# Evidence Summary on *Pediatric Vaccination* for the prevention of COVID-19

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## Section 1. Background

In March 2021, the Philippines started implementing COVID-19 vaccination for priority groups A1 to A5 (workers in frontline health services, senior citizens, persons with comorbidities, frontline personnel in essential sectors, including uniformed personnel, and indigent population) as part of the global and national exit strategies against COVID-19. From the roll out of these vaccines among the adult population, countries worldwide, including the Philippines, have started to plan for its expansion to the pediatric population.

Currently, the FDA Philippines allows and regulates two vaccine brands under EUA for pediatric use, specifically for 12 years of age and older:

- *Pfizer-BioNTech*
- *Moderna*

*Pfizer-BioNTech* is being implemented in 24 countries for the 12-17 age group and 2 countries are implementing the vaccine for 16 to 17 years age group; while *Moderna* is being implemented in 13 countries for the 12-17 age group.

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 for the COVID-19 Vaccine Implementation for 2022, this updated review looks at the currently available evidence on the use of five presently being used vaccines in the Philippines, for their expansion of use to the pediatric population:

1. *Pfizer-BioNTech*
2. *Moderna*
3. *AstraZeneca*
4. *Janssen*
5. *CoronaVac*

This review is part of an overarching evidence appraisal process that is currently being undertaken to assess the vaccination strategies being explored for the 2022 rollout: heterologous vaccination; booster vaccination; and additional dose vaccination.

This assessment follows the HTAC evaluation framework to evaluate 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

Should the DOH use ***Pfizer-BioNTech, Moderna, AstraZeneca, Janssen*** *and* ***CoronaVac*** for the **pediatric population** as part of the 2022 COVID-19 vaccination, to prevent COVID-19 cases, severe infection, and deaths?

## Section 2. HTAC Recommendation (as of 01 October 2021)

The HTAC maintains its recommendation to use *Pfizer-BioNTech* COVID-19 Vaccine among adolescents aged 16 to 17 years and extends this recommendation for use in children aged 12 to 15 years. The HTAC also recommends extending the use of COVID-19 Vaccine *Moderna* among children aged 12 to 17 years. Moreover, HTAC recommends compliance to standard vaccination program protocols in introducing vaccines for children with only Emergency Use Authorization (EUA).

Furthermore, this recommendation shall be revisited to possibly include children younger than 12 years old once data for this age group becomes available. On the other hand, HTAC does not currently recommend the use of *AstraZeneca, CoronaVac*, and *Janssen* among children and adolescents (12 to 17 years old) due to current limited clinical evidence on their use in the pediatric population.

The criteria considered by HTAC in crafting its recommendations for pediatric vaccination as well as the summary of evidence are shown in the table of the Overview of Evidence Considered below:

### *Overview of Evidence Considered and HTAC Judgments on Pediatric Vaccination*

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| **mRNA** | **mRNA** | **Vector vaccine (chimpanzee adenovirus)** | **Vector vaccine (Ad26 adenovirus)** | **Inactivated virus** |
| **Can the vaccine significantly reduce the magnitude and severity of COVID-19 in the pediatric population?** | | | | |
| Yes, *Pfizer-BioNTech* and *Moderna* have the potential to reduce the disease burden by averting a significant number of infections in the pediatric population (12 to less than 18 years old) including symptomatic and severe COVID-19 assuming sufficient vaccine coverage. The efficacy has not been studied among children < 12 years old. | | Potential to reduce the disease burden in the pediatric population cannot be assessed due to limited evidence. | | |
| **Is the vaccine safe and efficacious for the pediatric population?** | | | | |
| **Efficacy/Effectiveness**<br>Yes. Pfizer-BioNTech passed the preferred vaccine efficacy threshold against symptomatic COVID-19 and severe COVID-19 for the pediatric population aged 12-15 years old (Frenck et al., 2021), based on moderate certainty of evidence. Immunogenicity data on adolescents aged 12 to 15 years also demonstrated noninferiority when compared with young adults aged 16 to 25 years old.<br>Current real world studies (Bickel et al.; Seigel et al.; Delahoy et al., Gargano et al.; Public Health England) suggest its potential clinical benefits in terms of symptomatic COVID-19, moderate to severe COVID-19, and hospitalization due to COVID-19.<br><br>**Efficacy/ effectiveness against Variants** | **Efficacy/Effectiveness**<br>**Yes**. *Moderna* has passed the preferred vaccine efficacy threshold against symptomatic COVID-19 for the pediatric population aged 12 to 17 years old (Ali et al, 2021), based on moderate certainty of evidence. Immunogenicity data on adolescents also demonstrated noninferiority when compared with young adults aged 18 to 25 years old.<br><br>Real world effectiveness of *Moderna* in the pediatric population cannot be assessed due to lack of data.<br><br>**Efficacy/ effectiveness against Variants**<br>**Yes.** Real world evidence in individuals aged 16 and | Currently, there is limited evidence on the efficacy, effectiveness, and safety of *AstraZeneca, Janssen* in the pediatric population aged 18 years and below. | **Efficacy/effectiveness**<br><br>Currently, there is limited evidence on the efficacy of *CoronaVac* in the pediatric population.<br><br>However, there is currently available evidence limited to one immunogenicity trial (Han et al. 2021). It showed that *CoronaVac* was deemed highly immunogenic in children aged 3 to 17 years old, with geometric mean titers generally higher than adults aged 18 years and older. |

