the cost of the *Pfizer-BioNTech COVID-19 Vaccine to the total vaccine budget* is higher than the share of its target population *to the total population to be vaccinated, the gap is not too wide.*	The share of the cost to implement the COVID-19 vaccine in 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. **The vaccine unit cost is comparable with those in other ASEAN countries.*

	Does Pfizer-BioNTech COVID-19 Vaccine represent good value for money in terms of: *a. preventing COVID-19 mortality* *b. lowering hospitalization (moderate, severe and critical cases)* *c. lowering the incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases)*	Whether *Pfizer-BioNTech COVID-19 Vaccine* represents good value for money in terms of preventing COVID-19 mortality, lowering hospitalization (moderate, severe, and critical cases), and lowering the incidence of symptomatic (mild) 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:* Yes.** The HTAC deems that the health, economic, and social benefits of the vaccination program using *Pfizer-BioNTech COVID-19 Vaccine* outweigh the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system. There are challenges in the implementation because of logistical requirements.	The health, economic, and social benefits of the vaccination program outweigh the costs. The vaccine is likely cost-effective and represents an efficient allocation of resources Note: A full-blown cost-effectiveness analysis CEA 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	The ultra-cold temperature requirement of the vaccine at -60 to -80 degrees Celsius presents logistical challenges in deploying, storing and maintaining the efficacy/quality of the vaccine especially in rural areas where special freezers are not available. Airplanes	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.

	training of vaccinators; and access of the target population to the health care facility? *Are there plans to overcome significant barriers?*	also need retrofitting to carry dry-ice freezers that will enable deployment to other regions and provinces. More intensive training on vaccine storage and handling is required to ensure product integrity across the entire supply chain. Given the limited logistical capacity of the DOH, the vaccine can only be deployed in tertiary hospitals where special freezers are available. There is also a need to ensure the availability of trained personnel and equipment to manage anaphylaxis which is a rare adverse event linked to the vaccine and other medical events that could occur following vaccination. Plans to address the above barriers have been disclosed (e.g., inventory and procurement of additional ultra-low freezers, working with third-party logistics providers on cold chain, training modules developed and conducted). There is an ongoing survey or inventory of potential vaccinators and deployment of other vaccination team members. **HTAC JUDGMENT**: HTAC notes that there are ongoing preparations in place albeit identified barriers.	
4. **Household financial impact**	*Will Pfizer-BioNTech COVID-19 Vaccine reduce or not add further to the out-of-pocket expenses of Filipino households?*	Based on the interim results from the clinical trial, it is inconclusive whether Pfizer-BioNTech COVID-19 Vaccine can reduce the risk for hospitalization related to COVID-19. PhilHealth data shows that the median amount spent by patients with moderate and severe pneumonia is at	The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

		Php 290,058.50. On the other hand, PhilHealth claims for moderate and severe COVID-19 amounted to a median of Php 143,267.00. Out-of-pocket spending for patients with moderate and severe pneumonia can reach as high as Php 2.6M and Php 5M, respectively. **HTAC JUDGMENT:** Based on the current evidence, it is uncertain whether *Pfizer-BioNTech COVID-19 Vaccine* reduces out-of-pocket expenses of Filipino households due to COVID-19.	
5. Social impact	*Does Pfizer-BioNTech COVID-19 Vaccine possess the characteristics desired by the key stakeholders?* *(i.e., policy- and decision makers, health workers, program managers/implementers, patient groups, CSOs, communities, general public)?* *1) Safety* *2) Efficacy* *3) Availability* *4) Transparency in the regulatory/approval process and information on the vaccines* *5) Cost efficiency to the government* *6) Potential for high and equitable coverage*	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 Pfizer-BioNTech vaccine: 1) Safe and effective – for the general population and for some vulnerable groups like the older population and individuals with comorbidities. - Evidence from the clinical trial shows an acceptable safety profile for known short-term risks and significant efficacy to reduce the risk for symptomatic COVID-19 for the general population and some vulnerable groups such as the older population and individuals with comorbidities.	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

	7) Ease in logistical and implementation requirements *8) Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination* *9) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	2) Underwent a transparent regulatory process of being evaluated and approved by health authorities - Evidence: The Philippine FDA has issued an Emergency Use Authorization for *Pfizer-BioNTech COVID-19 Vaccine*. 3) Potential for high and equitable coverage across the population - Evidence: Due to stringent logistical requirements, the Pfizer-BioNTech COVID-19 Vaccine can only be deployed in tertiary hospitals where special freezers are available.The Pfizer BioNTech COVID-19 vaccine has low potential to be distributed to isolated geographic locations. 4) Ease in logistics and administration - Evidence: The Pfizer-BioNTech COVID-19 Vaccine may only be stored in ultra-cold freezers with a storage requirement of -60 to -80 degrees Celsius. More intensive training on the special storage, handling, and administration of the Pfizer-BioNTech COVID-19 vaccine is required to ensure product integrity across an uninterrupted cold chain. 5) Cost-effective - Evidence: The health, economic, and social benefits of implementing the vaccination program with Pfizer-BioNTech COVID-19 Vaccine outweigh the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption, and unprecedented challenges in the health system. Its cost is within the range of current new vaccines that are also part of the National Immunization Program (NIP).	