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|---|---|---|---|
| Yes. Real world evidence in individuals aged 16 and older across 4 studies [Lopez Bernal et al. (UK); Nasreen et al. (Canada); Dagan et al. (Israel); Barlow et al. (US)] showed that Pfizer-BioNTech passed the vaccine effectiveness in preventing symptomatic COVID-19 caused by Delta, Alpha, Beta, and Gamma variants. However, an Israel MOH report showed that it did not pass the minimum VE (14 days after 2nd dose) for symptomatic COVID-19 caused by the Delta variant. In another US study (Griffin et al.), although it did not report vaccine effectiveness, showed a decrease in rates of infection caused by the Delta variant in fully vaccinated individuals compared to partially vaccinated and unvaccinated individuals.<br><br>Israel MOH report showed that Pfizer-BioNTech passed the VE against severe COVID-19 caused by the Delta variant. Meanwhile, one real world study in Canada (Nasreen et al. 2021), showed that the vaccine also passed the minimum VE against severe COVID-19 caused by Alpha variant but failed against severe COVID-19 caused by the Delta variant.<br><br>We noted that these studies evaluating effectiveness against variants of concern included both children (16 year old and older) and adults.<br><br>**Safety**<br><br>Yes. Based on the current evidence from the phase III clinical trial with high certainty of evidence (Frenck et al.) and real world safety reports (Hause et al., Bickel et al.), short-term safety of Pfizer-BioNTech for the pediatric population (12 to 15 years old) is acceptable. However, further follow-up data is needed to establish longer-term safety. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the *Pfizer-BioNTech* (Pepe et al., Lane et al.), the benefits still outweigh the risks for vaccination in this population. | older in one study [Nasreen et al. (Canada)] showed that *Moderna* passed vaccine effectiveness against symptomatic COVID-19 caused by Alpha and Delta variants.<br><br>One real world study in Canada (Nasreen et al.) showed that the vaccine also passed the minimum VE against severe COVID-19 caused by Alpha and Delta variants.<br><br>We noted that these studies evaluating effectiveness against variants of concern included both children and adults.<br><br>**Safety**<br>**Yes.** Based on the current evidence from the phase III clinical trial with high certainty of evidence (Ali et al), short-term safety of *Moderna* for the pediatric population (12 to 17 years old) is acceptable. However, further follow-up data is needed to establish longer-term safety. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the *Moderna* (Pepe et al, Lane et al.), the benefits still outweigh the risks for vaccination in this population. | | Further studies are anticipated to strongly conclude its evidence for efficacy and effectiveness for the pediatric population aged 18 years and below.<br><br>**Efficacy/ effectiveness against Variants**<br><br>While there are countries using this vaccine for the pediatric population (e.g., Chile, China, Indonesia), there are no available reports on efficacy and effectiveness against variants of concern detected from these countries. Moreover, the trial of *CoronaVac* on the pediatric population did not evaluate its efficacy against variants of concern.<br>**Safety**<br><br>Currently, there is limited evidence on the safety of *CoronaVac* for the pediatric population. Current available evidence from the Phase I/II trial shows that short term safety in children and adolescents aged 3 to 17 years old were found to be similar to the adult population.<br><br>Further studies are anticipated to strongly conclude on its safety for this age group. |
| **Is the vaccine affordable and feasible to use in a national immunization program (viability) for the pediatric population?** | | | |
| **Affordability**<br>Yes, vaccinating children and adolescents aged 12 to 17 years using *Pfizer-BioNTech* and *Moderna* is affordable.<br><br>According to the DOF, the supply of Pfizer-BioNTech procured in 2021 are sufficient to vaccinate the pediatric population aged 12 to 17, thus, its implementation will not incur additional cost from the 2022 budget.<br><br>**Feasibility**<br>Yes, vaccinating children and adolescents aged 12 to 17 years using *Pfizer-BioNTech* and *Moderna* is feasible.<br><br>Although the implementation was generally challenging due to the intricacies in the storage, handling, and preparation of these vaccines, the NVOC implemented measures and ensured proper training and preparation prior to the rollout to mitigate these challenges. | Affordability and feasibility were not assessed due to limited clinical evidence in the pediatric population. Further, *AstraZeneca, Janssen,* and *CoronaVac* currently do not have EUA for the pediatric population. | | |

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|---|---|
| **Does the vaccine reduce out-of-pocket (OOP) expenses of households due to COVID-19?** | |
| Yes. Based on current evidence, *Pfizer-BioNTech* and *Moderna* have 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 | Out of pocket expenses were not assessed for *AstraZeneca, Janssen, CoronaVac* due to limited clinical evidence in the pediatric population. Further, this vaccine currently does not have EUA for the pediatric population. |
| **Does the vaccine possess the characteristics that are desired by key stakeholders?** | |
| Yes. *Pfizer-BioNTech* and *Moderna have been* issued an EUA by the FDA Philippines for the pediatric population.<br><br>Results of a survey conducted by the DOH-HPB on the acceptability of the pediatric population showed that COVID-19 vaccination is acceptable to adolescents (12 to 17 years old).<br><br>Another survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable to parents of children and adolescents below 18 years old. However, as it is an online survey, the study had limitations in terms of representativeness of the study population, i.e. lack of representation of the population without internet access.<br><br>Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need to get both parental consent and assent from the adolescent in the implementation, the need for additional human and logistical resources to accommodate the pediatric population.<br><br>The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools | *AstraZeneca, Janssen, and Coronavac* have not yet received an EUA from the Philippine FDA for the pediatric population. As such, public acceptability for its use was not assessed. |
| **Does the vaccine reduce or not further add to existing inequities in the health system?** | |
| **Yes, pediatric vaccination will reduce inequities in the health system**, assuming that the decision to vaccinate children is made in consultation with stakeholders, and pediatric vaccination shall be rolled out following the country's prioritization criteria, cognizant of the following:<br><br>Burden of COVID-19 to the pediatric population, especially those with comorbidities;<br><br>Sufficient supply to cover the pediatric population per DOF. | Not assessed for this domain due to limited clinical evidence in the pediatric population. Further, *AstraZeneca, Janssen, and CoronaVac* currently does not have EUA for the pediatric population. |

## Section 3. Presentation of Evidence on Pediatric Vaccination

### Criterion 1: Responsiveness to Disease Magnitude and Equity

***RQ1: Can the vaccine significantly reduce the magnitude and severity of COVID-19?***

***HTAC Specifications:*** *The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact). Trends in COVID-19 morbidity, mortality and hospitalization rates.*

In the pediatric population, the DOH Philippines recorded 122,487 COVID-19 cases in children less than 10 years old and 208,488 cases in adolescents aged 10 to 19 years old as of 14 October 2021. The CFRs in these age groups (<10 years old: 0.31%; 10-19 years old: 0.13%) are comparable to that of adults aged 20-39 years old (20-29 yo: 0.15%; 30-39 yo: 0.34%).

Based on data from the DOH-EB from June 2021 to September 2021, the largest percent increase in cases was observed in children aged 0-9 years old (268.54%). In children and adolescents aged 10-19, the percent increase for the same time period was at 215.51%. The proportion of deaths in the 0 to 9 year age group to the total number of deaths across age groups also increased from 0.73% in June 2021 to 3.10% in September 2021. Among the pediatric population, cases were highest in the 12 to 17 year subgroup (6.30% to 8.65%).

Meanwhile, the Salvacion Registry, a survey of COVID-19 in children, reported 1,811 cases as of 30 September 2021. Cases were highest in the 1 to 5 year subgroup (males: 15.2%; females: 11.3%). In terms of severity, the majority are mild cases (42.1%), followed by moderate (24.5%) and asymptomatic cases (17.3%); while the remaining are severe (8.2%) and critical cases (7.9%). Overall, 81.1% were recovered, 8.2% resulted in death, while the status of 10.7% of the cases were unknown. Among 17 comorbidities reported in the surveillance, the following are the most prevalent among conditions: hematologic/oncologic disease (7.2%), neurologic/developmental disease (7.0%), gastrointestinal disease (5.6%), cardiac disease (3.5%), obesity (3.3%), and kidney disease (3.2%). Further, the majority of cases (88.7%) were hospitalized, while 11.3% of cases were outpatients.

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| **HTAC judgment for *Pfizer-BioNTech and Moderna*:** *Pfizer-BioNTech* and *Moderna* have the potential to reduce the disease burden by averting a significant number of infections in the pediatric population (12 to less than 18 years old), including symptomatic and severe COVID-19 assuming sufficient vaccine coverage. The efficacy has not been studied among children < 12 years old. | | **HTAC judgment for *AstraZeneca, Janssen, CoronaVac*:** Potential to reduce the disease burden in the pediatric population cannot be assessed due to limited evidence. | | |

## Criterion 2: Clinical Efficacy, Effectiveness, and Safety

***RQ.2.1: What is the effectiveness of COVID-19 Vaccines in terms of: reducing incidence of: symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19 in the pediatric population?***

***HTAC Specifications:***
*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 (point estimate): at least 60% reduction*** *of symptomatic COVID-19;* ***at least 80% reduction*** *of severe COVID-19, hospitalization due to COVID-19;* ***at least 80% reduction*** *of death due to COVID-19*

Evidence on efficacy and effectiveness for the pediatric population is based on *Evidence Summary of Pfizer-BioNTech* Version 2, the review of the Philippine Living Clinical Practice Guidelines Group (LCPG Group) (updated as of 8 September 2021), International Vaccine Access Center (IVAC) (updated as of 23 September 2021), COVID-NMA (updated as of 29 September 2021) and an updated Morbidity and Mortality Weekly Report from US Center for Disease Control (CDC) by Olson et al. 2021.