		6) Public acceptability - Evidence: The requirements of the public for transparency, accountability, and regularity of procedures have been complied with the issuance of the EUA. 7) Availability of mechanisms to to compensate vaccine recipients for any untoward event following vaccination - Evidence: There has been no official issuance yet but the DOH already announced that all untoward events following vaccination shall be covered by PhilHealth. Likewise, Senate Bill No. 2015 was filed to establish the government vaccine indemnification program and provide funds for such. 8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities - Evidence: The *Pfizer-BioNTech COVID-19 Vaccine* has a vaccine efficacy of 95.3% in the population with comorbidities. For the older population, the *Pfizer-BioNTech COVID-19* Vaccine has a vaccine efficacy of 91.7% for at risk older adults and 100.0% for not at risk older adults. **HTAC JUDGMENT:** *Pfizer-BioNTech COVID-19 Vaccine* possesses most of the characteristics desired by key stakeholders except for wide and equitable coverage, given the logistical requirements for this vaccine.	
6. Responsiveness to equity	*How will Pfizer-BioNTech COVID-19 Vaccine and its use impact pre-COVID and*	*Pfizer-BioNTech COVID-19 Vaccine* has been shown to have an efficacy ranging from 82% to 100% in the general and special populations. There may be	Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible

	COVID-generated health and socioeconomic inequities? *Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of Pfizer-BioNTech COVID-19 Vaccine?*	issues/gaps in access for special and vulnerable populations such as individuals with any confirmed or suspected immunosuppressive or immunodeficient state, including people with HIV infection, pregnant and lactating women, who were excluded in the analysis/trials. As *Pfizer-BioNTech COVID-19 Vaccine* requires ultra-low temperatures of -60 to -80 degrees Celsius, the existing cold chain infrastructure of the Department of Health will only allow the distribution to tertiary hospitals which are mostly available in urban regions and localities (NCR and Region III- Central Luzon) resulting in inequities for rural areas with no specialized freezers and capacity to handle the vaccine. The requirement for two doses may also make compliance problematic for individuals who may have difficulty going to tertiary facilities such as indigents because of transportation costs and the elderly who may be unable to reach the tertiary facilities. **HTAC JUDGMENT**: Due to logistical requirements, *Pfizer-BioNTech COVID-19 Vaccine* worsens inequity related to isolated geographic and disadvantaged locations. The inclusiveness of the trial population makes it possible to address other sources of inequities like personal characteristics (e.g., age, race/ethnicity) and clinical characteristics (e.g., presence of comorbidities).	populations without aggravating existing health inequities especially for vulnerable sectors of our society.

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

Study characteristics

The appraisal of clinical evidence for the *Pfizer-BioNTech COVID-19 Vaccine* was limited to the latest published interim results of one Phase III randomized clinical trial of this vaccine (i.e., Clinical Trial NCT04368728) (Polack et al., 2020; published 31 December 2020) as this was the only published clinical evidence on this vaccine, to date. The trial was supported by BioNTech and Pfizer. The manuscript declared the following: Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript; BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data. Apart from the published trial results, we also referred to other supporting references for some key details on the trial such as the published trial protocol, the US FDA Briefing document, and the Advisory Council on Immunization Practices' (ACIP) Interim Recommendation for this vaccine.

The trial is an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial to study the efficacy and safety of the *Pfizer-BioNTech COVID-19 Vaccine* candidate involving 43,548 patients from six countries. The participant inclusion criteria of the study were as follows: adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection were deemed eligible. On 6 October 2020, the protocol was amended to include children 12-15 years old. Meanwhile, the trial excluded individuals with medical history of COVID-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition. Participants assigned to the intervention group were given 2 doses of 30 µg of the *Pfizer-BioNTech COVID-19 Vaccine*, intramuscularly, 21 days apart. Participants assigned in the placebo group were given 2 doses of 0.3 mL saline, intramuscularly, 21 days apart. For this interim analysis, efficacy and safety outcomes were observed for a median follow up of 2 months. The primary and secondary outcomes of interest in the trial are as follows:

- *First primary efficacy endpoint:* Efficacy of the *Pfizer-BioNTech COVID-19 Vaccine* against *confirmed COVID-19* with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose
    - *Confirmed COVID-19 defined as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification-based testing*
- *Second primary efficacy endpoint:* Efficacy of the *Pfizer-BioNTech COVID-19 Vaccine* against confirmed COVID-19 with onset at least 7 days after the second dose in participants with and participants without evidence of prior infection
- *Secondary efficacy endpoin*t: Efficacy of the *Pfizer-BioNTech COVID-19 Vaccine* against severe COVID-19
    - *severe COVID-19 defined as confirmed COVID-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction, admission to an intensive care unit or death*
- *Primary safety endpoint:* Solicited, specific, local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo as prompted by an electronic diary in a subset of participants
- *Primary safety endpoint:* Unsolicited adverse events through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose

Vaccine efficacy (VE) was calculated using the formula: 100 x (1-Incidence Rate Ratio (IRR)) wherein IRR is the ratio of the cases of COVID-19 per 1000 person-years in the intervention arm to the cases of COVID-19 per 1000 person-years in the placebo arm.