### Pfizer-BioNTech

Overall, there are nine studies relevant to this sub-theme - two RCTs and seven real world studies.

***Evidence from clinical trials***
***Efficacy outcomes***
***Description of evidence***
For clinical trial evidence on the efficacy two trials reporting efficacy of *Pfizer-BioNTech* for the pediatric population was detected.

One trial evaluated its efficacy in the pediatric population aged 12 to 15 years old. For this, you may refer to the *Evidence Summary of Pfizer-BioNTech* (Version 2). This shall be updated once new clinical evidence on this population has been reviewed. In summary, the vaccine efficacy values captured in the review are as follows:

| **Frenck et al (2021) [published]** | |
|---|---|
| Outcomes | VE (95% CI) |

### Moderna

Overall, the reference reviews have detected one randomized control trial relevant to this subtheme (Ali et al, 2021) which measured clinical efficacy and immunogenicity outcomes.

***Evidence from clinical trials***
***Efficacy outcomes***

***Description of evidence***
The LCPG review has detected one ongoing Phase II/III, placebo controlled trial by Ali et al, 2021 which evaluated the safety of *Moderna* in adolescents aged 12-17 years. The table below summarizes the characteristics of the study:

| | |
|---|---|
| **Population** | Healthy adolescents, 12 to 17 years of age<br>N = 3,726 |
| **Inclusion criteria** | 12 to <18 years of age at the time of consent who is in good general health based on review of medical history and screening physical examination; BMI at or above the third percentile |

### AstraZeneca

Overall, the reference reviews detected no clinical trials or real world evidence relevant to this sub-theme. We noted a paused trial of *AstraZeneca* in children below 18 years.

***Evidence from Clinical trials***
There are currently no clinical trials with interim results detected by the LCPG on the efficacy of *AstraZeneca* in children and adolescents below 18 years. We noted that a Phase II trial from the United Kingdom on the efficacy and safety of *AstraZeneca* on healthy children aged 6-17 years old by Pollard et al (2021) which began recruitment on 2 September

### Janssen

There is currently no evidence detected by the relevant reviews on the efficacy (from trials) or effectiveness (from real world data) of *Janssen* in children and adolescents aged 18 years and younger.

### CoronaVac

Overall, there are 2 studies relevant to this sub-theme - 1 Phase I/II trial with interim results and 1 ongoing Phase III trial without available interim results.

No efficacy and effectiveness trials or real world studies were detected from the IVAC living systematic review (as of 24 September 2021) or the COVID-NMA review (as of 23 September 2021).

***Evidence from Clinical Trials***
***Efficacy outcomes***
The NCPG detected one ongoing Phase III clinical trial in children aged 6 months to 17 years and which evaluated for clinical efficacy outcomes of *CoronaVac* for the pediatric population. This trial is still in the recruiting phase, thus, interim results are not yet available. The trial aims to evaluate the efficacy, immunogenicity and safety of the vaccine in the target population.

| | |
|---|---|
| VE against symptomatic COVID-19 | 100% (not estimable) |
| VE against severe and hospitalized COVID-19 | Remains to be demonstrated due to zero events |
| VE against death due to COVID-19 | |

Meanwhile, the COVID-NMA Review detected one Phase II/III trial, Thomas, et al, 2021, on the efficacy of the *Pfizer-BioNTech* among the general population including children and adolescents aged 12 to 17 years old.

***Key Findings***

*Quality of Study*

The COVID-NMA Review assessed that the overall risk of bias (RoB) of Thomas, et al., is 'Some Concerns' due to deviations from intervention.

*Clinical Effectiveness Results*

Thomas et al included the same population analysed in Freck et al (2021). Further, Thomas et al 2021 only provided subgroup analysis for the pediatric population aged 16 to 17 years old which showed a vaccine efficacy of 100% (95% CI: 58.2 to 100) against symptomatic COVID-19.

***Immunogenicity outcomes***

For clinical trial evidence on the immunogenicity for the pediatric population (12 to 15 years old), you may refer to the *Evidence Summary of Pfizer-BioNTech* (Version 2). This shall be updated once new clinical evidence on this population has been reviewed. In summary, the Geometric Mean Ratio (GMR) of 1.76 (95%CI 1.47, 2.10) when the vaccinated 12-15 year olds were compared to the vaccinated 16-25 year olds. With the lower limit meeting the criteria of >0.67, the Frenck et al. 2021 study concluded that vaccination in the pediatric population (12-15 years old) is 'non-inferior' to vaccination in the 16-25 year old group.

***Evidence from Real World Studies***

***Effectiveness outcomes***

***Description of evidence***

The LCPG Group review has detected two real world

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| **Exclusion criteria** | Travel outside of the United States in the 28 days before screening, pregnancy or breast-feeding, acute illness or fever 24 hours before or at screening, previous administration of an investigational vaccine against SARS-CoV-2, or current treatment with investigational agents or prophylaxis against COVID-19 |
| **Intervention** | mRNA-1273 100ug, 2 doses, 28-day interval<br>N=2489<br>Received Dose 1: 2486<br>Received Dose 2: 2480<br>Discontinued: 57<br>Completed= 2139<br>Immunogenicity population: 340 |
| **Comparator** | 0.9 NaCl 0.5mL<br>N = 1243<br>Received Dose 1: 1240<br>Received Dose 2: 1222<br>Discontinued: 188<br>Completed: 1042 |
| **Outcomes** | Safety<br>o Solicited local and systemic ARs through 7 days after each dose<br>o Unsolicited AEs through 28 days after each injection<br>o MAAEs, SAEs, AESI of MIS-C through the entire study period<br><br>Immunogenicity<br>o non-inferiority of the geometric mean (GM) value of serum antibody (Ab) from a subgroup of the study participants compared with those obtained from young adults (≥18 to 25 years of age) of another study<br>(Non-inferiority : lower bound of the 95% CI of the GMR was > 0.67 based on the non-inferiority margin of 1.5, and the GMR point estimate is >0.8 (minimum threshold).<br>o non-inferiority of the seroresponse rate of a subgroup of the study participants compared with those obtained from young adults (≥18 to 25 years of age) of another study<br>(Non-inferiority: lower bound of the 95% of the sero-response rate difference is >-10%, based on the non-inferiority margin of 10%, and the |

2020 was paused due to safety concerns over thrombotic events. Children already enrolled continue to be followed up although recruitment has stopped.

***Evidence from Real World Studies***

There is currently no evidence (from real world data) detected by the LCPG on the effectiveness of *AstraZeneca* in children and adolescents aged 18 years and younger.

***Immunogenicity outcomes***

***Description of evidence***

The search performed by the NCPG Group detected one randomized, double blind Phase I/II study reported on the immunogenicity of *CoronaVac* (Han, 2021). Han et al. (2021) included children from 3 to 17 years and subgrouped into 3: (a) 3-5 years old, (b) 6-11 years old, and (c) 12 -17 years. The intervention group was blocked into two: (1) high dose (3 ug) and low dose (1.5ug). Random allocation to intervention versus placebo and allocation by dose was 1:1. The table below summarizes the characteristics of the Han et al., 2021 study:

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|---|---|
| PARTICIPANTS | total enrolled : Ph I = 72, Ph 2 = 480<br>balanced baseline characteristics |
| Inclusion criteria | Included healthy children from age 3-17 years |
| Exclusion criteria | o travel or residence history in communities with case reports, or contact history with someone infected with SARS-CoV-2)<br>o history of severe acute respiratory syndrome or SARS-CoV-2 infection<br>o axillary temperature of more than 37·0°<br>o history of allergy to any vaccine component |

studies (i.e. Bickel, et al, 2021 and Siegel et al, 2021) on the effectiveness of the *Pfizer-BioNTech* in children. The Bickel, et al, 2021 study is a retrospective case series of 31 long term pediatric care facility residents in the United States aged 16-25 years old. On the other hand, the Siegel et al, 2021 study by the US CDC examined COVID-19 cases and hospitalizations in children 0-17 years old, including vaccinated pediatric patients (12-17 years old) in the US. To note, as of August 2021, only the *Pfizer-BioNTech* has been granted EUA by the US FDA for pediatric patients 12-17 years old.

Four additional real world studies on effectiveness of the *Pfizer-BioNTech* in children were found: Gargano et al, 2021, Delahoy et al, 2021 PHE, 2021 and Olson et al., 2021. The study by Gargano et al, 2021 ,Delahoy et al, 2021 and Olson et al., 2021 studied the effectiveness of the vaccine in children in the US. Gargano et al, 2021 is a report of rapid reviews of use of *Pfizer-BioNTech* in children aged 12-17 years while Delahoy et al, 2021 is a surveillance report of children aged 0-17 years. Both the Delahoy and Gargano et al studies evaluated COVID-19 infection, hospitalization and death. Meanwhile, the Olson et al, 2021 study reported the vaccine effectiveness against hospitalization alone in the 12 to 18 years age group. Lastly, PHE, 2021 study is a surveillance report which measured rates of COVID-19 cases, COVID-19 cases presenting to emergency care, and COVID-19 deaths in children aged 18 years below in the UK.

***Key Findings***

*Quality of Studies*

Bickel et al. and Olson et al. had a 'very serious' RoB due to lack of randomization, allocation concealment, blinding of participants, investigators and assessors, and low control for confounders. Meanwhile, the RoB for Seigel et al., Gargano et al., Delahoy et al., and PHE report was not performed as these are surveillance studies.

*Clinical Effectiveness Results*

**Any SARS-CoV-2 infection**

- Bickel, et al, 2021 study reported that none of the vaccinated patients tested positive for COVID-19

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|---|---|
| | sero-response rate difference point estimate > 5% (minimum threshold)<br><br>Clinical Efficacy (Vaccine efficacy)<br>o COVID-19 per secondary case definition (clinical symptoms and a positive RT-PCR 14 days after second dose)<br>o SARS-CoV-2 infection (symptomatic and asymptomatic)<br>o asymptomatic SARS-CoV-2 infection COVID-19 |
| **Date cut-off** | May 8, 2021 |
| **Median follow-up** | 53 days after dose 2 |

***Key findings***

*Quality of studies*

The risk of bias (RoB) was high due to incomplete outcome data considering that the published result of the Phase II/III trial was an interim analysis, thus, full assessment could not be made. Details of the RoB assessment of Ali et al. (2021) is presented in Table X of Appendix 2.

*Clinical Efficacy Results*

*VE according to the CDC definition/criteria of COVID-19 (with onset of one systemic or respiratory symptom and a positive RT-PCR for SARS-CoV-2):*

- VE = 93.3% (95% CI: 47.9 to 99.9) in the per-protocol population. The study reported high efficacy 14 days after the second dose.
- VE = 92.7% (95% CI: 67.8 to 99.2) in the mITT population. The study reported high efficacy 14 days after the second dose.

*VE of SARS-CoV-2 based on primary case definition (with onset of at least two systemic symptoms or at least one respiratory symptom plus at least one nasopharyngeal swab, nasal swab, or saliva sample positive for SARS-CoV-2 by RT-PCR):*

- VE = 55.7% (95% CI: 16.8 to 76.4) in the

| | |
|---|---|
| INTERVENTION | *CoronaVac* 1.5 or 3.0ug in 0.5ml aluminum hydroxide adjuvant, 2 doses, 28 days apart |
| COMPARATOR | aluminum hydroxide only |
| OUTCOMES | Safety<br>o Any vaccine related AE within 28 days after administration<br>▪ Solicited AEs – first 7 days<br>▪ Spontaneous reporting of AEs – until 28 days<br>o Serious adverse events (until 12 months)<br>o Abnormal changes in lab measurement at day 3<br>Immunogenic<br>o Seroconversion rate of neutralizing antibodies at day 28 after second dose<br>o Seropositive rates (4-fold rise from baseline)<br>o GMT of neutralizing antibodies to live SARS-CoV-2 (positive cut off was 1/8)<br>o Geometric mean increase<br>Planned follow up until 12 months after dose 2 |
| METHODS | Ph1 – age de-escalation and dose escalation study (n= 72)<br>Ph2 – main safety/efficacy trial |

nor developed COVID-19 symptoms. However, the duration of follow-up was not mentioned in the study.

- The Gargano et al, 2021 study reported 8,500 COVID-19 prevented cases per million doses administered in females, and 5,700 cases prevented in males after vaccination with *Pfizer-BioNTech*.
- The PHE, 2021 study by the UK reported a rate of 458.2 COVID-19 cases per 100,000 for the fully vaccinated cohort. Meanwhile, the study reported a rate of 1,362.3 COVID-19 cases per 100,000 for the unvaccinated cohorts.

**Symptomatic COVID-19**

- Bickel, et al, 2021 study reported that none of the vaccinated developed COVID-19 symptoms. However, the duration of follow-up was not mentioned in the study.

**Hospitalization due to COVID-19**

- Siegel et al, 2021 study by the US CDC reviewed emergency department (ED) visits and hospital admissions between August 14-27, 2021 obtained from three different surveillance systems. The study compared the percentage of ED visits and hospitalizations among states with the highest and lowest vaccination coverage. The state-specific percentage of the population aged ≥12 years that had completed the COVID-19 vaccination series as of July 31, 2021, was used to put quartile group states into vaccination coverage. The report stated that for children aged 0–17 years, the states with the lowest vaccination coverage had:
  - COVID-19–related ED visits 3.38 (95% CI 3.24, 3.52) times higher than that of the states with the highest vaccination coverage.
  - COVID-19-related hospital admissions percentage 3.70 (95% CI 2.32, 5.90) times higher than that of states with the highest vaccination coverage.
- Olson et al. reported that *Pfizer-BioNTech* has VE of 93.0% (CI: 83%-97%) against hospitalizations related to COVID-19 14 days after the second dose based on data from 464 hospitalized adolescents

per-protocol population 14 days after the second dose.
- VE = 69.8% (95% CI: 49.9 to 82.1) in the mITT population 14 days after the second dose.

*VE against symptomatic COVID-19:*

- VE = 100% (95% CI: 28.9, NE) in the per-protocol population 14 days after the second dose.