Generally, per protocol analysis was utilized for all outcomes except for VE against symptomatic COVID-19 after dose 1, VE against severe COVID-19 after dose 1, serious adverse events, and death (all-cause mortality). Polack et al, utilized intention-to-treat (ITT) for serious adverse events. ITT was also used by the reviewers to compute for the relative risk of all-cause mortality. Meanwhile, Polack et al. used a modified ITT (mITT) to analyze VE against symptomatic COVID-19 after dose 1 and VE against severe COVID-19 after dose 1. The modified ITT population included all participants aged 12 years and above who received at least one dose of the vaccine or placebo.

Methodology

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

Population: General and vulnerable population

Intervention: Pfizer-BioNTech COVID-19 Vaccine

Comparator: Placebo (Saline)

Outcomes: Vaccine efficacy (VE) and safety (see table below for details)

Table 2.1 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
VE against Hospitalization due to COVID-19 (Data not reported)	Hospital admission for the management of COVID-19	**CRITICAL** to decision making
VE Severe COVID-19 Occurrence after at least 1 dose	Symptomatic COVID-19 after dose 1 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 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 1 dose	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 asymptomatic COVID-19	Absence of COVID-19 symptoms but with positive NAAT results	**IMPORTANT** but not critical to decision-making

Table 2.2 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)		

The risk of bias for each outcome was assessed through Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2 tool). Two reviewers independently appraised the risk of bias. Any disagreements between reviewers were resolved through consensus. After which, quality of evidence was appraised by two reviewers through the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Approach.

Appraisal of findings

The interim results covered data gathered from 27 July 2020 to 14 November 2020. Overall, there were 43,448 participants enrolled in the trial across six countries (USA, Argentina, Brazil, South Africa, Germany, and Turkey). Of these, 21,720 participants were assigned to receive the *Pfizer-BioNTech COVID-19 Vaccine* and 21,728 participants were assigned to receive placebo. The participants were mostly White at 82.9%. Asians comprised 4.3% of the study population while Native Hawaiian or other Pacific Islanders comprised 0.2% of the study population. More than half (57.8%) of the study population was 16-55 years old while 42.2% was older than 55 years old.

Of the eight efficacy outcomes and four safety outcomes of interest to the HTAC, the current trial has measured and reported all of the outcomes except for VE against asymptomatic COVID-19. Below are the outcomes measured and reported by the trial and the matching outcomes of interest in our research question:

Table 2.3 HTAC outcomes of interest and the corresponding outcomes reported by Polack et al., 2020

HTAC outcome of interest	**Matching reported outcome from the *Pfizer-BioNTech COVID-19 Vaccine* trial** *(Polack, et al., 2020)*	**Definition of outcome from the *Pfizer-BioNTech COVID-19 Vaccine* trial** *(Polack, et al., 2020)*
Efficacy outcomes		
VE against symptomatic COVID-19 after dose 2	VE against COVID-19 occurrence at least 7 days after the second dose in participants without evidence of previous infection	COVID-19: Presence of at least one of the following symptoms: fever, new or increased cough, new of increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during symptoms or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification-based testing (NAAT). COVID-19 in subjects with no evidence of previous infection ≥7 days after dose 2
VE against hospitalization due to COVID-19	Not reported	Not reported
VE against severe COVID-19 after at least dose 1	Vaccine Efficacy of Severe COVID-19 Occurrence after Dose 1	Severe COVID-19: COVID-19 symptoms and the following: respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction, admission to an ICU, or death First severe COVID-19 occurrence in subjects without evidence of previous infection with onset at any time after dose 1

VE against severe COVID-19 after dose 2	Vaccine Efficacy of Severe COVID-19 Occurrence after ≥7 days after dose 2	Severe COVID-19: COVID-19 symptoms and the following: respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction, admission to an ICU, or death First severe COVID-19 occurrence in subjects without evidence of previous infection ≥7 days after dose 2
VE against symptomatic COVID-19 after at least 1 dose	Efficacy of BNT162b2 against Covid-19 after the First Dose	COVID-19: Presence of at least one of the following symptoms: fever, new or increased cough, new of increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during symptoms or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification-based testing (NAAT). COVID-19 in subjects with no evidence of previous infection after dose 1
VE against symptomatic COVID-19 after dose 2 in older adults	Vaccine Efficacy Subgroup (≥65 years old) in Participants without Evidence of Infection before 7 Days after Dose 2	COVID-19 in subjects aged ≥ 65 years old with no evidence of previous infection ≥7 days after dose 2
VE against symptomatic COVID-19 after dose 2 in population with comorbidities	Vaccine Efficacy from 7 Days after Dose 2 by Underlying Comorbidities among Participants without Evidence of Infection Prior to 7 Days after Dose 2	COVID-19 in subjects with underlying comorbidities with no evidence of previous infection ≥7 days after dose 2 Underlying comorbidities: Participants with at least one of the Charlson Comorbidity Index categories or obesity (body mass index [BMI] ≥30 kg/m2).
VE against asymptomatic COVID-19	Not reported	Not defined
Safety outcomes		
Serious adverse events	Serious adverse events	Clinical manifestations not defined; serious adverse events unsolicited reports within 6 months after receipt of dose 2
Death (all-cause mortality)	Death	Reported deaths regardless of cause
Systemic reactogenicity	Systemic reactogenicity	Fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain, use of antipyretic medication within 7 days after each vaccination