*VE against asymptomatic COVID-19:*

- VE = 39.2% (95% CI: −24.7 to 69.7) in the per-protocol population 14 days after the second dose.
- VE = 59.5% (95% CI: 28.4 to 77.3) in the mITT population 14 days after the second dose.

It was noted that the vaccine efficacy of *Moderna* at 14 days after the second dose was difficult to assess precisely because of the low incidence of COVID-19 in the trial population.

***Immunogenicity outcomes***

***Description of evidence***

The LCPG review has detected one ongoing Phase II/III, placebo controlled trial by Ali et al, 2021 which evaluated the immunogenicity of *Moderna* in adolescents aged 12-17 years. Table 1.2.1 above summarizes the characteristics of the study.

***Key findings***

Ali et. al. (2021) concluded that the geometric mean (GM) value of serum antibody (Ab) of adolescents (aged 15 to 17 years) was non-inferior compared with those obtained from young adults (≥18 to 25 years of age). Non-inferiority was declared, as the lower bound of the 95% CI of the GMR [1.08 (95% CI: 0.94 to 1.24)] was greater than 0.67 based on the non-inferiority margin of 1.5, and the GMR point estimate is greater than 0.8 (minimum threshold). Similarly, it was concluded that the seroresponse rate of adolescents is non-inferior [0.2 (95% CI: 1.8 to 2.4)] with that of young adults. Non-inferiority was declared as the lower bound of the 95% of the sero-response rate difference is ≥10%, based on the non-inferiority margin of 10%, and the sero-response rate difference point estimate ≥5% (minimum threshold).

***Key Findings***

*Quality of the study*

For the appraisal of Han et al. 2021, refer to the safety section as safety is the only clinical outcome reported in this trial.

*Immunogenicity results*

The Phase I intervention group (both doses) had a 100% seroconversion rate. None of the participants in the placebo group became seropositive. For phase II, seroconversion rates were as follows: 1.5ug : 96.8% (93.1-98.8), 3.0ug : 100% (98.0-100.0), placebo : 0% (0.0- 3.9) (p value : <0.0001). *CoronaVac* was found to be highly immunogenic with GMTs generally higher than those found in adults. Geometric mean titers of the different treatment groups at 28 days after dose 2 are presented in the table below.

| | 1.5ug | 3.0ug | p-value |
|---|---|---|---|
| **Phase I** | | | |
| 3-17 years (all) | 55.0 (38.9, 77.9) | 117.4 (87.8, 157.0) | 0.0012 |
| 3-5 years | 71.9 (38.0, 136.0) | 212.6 (132.2, 342.1) | 0.0063 |
| 6-11 years | 50.5 (30.9, 82.6) | 101.6 (64.0, 161.2) | 0.030 |
| 12-17 years | 45.9 (19.2, 109.8) | 70.8 (47.5, 105.7) | 0.33 |
| **Phase II** | | | |
| 3-17 (all) | 86.4 | 142.2 | 0.0001 |

(179 case patients, 285 controls) aged 12-18 years old during the period of June to September 2021.

- The Gargano et al, 2021 study reported hospitalizations and ICU admission prevented:
  - Hospitalizations prevented: 183 COVID-19 hospitalizations prevented per million doses administered in females, and 215 hospitalizations prevented in males after vaccination with *Pfizer-BioNTech*.
  - ICU admissions prevented: 38 COVID-19 ICU admissions prevented per million doses administered in females, and 71 ICU admissions prevented in males after vaccination with *Pfizer-BioNTech*.
- The Delahoy et al, 2021 study reported that the hospitalization rate among unvaccinated adolescents (aged 12–17 years) was 10.1 times higher than that among fully vaccinated adolescents.
- The PHE, 2021 study by the UK reported a rate of 0.0 hospitalization per 100,000 for the fully vaccinated cohort. Meanwhile, the study reported a rate of 4.2 hospitalizations per 100,000 for the unvaccinated cohorts.

**Death due to COVID-19**

- The Gargano et al, 2021 study reported 1 COVID-19 death prevented per million doses administered in females, and 2 COVID-19 deaths prevented in males after vaccination with *Pfizer-BioNTech*.
- The PHE, 2021 study by the UK reported a rate of 0.0 deaths per 100,000 for both fully vaccinated and unvaccinated cohorts.

***Immunogenicity outcomes***

***Description of evidence***

The LCPG Group review has detected one real world study on the immunogenicity of the *Pfizer-BioNTech* in children (Revon-Riviere et al 2021). The Revon-Riviere, G. et al, 2021 is a case series of 13 patients 16-21 years of age and with solid tumors in France. Of the 13 patients, 7 are on chemotherapy, 2 are on immunotherapy, 2 are on targeted therapy and 2 are on follow-up.

***Evidence from Real World Studies***

There is currently no real world evidence detected by the LCPG group on the effectiveness and immunogenicity of *Moderna* in children and adolescents aged 17 years and below.

| | | | |
|---|---|---|---|
| | (73.9, 101.0) | (124.7, 162.1) | |
| 3-5 years | 94.1 (71.2, 124.2) | 140.5 (113.4, 174.0) | 0.024 |
| 6-11 years | 90.3 (72.6, 112.2) | 139.7 (112.7, 173.1) | 0.0050 |
| 12-17 years | 78.3 (57.5, 106.6) | 146.0 (114.2, 186.8) | 0.0022 |

***Evidence from Real world studies***

There are currently no detected real world studies detected by the NCPG on the effectiveness of *CoronaVac* in children and adolescents aged 17 years and younger.

| | | | | |
|---|---|---|---|---|
| ***Key Findings***<br>The study of Revon-Riviere et al, 2021 reported the following seroconversion rates in pediatric patients with solid tumors:<br>● *Seroconversion after dose 1:* 6 out of 10 (60%) patients that are seronegative at baseline seroconverted.<br>● *Seroconversion one month after dose 2:* 9 out of the 10 (90%) patients that are seronegative at baseline seroconverted.<br>● One patient who was seropositive at the time of the first dose was found to be seronegative one month after the second dose but still had detectable neutralizing antibodies. | | | | |
| **HTAC judgment for *Pfizer-BioNTech*:** *Pfizer-BioNTech* passed the preferred vaccine efficacy threshold against symptomatic COVID-19, based on moderate certainty of evidence as appraised by HTAC (Frenck et al., 2021), and severe COVID-19 (Thomas et al. 2021, with low RoB based on COVID-NMA appraisal), for the pediatric population aged 12-15 years old (,. Immunogenicity data on adolescents aged 12 to 15 years also demonstrated noninferiority when compared with young adults aged 16 to 25 years old.<br><br>Current real world studies (Bickel et al; Seigel et al; Olson et al.; Delahoy et al, Gargano et al; Public Health England) suggest its potential clinical benefits in terms of symptomatic COVID-19, moderate to severe COVID-19, and hospitalization due to COVID-19. | **HTAC judgment for *Moderna*:** *Moderna* has passed the preferred vaccine efficacy threshold against symptomatic COVID-19 for the pediatric population aged 12 to 17 years old (Ali et al., 2021), based on moderate certainty of evidence as appraised by LCPG Group. Immunogenicity data on adolescents also demonstrated noninferiority when compared with young adults aged 18 to 25 years old.<br><br>Real world effectiveness of *Moderna* in the pediatric population cannot be assessed due to lack of data. | **HTAC judgment for *AstraZeneca and Janssen*:** Currently, there is limited evidence on the efficacy and effectiveness of *AstraZeneca and Janssen* in the pediatric population aged 18 years and below. | | **HTAC judgment for *CoronaVac*:** Currently, there is limited evidence on the efficacy of *CoronaVac* in the pediatric population. However, there is currently available evidence limited to one immunogenicity trial (Han et al. 2021). It showed that *CoronaVac* was deemed highly immunogenic in children aged 3 to 17 years old, with geometric mean titers generally higher than adults aged 18 years and older.<br><br>Further studies are anticipated to strongly conclude its evidence for efficacy and effectiveness for the pediatric population aged 18 years and below. |
| ***RQ.2.2: What is the effectiveness of COVID-19 Vaccines in terms of: reducing incidence of: symptomatic and severe COVID-19, hospitalization due to COVID-19 and death due to COVID-19 caused by variants of concern in the pediatric population?***<br><br>***HTAC Specifications:***<br>*The vaccine achieves the following efficacy parameters:*<br><br>***Preferred VE: ≥70% reduction*** *in the risk of symptomatic infection with vaccination versus no vaccination*<br><br>***Minimum acceptable VE (point estimate): at least 60% reduction*** *of symptomatic COVID-19;* ***at least 80% reduction*** *of severe COVID-19, hospitalization due to COVID-19;* ***at least 80% reduction*** *of death due to COVID-19* | | | | |