Local reactogenicity	Local reactogenicity	Pain, redness, swelling at the injection site within 7 days after each vaccination

In the US FDA briefing document, the investigators reported three serious adverse events in the *Pfizer-BioNTech COVID-19 Vaccine* group which were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. Upon review, it is to the opinion of the US FDA that only two of these events were considered as possibly related to vaccine:

- Shoulder injury
  - possibly related to vaccine administration or to the vaccine itself
- Lymphadenopathy involving the axilla contralateral to the vaccine injection site
  - the event was temporally associated and biologically plausible

Meanwhile, it was also noted in the US FDA Briefing document that several serious adverse events were considered unrelated to the vaccine, to wit:

- Deaths
  - Six (2 in vaccine group; 4 in placebo group) of 43,448 enrolled participants (0.01%)
  - All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.
- Appendicitis
  - 12 participants, and numerically higher in the vaccine group: 8 vaccine participants and 4 placebo participants
  - Considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk
- Facial bones fracture
  - Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture
  - Not considered related to study intervention by the investigator

As for the contraindication of the *Pfizer-BioNTech COVID-19 Vaccine*, a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine was noted. In particular, it should not be administered to individuals with a known history of severe allergic reaction to polyethylene glycol (PEG) or related molecules as PEG is a component of the vaccine.

The results of our appraisal of the clinical evidence for the efficacy and safety of the *Pfizer-BioNTech COVID-19 Vaccine* using GRADE approach are shown in *Table 2.4 and Table 2.5*. respectively. Links to the risk of bias appraisal sheets are provided *Table 2.6*. **Discussion on effect size and rating of evidence for each outcome is further elaborated in the next sections.**

Overall, the *Pfizer-BioNTech COVID-19 Vaccine* showed benefit for the following outcomes of interest ranging from 82 to 100%:

- VE against symptomatic COVID-19 after dose 2
- VE against severe COVID-19 after at least 1 dose
- VE against symptomatic COVID-19 after at least 1 dose
- VE against symptomatic COVID-19 after dose 2 in ‘at risk’ older adults
- VE against symptomatic COVID-19 after dose 2 in ‘not at risk’ older adults
- VE against symptomatic COVID-19 after dose 2 in population with comorbidities

Of these outcomes, the reported VE was highest for the prevention of symptomatic COVID-19 after dose 2 in at risk older adults *(important outcome)* at 100% (95% CI: 29.0 to 100.0), followed by VE against symptomatic COVID-19 after dose 2 in population with comorbidities *(important outcome)* at 95.3% (95% CI: 87.7 to 98.8) and VE against symptomatic COVID-19 after dose 2 *(critical outcome)* at 95% (95% CI: 90.3 to 97.6). VE was lowest in symptomatic COVID-19 after at least dose 1 *(critical outcome)* at 82% (95% CI: 75.6 to 86.9). However, two of these outcomes, namely, VE against symptomatic COVID-19 after dose 2 among 'not at risk' older adults *(important outcome)* and VE against severe COVID-19 after dose 1 *(critical outcome)* were noted to have a wide confidence interval of 29.0 to 100.0 and 20.1 to 99.7, respectively. Moreover, the lower limits of the confidence intervals for these two outcomes fell below the minimum acceptable vaccine efficacy threshold set by the HTAC. Hence, both these outcomes were rated serious for imprecision. Nevertheless, the point estimates are generally high for these outcomes.

Meanwhile, the VE against hospitalization due to COVID-19 *(critical outcome)* (VE: 100%, 95% CI: -9.9 to 100) and VE against severe COVID-19 after dose 2 *(critical outcome)* (VE: 66.3%, 95% CI -125.5 to 96.3) were inconclusive based on their confidence intervals.

As for vaccine safety, participants who received the vaccine, compared to those who received placebo, and followed up for a median period of 2 months were noted to have higher risk for systemic reactogenicity *(critical outcome)* by 1.26 more (95% CI: 1.21 to 1.31) after dose 1, and by 2.07 times more (95% CI: 1.97 to 2.17) after dose 2. For local reactogenicity *(important but not critical outcome), the risk was higher* by 6.12 more (95% CI: 5.64 to 6.64) after dose 1, and by 6.92 more (95% CI: 6.29 to 7.61) after dose 2 more, compared to the risk of those who received placebo. The relative risk for critical outcomes, serious adverse events (RR: 1.14, 95% CI: 0.88 to 1.47) and death (all-cause mortality) (RR: 0.50, 95% CI: 0.09 to 2.73) were inconclusive. We noted that the median follow up period of 2 months was deemed insufficient for these outcomes since a longer observation period is needed to observe such events.

Table 2.4. Summary of findings for efficacy outcomes

EFFICACY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies columns 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**	**BNT162b2 n/N (person-time)**	**Placebo n/N (person-time)**	**Effect Size**		
1. VE against symptomatic COVID-19 after dose 2	Not serious	NA	Not serious	Not serious	None	8/17411 (2.214)	162/17511 (2.222)	**VE 95.0%** (90.3 to 97.6)	⊕⊕⊕⊕ **HIGH**	CRITICAL
2. VE against hospitalization due to COVID-19 *(appraisal results of ACIP)*	Not serious	Not serious	Serious [a,b,c]	Serious [d]	None	0/17399 *(not reported)*	5/17495 *(not reported)*	**VE 100.00%** (-9.9 to 100)	⊕⊕◯◯ **LOW**	CRITICAL
3A. VE against severe COVID-19 after at least 1 dose	Not serious	NA	Serious [c]	Serious [e]	None	1/21314 (4.021)	9/21259 (4.006)	**VE 88.9** (20.1 to 99.7)	⊕⊕◯◯ **LOW**	CRITICAL
3B. VE against severe COVID-19 after Dose 2 *(data taken from the US FDA VRBPAC Briefing Document)*	Not serious	NA	Serious [c]	Serious [h]	None	1/18566 (2.333)	3/18733 (2.358)	**VE 66.3%** (-125.5 to 96.3)	⊕⊕◯◯ **LOW**	CRITICAL

4. VE against symptomatic COVID-19 after at least 1 dose	Not serious	NA	Not serious	Not serious	None	50/21314 (4.015)	275/21258 (3.982)	**VE 82.0%** (75.6 to 86.9)	⊕⊕⊕⊕ **HIGH**	CRITICAL
5A. VE against symptomatic COVID-19 after dose 2 in <u>at risk</u> older adults	Not serious	NA	Not serious	Not serious	None	1/2147 (0.281)	12/2109 (0.279)	**VE 91.7%** (44.2 to 99.8)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
5B. VE against symptomatic COVID-19 after dose 2 in <u>not at-risk</u> older adults	Not serious	NA	Not serious	Serious [e]	None	0/1701 (0.227)	7/1771 (0.233)	**VE 100.0** (29.0 to 100.0)	⊕⊕⊕◯ **MODERATE**	IMPORTANT
6. VE against symptomatic COVID-19 after dose 2 in population <u>with comorbidities</u>	Not serious	NA	Not serious	Not serious	None	4/8030 (1.025)	86/8029 (1.025)	**VE 95.3** (87.7 to 98.8)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
7. VE against asymptomatic COVID-19	No data	No data	No data	No data	No data	No data	No data	No data	No data	IMPORTANT

Note/s:

NA- not assessed at this moment/ not applicable

a. The RCT excluded persons with prior COVID-19 diagnosis, pregnant or breastfeeding women, and persons who were immunocompromised. The population included in the RCT may not represent all persons aged ≥16 years.

b. The effect shown is from an analysis of the evaluable efficacy population, with outcomes assessed at least 7 days post dose 2, among persons who received 2 doses, and had no evidence of prior SARS-CoV-2 infection. In an analysis using the all-available efficacy population (including persons who received at least 1 dose, among those with or without evidence of prior infection), 1 hospitalized case occurred among 21,299 persons who received the vaccine, and 14 hospitalized cases occurred among 21,238 persons who received the placebo (RR=0.07; 95% CI: 0.02 to 0.47).

c. Serious concern for indirectness was noted due to the short duration of follow-up in the available body of evidence. Severe COVID-19 cases and COVID-19 cases leading to hospitalization may not have had time to occur in a median 2-month follow-up.
d. Serious concern for imprecision was present due to the small number of events that were observed.
e. There is serious concern for imprecision due to the wide range of the confidence interval.
f. The high risk of bias is attributed to the deviation from the intended intervention.
g. The median follow-up period of 2 months is insufficient to ascertain the accuracy results for the outcome.
h. The confidence interval of the VE/risk ratio crosses the value of no effect.
i. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia).

Table 2.5. Summary of findings for safety outcomes

SAFETY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies columns 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**	**BNT162b2 n/N (% risk)**	**Placebo n/N (% risk)**	**Relative Risk**		
1. Serious adverse events	Not serious	NA	Serious[a]	Serious[b]	None	126/21621 (0.6%)	111/21631 (0.5%)	**1.14** (0.88 to 1.47)	⨁⨁◯◯ **LOW**	CRITICAL
1A. Death (all-cause mortality)	Serious	NA	Serious [d]	Serious [e]	None	2/21621 (0.0%)	4/21631 (0.0%)	**RR 0.50** (0.09 to 2.73)	⨁◯◯◯ **VERY LOW**	CRITICAL
2A. Systemic reactogenicity (Dose 1)	Not serious	NA	Not serious	Not serious	None	2421/4093 (59.1%)	1922/4090 (47.0%)	**1.26** (1.21 to 1.31)	⨁⨁⨁⨁ **HIGH**	CRITICAL