Evidence on efficacy and effectiveness *against variants of concern* for the pediatric population is based on *Evidence Summary of Pfizer-BioNTech* Version 2, the review of the Philippine Living Clinical Practice Guidelines Group (LCPG Group) (updated as of 8 September 2021), International Vaccine Access Center (IVAC) (updated as of 23 September 2021), COVID-NMA (updated as of 29 September 2021) and an additional study presented in a letter to the editor by Reis et al. 2021.

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|

Overall, there were seven studies that are relevant to this sub-theme, all of which are real-world studies.

***Evidence from clinical trials***

There are currently no trials detected by the LCPG Group, IVAC or COVID-NMA on its efficacy or immunogenicity against variants of concern.

***Evidence from Real world studies***

***Effectiveness outcomes***

***Description of evidence***

All of the seven real world studies include adults in their study population. The tables below summarizes the characteristics of the studies.

| **Lopez-Bernal, et al, 2021<br>UK<br>Test Negative Case Control** | |
|---|---|
| Population | ≥ 16 year old in the reporting symptoms and tested w/in 10 days of symptoms onset<br><br>UK<br><br>N=14,837<br>N (sequenced)= 12,675<br>Delta N = 1,054 |
| Intervention | *Pfizer-BioNTech*<br>*AstraZeneca* |
| Comparator | Unvaccinated population with VOC infection |
| Outcome | Vaccine Effectiveness (VE) against symptomatic COVID-19<br><br>Odd ratio (OR) on Delta Variant infections |

Overall, they have detected one real-world study relevant to this sub-theme.

***Evidence from clinical trials***

There are currently no trials detected by the LCPG Group or COVID-NMA examining the clinical efficacy or immunogenicity of *Moderna* against variants of concern for the pediatric population. Evidence shall be updated once new clinical evidence becomes available.

***Evidence from Real world studies***

***Effectiveness outcomes***

***Description of evidence***

One real world study from Canada (Nasreen et al. 2021) detected by both LCPG Group and COVID-NMA measured clinical effectiveness outcomes against COVID-19 variants of concern. These studies target the general population but also include a pediatric subgroup (aged 16 and above). The mean ages of cases per variant in the study are as follows: 40.8 years for Alpha, 41.9 years for Beta/Gamma, and 39.3 years for Delta. The study did not disaggregate the pediatric population from the young adult population (grouped as 16-29 years old), thus, proportion of the pediatric population cannot be retrieved. The characteristics of the real-world studies are presented in the table below.

| **Nasreen, et al, 2021<br>Test Negative Case Control [Preprint]** | |
|---|---|
| **Population** | ≥ 16 year old reporting symptoms and tested positive for COVID-19<br><br>Canada |

There is currently no evidence detected from relevant reviews on the efficacy (from trials) or effectiveness (from real world data) of *AstraZeneca, Janssen, and CoronaVac* against variants of concern in children and adolescents aged 18 years and younger.

| Nasreen, et al, 2021<br>Canada<br>Test Negative Case Control [Preprint] | |
|---|---|
| Population | ≥ 16 year old reporting symptoms and tested positive for COVID-19<br><br>Canada<br><br>N = 772,613 (421,073 COVID-infections; 351,540 controls) |
| Intervention | *Pfizer-BioNTech*<br>*AstraZeneca*<br>*Moderna* |
| Comparator | Symptomatic RT-PCR negative |
| Outcome | VE against symptomatic COVID-19<br>VE against Severe COVID-19<br><br>Timing of assessments:<br>*fully vaccinated*: tested 7 and 14 days after dose 2, *partially vaccinated*: tested 14 and 21 days after dose 1 |

| Dagan et al, 2021<br>Israel<br>Retrospective Cohort | |
|---|---|
| Population | Newly vaccinated patients of 4 integrated health care organizations<br><br>Israel<br>N = 596,618<br><br>Median age: 45 years old |
| Intervention | *Pfizer-BioNTech* |
| Comparator | Unvaccinated population |
| Outcome | VE against infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptomatic Covid-19, Covid-19–related hospitalization, severe |

| | |
|---|---|
| | N = 772,613 (421,073 COVID-infections; 351,540 controls) |
| **Intervention** | *Pfizer-BioNTech COVID-19 Vaccine, AstraZeneca, Moderna* |
| **Control** | Symptomatic RT-PCR negative |
| **Outcome** | VE against symptomatic COVID-19<br>VE against severe COVID-19<br><br>Timing of assessments:<br>*fully vaccinated*: tested 7 and 14 days after dose 2, *partially vaccinated*: tested 14 and 21 days after dose 1 |

***Key Findings***

*Quality of studies*

The LCPG group noted that Nasreen, et al, 2021 controlled for all three confounders, namely age, exposure risk, and comorbidities. However, since this real world effectiveness study was observational in design, it was deemed to have 'high RoB' due to lack of randomization, lack of allocation concealment, and lack of blinding of participants. Details on the RoB assessment conducted is indicated in Table A2.2 in the Appendix 2.