2B. Systemic reactogenicity (Dose 2)	Not serious	NA	Not serious	Not serious	None	2627/3758 (69.9%)	1267/3749 (33.8%)	**2.07** (1.97 to 2.17)	⊕⊕⊕⊕ **HIGH**	CRITICAL
3A. Local reactogenicity (Dose 1)	Not serious	NA	Not serious	Not serious	None	3216/4093 (78.6%)	525/4090 (12.8%)	**6.12** (5.64 to 6.64)	⊕⊕⊕⊕ **HIGH**	IMPORTANT
3B. Local reactogenicity (Dose 2)	Not serious	NA	Not serious	Not serious	None	2748/3758 (73.1%)	396/3749 (10.6%)	**6.92** (6.29 to 7.61)	⊕⊕⊕⊕ **HIGH**	IMPORTANT

Note/s

NA- not assessed at this moment/ not applicable

a. The median follow-up period of 2 months is insufficient to ascertain the accuracy results for the outcome.
b. The confidence interval of the risk ratio crosses the value of no effect.
c. The high risk of bias is attributed to the deviation from the intended intervention.
d. The median follow-up period of 2 months is insufficient to ascertain the accuracy results for the outcome.
e. The confidence interval of the VE/risk ratio crosses the value of no effect.

Table 2.6. Links to Risk of Bias 2 appraisal sheets for Polack et al, 2020

Outcome of Interest	Link to RoB sheets
Efficacy outcomes	
VE against symptomatic COVID-19 after dose 2	https://drive.google.com/file/d/1xGg8J527gMCUoPqRrvnol0VxIFAbh-BD/view?usp=sharing
VE against hospitalization due to COVID-19	Not performed
VE against Severe COVID-19 after at least dose 1	https://drive.google.com/file/d/1xGg8J527gMCUoPqRrvnol0VxIFAbh-BD/view?usp=sharing
VE against Severe COVID-19 after dose 2	https://drive.google.com/file/d/13T0WDMFi1G3tTh0xe0r--VAdRxRvqeg0/view?usp=sharing
VE against death (All-cause mortality)	https://drive.google.com/file/d/1xGg8J527gMCUoPqRrvnol0VxIFAbh-BD/view?usp=sharing
VE against symptomatic COVID-19 after at least dose 1	https://drive.google.com/file/d/1ix6BQlAEcsmPjJtndA8nP8kBPxUPEx9_/view?usp=sharing
VE against symptomatic COVID-19 after dose 2 in older adults	https://drive.google.com/file/d/1h4qUmI8N0em6rAEsO4LhPW9-lB3fP2QF/view
VE against symptomatic COVID-19 after dose 2 in population with comorbidities	https://docs.google.com/document/d/1uStERJnrVOKkHmT6u6f4fLLv2YkmbgSw/edit#
VE against asymptomatic COVID-19	Not performed
Safety outcomes	

Serious adverse events	https://docs.google.com/document/d/1XvnZM2LgphkDa1IVrbnxA7tCu-pTXGNKTN-IFTBtECk/edit
Systemic reactogenicity	https://docs.google.com/document/d/1MUJ5O6vgVTy9YnUyPexp2feThGfWE9E1/edit
Local reactogenicity	https://docs.google.com/document/d/1yzlaVMac_9W0vaFeu5O4iQTZf4NBW1LN/edit?pli=1

The following tables summarize the reported adverse events in countries which started implementing *Pfizer-BioNTech COVID-19 vaccine.*

Table 2.7 Reported All-cause mortality based on Global Vaccine Implementation

Country	Date Reported	Number of Deaths	Total Vaccinated Population	Remarks
Belgium (Federal Agency for Medicines and Health Products, 2021)	14 January 2021	1	34,979 as of 12 January 2021 (Federal Agency for Medicines and Health Products, 2021)	Under investigation if the event is linked to the vaccine ● 5 days after vaccination ● 82 years old with health problems ● Cause of death still unknown
Norway (Norwegian Medicines Agency, 2021)	14 January 2021	23	44,163 as of 14 January 2021 (Norwegian Institute of Public Health, 2021)	Under investigation if the event is linked to the vaccine ● All very frail elderly adults with very serious disease, died shortly after vaccination. ● Conclusion from 13 deaths: common adverse reactions, such as fever, nausea, and diarrhea, may have contributed to fatal outcomes in some of the frail patients
Sweden (Medical Products Agency, 2021)	18 January 2021	8	~147,000 as of 17 January 2021 (Public Health Agency of Sweden, 2021)	Reference report did not mention if the event is linked to the vaccine

Table 2.8 Reported Serious Adverse Events based on Global Vaccine Implementation

Country	Date Reported	Number of cases	Total Vaccinated Population	Serious Adverse Event/s	Remarks
Belgium (FAMHP, 2021)	12 January 2021	1	34,979 as of 12 January 2021 (FAMHP, 2021)	Dizziness, raised blood pressure, contractions of the respiratory muscles with reduced blood oxygen levels and chest pain	Reference report did not mention if the event is linked to the vaccine ● Dizziness, raised blood pressure, contractions of the respiratory muscles with reduced blood oxygen levels and chest pain ● Within 15 minutes after vaccination ● Recovered after treatment
Mexico (Government of Mexico, 2021)	01 January 2021	1	25,798 as of 30 December 2020 (Government of Mexico, 2021)	Encephalomyelitis: Skin rash, seizures, decreased muscle strength and respiratory distress	Under investigation if the event is linked to the vaccine ● 32 years old ● Within 30 minutes after vaccination ● History of allergies
Netherlands (Medicines Evaluation Board, 2021)	14 January 2021	2	~47,000 as of 13 January 2021 (National Institute for Public Health and the Environment, 2021)	Serious allergic reaction (unspecified)	Reference report stipulates that the event is linked to the vaccine ● A known side effect. Patients were treated and recovered quickly and adequately.
Sweden (MPA, 2021)	18 January 2021	37	~147,000 as of 17 January 2021	Complete AV block, Myelosuppression, Lymphadenopathy, Cardiac Arrest, Cardiac Failure, Myocardial Infarction, Asthenia, General physical health deterioration, Anaphylaxis, Anaphylactic shock,	Reference report did not mention if the events are linked to the vaccine

			(Public Health Agency of Sweden, 2021)	Hypersensitivity, Sepsis, Urosepsis, Facial paresis, Motor dysfunction, Syncope, Visual hallucination, Confusional state, Urinary incontinence, Dyspnea, Hyperhidrosis, Hypotension	
United Kingdom (Medicines and Healthcare products Regulatory Agency, 2021)	09 December 2020	2	663,809 as of 20 December 2020 (Government of the United Kingdom, 2020)	Anaphylaxis	Under investigation if the event is linked to the vaccine ● Both had history of allergic reactions and recovered after treatment
United States of America (USA) (Centers for Disease Control and Prevention, 2021)	23 December 2020	21	1,893,360 as of 23 December 2020 (Centers for Disease Control and Prevention, 2021)	Anaphylaxis	Under investigation if the event is linked to the vaccine ● Median age of 40 years old (27-60 years) ● 17 w/ history of allergy or allergic reactions ● 7 w/ history of anaphylaxis (1 after rabies vaccines, 1 after influenza A(H1N1) vaccine) ● Median onset of 13 minutes after vaccination (15 w/in 15 mins, 3 from 15-30 minutes, 3 after 30 minutes) ● 4 hospitalized (3 in ICU), 17 treated in the ER ● Different vaccine lots

Table 2.9. Reported Systemic and Local Reactogenicity based on Global Vaccine Implementation

Country	Date Reported	Number of cases	Total Vaccinated Population	Type of Reaction	Remarks
Sweden (MPA, 2021)	18 January 2021	112	~147,000 as of 17 January 2021 (Public Health Agency of Sweden, 2021)	Systemics: Palpitations, Tachycardia, Vertigo, diarrhea, vomiting, chills, fatigue, feeling cold, feeling hot, generalized edema, malaise, increased HR, decreased appetite, hyperglycemia, hypoglycemia, dizziness, Headache, pyrexia	Reference report did not mention if event is linked to the vaccine
		59		Localized reactions: Lip swelling, oral pruritus, swollen tongue, oral paresthesia, vaccine site erythema, vaccine site pain, vaccine site pruritus, vaccine site warmth, Epistaxis, Pain in extremities, Myalgia, Anosmia	Under investigation if linked to the vaccine
United Kingdom (MHRA, 2021)	23 December 2020	1	663,809 as of 20 December 2020 (Government of the United Kingdom, 2021)	Allergic reaction	Reference report stipulates that the event is linked to the vaccine
USA (CDC, 2021)	23 December 2020	83	1,893,360 as of 23 December 2020 (CDC, 2021)	Allergic reaction: pruritus, rash, itchy and scratchy sensations in the throat, and mild respiratory symptoms	Under investigation if linked to the vaccine ● Median onset: 12 minutes ● 56 had history of allergic reactions
Belgium (FAMHP, 2021)	12 January 2021	9	34,979 as of 12 January 2021 (FAMHP, 2021)	General Conditions/Administration site conditions; Nervous system disorders; Respiratory, thoracic and mediastinal disorders; Gastrointestinal disorders; Skin and subcutaneous tissue disorders; Vascular disorders; Eye disorders; Ear and labyrinth disorders	Under investigation if linked to the vaccine ● 7 were below 65 years old ● 2 cases are still under investigation

Table 2.10 Other Reported Adverse Events based on Global Vaccine Implementation

Country	Date Reported	Number of cases	Total Vaccinated Population	Remarks	Remarks
Netherlands (MEB, 2021)	14 January 2021	~100	~47,000 as of 13 January 2021 (National Institute for Public Health and the Environment, 2021)	Consistent with clinical trial expected reactions. Mostly injection site reaction, fatigue, muscle pain, and headache.	Reference report stipulates that the event is linked to the vaccine
USA (CDC, 2021)	23 December 2020	4,393	1,893,360 as of 23 December 2020 (CDC, 2021)	Unspecified adverse events	Under investigation if linked to the vaccine Adverse events reported to the Vaccine Adverse Events Reporting System from 14 - 23 December 2020

Appendix 2. Evidence for Criteria 3 - Affordability and viability

Cost of Implementing *Pfizer-BioNTech COVID-19 Vaccine*

The following cost items were identified in calculating for the total resource requirement in implementing the *Pfizer-BioNTech COVID-19 V*accine to the Philippine government: the *Pfizer-BioNTech COVID-19 V*accine and vaccine consumables; logistics (hauling, storage, and transport); and operations (recruitment and training of vaccinators). The source of these costs was derived from the DOH - Disease Prevention and Control Bureau's (DPCB) overall vaccine budget plan. Overall, the projected cost of vaccine and consumables, logistics and operations based on the data is Php 26,090,644,000. The paragraphs below will detail the costing calculation for cost components.