*Clinical effectiveness results*

Nasreen et al (2021) tested for vaccine effectiveness against symptomatic and severe COVID-19 caused by four variants of concern (Delta, Alpha, Beta, Gamma) 14 days after participants received their second dose. The following outcomes for *Moderna* were available:

- VE against symptomatic Delta variant infection: 100% (CI not estimable; based on zero vaccinated test-positive cases)
- VE against severe Delta variant infection: 96% (95% CI, 72-99%)
- VE against symptomatic Alpha variant infection: 91% (95% CI, 84-95%)
- VE against severe Alpha variant infection: 94% (95% CI, 90-97%).

| | |
|---|---|
| | illness, and death. |

| **Griffin et al**<br>**US**<br>**Cohort Review** | |
|---|---|
| Population | Laboratory-confirmed cases of SARS-CoV-2 Los Angeles County<br><br>N= 9,651,332 |
| Intervention | *Pfizer-BioNTech*<br>*Moderna*<br>*Janssen* |
| Comparator | Unvaccinated individuals |
| Outcome | Case rates of vaccinated, partially vaccinated and unvaccinated patients based on hospitalization, admission to intensive care unit, death |

| **Barlow et al**<br>**US**<br>**Test negative design matched case control analysis** | |
|---|---|
| Population | Individuals aged 16 and above who tested positive for SARS-CoV-2<br><br>US<br><br>N=1000 (500 case-control pairs)<br><br>Median age: 37 years |
| Intervention | *Pfizer-BioNTech*<br>*Moderna* |
| Comparator | Individuals who tested negative for SARS-CoV-2 |
| Outcome | Vaccine effectiveness against SARS-CoV-2 infection |

| **Israel MOH**<br>**Israel**<br>**Cohort Review** | |
|---|---|
| Population | residents16 years and older<br><br>Israel<br><br>N = 1,848,168 |
| Intervention | *Pfizer-BioNTech* |
| Comparator | Unvaccinated individuals |
| Outcome | VE against symptomatic COVID-19, severe COVID-19, hospitalization, SARS-CoV-2 infection on Delta variant |

| **Reis et al. 2021**<br>**Israel**<br>**Letter to the Editor (Results of Matched Case Control Study)** | |
|---|---|
| Population | Clalit Health Services (CHS) members, 12 to 18 years old<br><br>Israel<br><br>N= 94, 354 |
| Intervention | *Pfizer-BioNTech* |
| Comparator | No vaccination |
| Outcome | Documented SARS-CoV-2 infection (PCR-positive), symptomatic SARS-CoV-2 infection caused by the Delta variant. |

***Key Findings***

*Quality of studies*

The LCPG group noted that two of the studies (i.e. Lopez-Bernal, et al, 2021 and Nasreen, et al, 2021) controlled for all three confounders, namely age,

| | | |
|---|---|---|
| exposure risk, and comorbidities. However, since both of the real world effectiveness studies were observational in design, all were deemed to have 'high RoB' due to lack of randomization, lack of allocation concealment, and lack of blinding of participants.<br><br>Meanwhile, based on the appraisal of COVID-NMA, the study of Dagan et al, 2021 was found to have an overall 'unclear RoB' due to unclear risk of bias due to confounding and outcome measurement. Meanwhile, the study by Barlow et al., 2021 was assessed by the COVID-NMA as having an overall 'Serious RoB' due to the presence of uncontrolled confounding factors.<br><br>Based on the appraisal of HTAU on the matched case control study reported in the letter to the editor by Reis et al. (2021), the study had an overall 'serious RoB' due to lack of randomization, allocation concealment, and blinding of participants, investigators and assessors. However, it was noted that the study had high control for confounders.<br><br>The Israel MOH and Griffin et al. were not assessed for the RoB as these are surveillance studies.<br><br>*Clinical effectiveness results*<br>**Any SARS-CoV-2 infection**<br>● The Barlow et al, 2021 study reported that the vaccine effectiveness of Pfizer-BioNTech against infection of completed mRNA series during Delta variant surge is at 73% (49-86%).<br>● Griffin et al, 2021 reported an 8.6 to 91.2% infection rate in fully vaccinated population, 0.0% to 88.1% in partially vaccinated population, and 8.2 to 87.1% in the unvaccinated population. These rates were measured during dominance of Delta variant.<br>● The Reis et al. 2021 reported the vaccine effectiveness of 90% (95% CI: 88% to 92%) against any documented SARS-CoV-2 infection caused by the Delta variant 7 to 21 days after the second dose.<br><br>**Symptomatic COVID-19**<br>● The Lopez-Bernal, et al, 2021 study reported that | | |

| | | |
|---|---|---|
| vaccine effectiveness of *Pfizer-BioNTech* against symptomatic COVID-19 caused by delta variant is 93.7% (95% CI, 91.6-95.3%). The result shows that in individuals 16 year old and above, the *Pfizer-BioNTech* is effective against symptomatic COVID-19 caused by the Delta variant.<br>● The study of Nasreen, et al, 2021 reported that the vaccine effectiveness of *Pfizer-BioNTech* against symptomatic COVID-19 caused by Alpha variant is at 89% while vaccine effectiveness against symptomatic COVID-19 caused by Beta/Gamma variant is at 84%.<br>● The Dagan et al, 2021 study reported a vaccine effectiveness of 94% (95% CI, 87 to 98) against symptomatic illness caused by the Alpha variant 7 days after 2nd dose<br>● The Israel MOH, 2021 reported a vaccine effectiveness 4of 0.5% (95% CI: 8.7 to 61.20) against symptomatic COVID-19 caused by the Delta variant after 7 days or longer after the second dose<br>● The Reis et al, 2021 reported the vaccine effectiveness of 93% (95% CI: 88% to 97% against symptomatic COVID-19 caused by the Delta variant 7 to 21 days after the second dose<br><br>**Severe COVID-19**<br>● The Dagan et al, 2021 study reported a vaccine effectiveness of 92% (95% CI, 75 to 100) against severe COVID-19 caused by the Alpha variant 7 days after 2nd dose<br>● The Israel MOH, 2021 reported a vaccine effectiveness of 91.4% (95% CI: 82.5 TO 95.7) against severe COVID-19 caused by the Delta variant after 7 days or longer after the second dose:<br><br>**Hospitalization due to COVID-19**<br>● The Dagan et al, 2021 study reported a vaccine effectiveness of 87% (95% CI, 55 to 100) against hospitalization due to COVID-19 caused by the Alpha variant 7 days after 2nd dose<br>● The Israel MOH, 2021 reported a vaccine effectiveness of 88.0% (95% CI: 78.9 to 93.2) against hospitalization due to COVID-19 caused by the Delta variant after 7 days or longer after the | | |

| | | |
|---|---|---|
| second dose<br>● Griffin et al, 2021 reported a 3.2% hospitalization rate in fully vaccinated population, 6.2% in partially vaccinated population, and 7.6% in the unvaccinated population. The study also reported an ICU admission rate of 0.5% in the fully vaccinated group, 1% in the partially vaccinated group, and 1.5% in the unvaccinated group. These rates were measured during dominance of Delta variant.<br><br>**Death due to COVID-19**<br>● The study by Dagan et al. reported the following vaccine effectiveness against death caused by Alpha variant:<br>○ After 14-20 days: 72% (95% CI, 19 to 100)<br>○ After 21-27 days: 84% (95% CI, 44 to 100)<br>The study did not report VE against death after the second dose.<br>● Griffin et al, 2021 reported a 0.2% death rate in fully vaccinated population, 0.5% in partially vaccinated population, and 0.6% in the unvaccinated population. These rates were measured during dominance of Delta variant. | | |
| **HTAC judgment for *Pfizer-BioNTech*:** Real world evidence in individuals aged 16 and older across 5 studies [Lopez Bernal et al (UK); Nasreen et al (Canada); Dagan et al (Israel); Barlow et al (US); Reis et al. (Israel)] showed that *Pfizer-BioNTech* passed the vaccine effectiveness in preventing symptomatic COVID-19 caused by Delta, Alpha, Beta, and Gamma variants. However, an Israel MOH report showed that it did not pass the minimum VE for symptomatic COVID-19 caused by the Delta variant. Another US study (Griffin et al), although it did not report vaccine effectiveness, showed a decrease in rates of infection caused by the Delta variant in fully vaccinated individuals compared to partially vaccinated and unvaccinated individuals.<br><br>Israel MOH report showed that *Pfizer-BioNTech* passed the VE against severe COVID-19 caused by the Delta variant. Meanwhile, one real world study in Canada (Nasreen et al 2021), showed that the vaccine also | **HTAC judgment for *Moderna*:** Real world evidence in individuals aged 16 and older in one study [Nasreen et al. (Canada)] showed that Moderna passed vaccine effectiveness against symptomatic COVID-19 caused by Alpha and Delta variants.<br><br>One real world study in Canada (Nasreen et al.) showed that the vaccine also passed the minimum VE against severe COVID-19 caused by Alpha and Delta variants.<br><br>We noted that these studies evaluating effectiveness against variants of concern included both children and adults. | **HTAC judgment for *AstraZeneca, Janssen, and CoronaVac*:** Currently, there is limited evidence on the efficacy and effectiveness of *AstraZeneca, Janssen, and CoronaVac* against variants of concern in the pediatric population aged 18 years and below. |