Vaccine and Vaccine Consumables

The total cost of vaccines and vaccine consumables for 21 million Filipinos will amount to Php 22,338,936,000.00. This amount takes into account 5% estimated wastage of vaccines and cost of two doses of the *Pfizer-BioNTech COVID-19 Vaccine* for every vaccinee. Vaccine consumables include personal protective equipment (PPE) of the vaccination team and injection devices.

Logistics

In terms of logistics costs, included are hauling costs, and storage and transport costs. For hauling costs, this includes the procurement of 150 ultra-low freezers capable of storing vaccines at -60 degrees Celsius to -80 degrees Celsius, which is estimated to cost Php 300,000,000. For storage and transport, it is planned to be provided by a third-party provider. As of this writing, the DOH Supply Chain Management Office (SCMO) estimated the storage and transport cost at Php 1,980,000,000. Further, in handling of the *Pfizer-BioNTech COVID-19 Vaccine*, thermal containers with dry ice will be utilized. It must be noted however that dry ice was not included in the logistics costing provided. In the absence of ultra-low freezers, thermal containers may be used as temporary storage when consistently re-filled with dry ice. Despite having special thermal containers as alternative, these can only be used as a temporary storage and the vaccines must be re-iced once an ultra-low freezer is available.

Operations

Operations cost includes mobilization, hiring costs, as well as training for vaccine implementation. Since it is projected that 21,000,000 Filipino will receive the *Pfizer-BioNTech COVID-19 Vaccine*, it is assumed that 150,000 vaccinators will be needed for the rollout. Further, the number of supervisors needed is estimated at 50,000, with the assumption that one supervisor is needed per three vaccinators. The duration of the activity provided by DPCB was seven (7) days. With a salary of Php 500 per day for 7 days, the cost of mobilization of these individuals is estimated to be Php 700,000,000. For the training of the vaccinators and supervisors, two days are allotted to train them with a cost of Php 1,200 per head per day. We note that in the training costing, DPCB included an input value of 121,545 on top of the total number of trainees (i.e., 200,000) multiplied by the cost of training per day. This input value is currently being validated with DPCB. In total, the operations cost is computed at Php 1,471,708,000. 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 and service delivery.

Table 3.1 elaborates the resource requirement costs and assumptions in the roll-out of the *Pfizer-BioNTech COVID-19 Vaccine* in the Philippines in 2021.

Table 3.1 Resource requirement costs in the roll-out of the *Pfizer-BioNTech COVID-19 Vaccine* in the Philippines in 2021

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	**Php 22,338,936,000.00**	For 2 doses, with 5% wastage; consumables include syringes, personal protective equipment, hand rub, cotton *(estimated costs for vaccinating 21,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
Logistics	**Php 2,280,000,000.00**	For -60°C to -80°C vaccine storage temperature only. This includes hauling, storage, and transport costs. *(estimated costs for vaccinating 21,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB

Operations	**Php 1,471,708,000.00**	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 7 days. *(estimated costs for vaccinating 21,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
TOTAL COST	**Php 26,090,644,000.00**		
TOTAL VACCINATION COST PER INDIVIDUAL	**Php 1,242.41**		

Acronym: **DPCB:** Disease Prevention and Control Bureau

Based on the projected calculations, the total cost of the *Pfizer-BioNTech COVID-19 Vaccine* for 21,000,000 Filipinos would amount to Php 26,090,644,000.00 (which translates to Php 1,241.41 per individual). This would entail utilization of 31.63% of the total allocated budget for vaccination while the rollout of the *Pfizer-BioNTech COVID-19 Vaccine* will cover 30% of the target vaccinees for 2021.

Logistics, Deployment, and Feasibility

The COVID-19 Vaccine Deployment Plan outlines the prioritization of eligible populations in receiving the COVID-19 vaccine which includes the *Pfizer-BioNTech COVID-19 Vaccine*. 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 ultra-cold temperature requirement of the *Pfizer-BioNTech COVID-19 Vaccine* at -60 to -80 degrees Celsius presents logistical challenges in deploying, storing, and maintaining the efficacy/quality of the vaccine especially in geographically isolated and disadvantaged areas (GIDA) where special freezers are not available. Given the limited logistical capacity of the DOH, the *Pfizer-BioNTech COVID-19 Vaccine* can only be deployed to tertiary hospitals where the ultra-low freezers are available. To address this, the DOH-DPCB reported that the plan for hauling the vaccines with the said temperature requirement involves procuring 150 additional ultra-low freezers. To transport these vaccines, airplanes also need retrofitting to carry dry ice and dry-ice freezers that will enable deployment to other regions and provinces.

Other needs for deployment include more intensive 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 and equipment to manage anaphylaxis, a rare adverse event linked to the vaccine and other medical events that could occur following vaccination.

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- DOH- Epidemiology Bureau (EB)
- Philippine Statistics Authority (PSA)
- Philippine General Hospital (PGH)
- DOH- Supply Chain Management Office (SCMO)