| | | |
|---|---|---|
| passed the minimum VE against severe COVID-19 caused by Alpha variant but failed against severe COVID-19 caused by the Delta variant.<br><br>We noted that these studies evaluating effectiveness against variants of concern included both children and adults except Reis et al. which evaluated the vaccine effectiveness in children and adolescents aged 12 to 18 years old. | | |

***RQ.2.3: What is the safety of COVID-19 vaccines in the pediatric population in terms of:***

- ***serious adverse events,***
- ***all-cause mortality***
- ***systemic reactogenicity***
- ***local reactogenicity***
- ***special adverse events of interest (i.e. Bell's palsy, Myocarditis/Pericarditis, Thrombosis with Thrombocytopenia Syndrome, Capillary Leak Syndrome, Immune Thrombocytopenia)***

***HTAC Specifications:***
*Local and systemic reactions are tolerable, self-limiting and do not require hospitalization.*
*No serious adverse events were caused by the vaccine.*

***Short term outcomes*** *(e.g., reactogenicity and allergic reactions, SAEI): at least 2 months*
***Long term outcomes*** *(e.g., serious AEs, all-cause mortality, SAEI, Vaccine-associated enhanced disease): at least 1 year*

Evidence on safety for the pediatric population is based on *Evidence Summary of Pfizer-BioNTech* Version 2, the review of the Philippine Living Clinical Practice Guidelines Group (LCPG Group) (updated as of 8 September 2021), International Vaccine Access Center (IVAC) (updated as of 23 September 2021), COVID-NMA (updated as of 29 September 2021), and two additional studies -one from the US CDC and one retrospective study on myocarditis cases in the pediatric population (Jain et al. 2021).

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| Overall, the relevant reviews detected fourteen studies relevant to this sub-theme - two RCTs and twelve real world studies. Reports from two national regulatory agencies were also found.<br><br>***Safety data from clinical trials***<br>***Description of Evidence***<br>For clinical trial evidence on the pediatric population, you may refer to the *Evidence Summary of Pfizer-BioNTech* Version 2 which shows that the vaccine | Overall, the relevant reviews detected three studies relevant to this subtheme - one randomized control trial (RCT) and two real-world studies. Reports from two national regulatory agencies were also found.<br><br>***Safety data from Clinical trials***<br>***Description of evidence***<br>The LCPG review has detected one ongoing Phase II/III, placebo controlled trial by Ali et al, 2021 reported on the safety of *Moderna*. The study characteristics for this trial | There is currently no evidence detected by the relevant reviews on the efficacy (from trials) or effectiveness (from real world data) of *AstraZeneca and Janssen* against variants of concern in children and adolescents aged 18 years and younger. | | Overall, the relevant reviews detected only one study relevant to this sub-theme which is an RCT.<br><br>Targeted search for safety reports of countries implementing the vaccine for the pediatric population (Chile, Indonesia, and China) were conducted.<br><br>***Safety data from Clinical trials*** |

is safe in the known short-term safety outcomes, based on high certainty of evidence. However, its long term safety remains inconclusive, based on low certainty of evidence. In addition, one RCT was detected by the COVID-NMA, Thomas et al, 2021. Details of this trial can be found in the efficacy section.

***Key Findings***
*Quality of the study*
Thomas, et al., had an overall risk of bias of 'Some Concerns' as assessed by the COVID-NMA due to deviations from intervention.

*Clinical safety result*
The Thomas et al, 2021 study reported the following safety outcomes:

- Serious adverse event: RR=1.09 (0.85-1.41)
- All cause-mortality: RR= 0.6 (0.14-2.51)
- Incidence of any adverse event: RR=2.17 (2.09-2.26)

***Safety from Real World Evidence***
***Description of evidence***
Of the twelve real world studies, five were case series (Bickel, et al, 2021; Das, et al, 2021; Revon-Riviere, G. et al, 2021; Snapiri, et al, 2021; Tano, et al, 2021), one is a case study (Schauer, et al, 2021), and four cohort reviews (Hause, et al, 2021, Gargano, et al, 2021, and Pepe et al, 2021; Lane et al 2021; Boehmer et al. 2021; Jain et al. 2021) to which three are by the US Center for Disease Control's Advisory Committee on Immunization Processes [CDC-ACIP].

Three studies (i.e. Bickel, et al, 2021 and Revon-Riviere, G. et al, 2021, and Hause, et al, 2021) reported real world safety in general, while the other nine focused on myocarditis cases only. The Bickel, et al, 2021 study is a retrospective case series of 31 long term pediatric care facility residents aged 16-25 years old. Meanwhile, Revon-Riviere, G. et al, 2021 is a case series of 13 patients 16-21 years of age and with solid tumors. Of which, 7 patients are on chemotherapy, 2 on immunotherapy, 2 on targeted therapy and 2 that are on follow-up. Hause et al 2021 is a review of reports to the

is shown in the previous section.

***Key Findings***
*Quality of the study*
The risk of bias (RoB) was high due to incomplete outcome data considering that the published result of the Phase II/III trial was an interim analysis, thus, full assessment could not be made. Details of the RoB assessment of Ali et al. (2021) is presented in Appendix 2.

*Results on Safety*
*Short term outcomes*
The incidence of local adverse events (AEs) was higher in the *Moderna* group compared with the placebo group after any and after each dose. The most frequently reported local solicited AR in the *Moderna* group was injection site pain reported by 97.2% (93.1% after D1, 92.4% after D2). Majority of solicited local ARs was mild to moderate.

The incidence of systemic AEs was higher in the *Moderna* group compared with the placebo group after any and after each dose. The most frequently reported systemic solicited AR in the *Moderna* group after any dose was headache. The incidence of solicited systemic ARs was notably higher after dose 2 compared with dose 1. The majority of systemic solicited ARs was mild to moderate. Severity of systemic AEs increased from dose 1 to dose 2. Grade 4 solicited systemic ARs were recorded for 3 subjects in the *Moderna* group (fever, headache, nausea/vomiting).

There was an imbalance regarding the number of subjects reporting unsolicited AEs up to 28 days after any vaccination. The difference was mainly caused by injections site reactions (e.g., injection site lymphadenopathy, injection site erythema) persisting beyond day 7 after vaccination. There was no difference regarding the incidence of MAAEs between the vaccine and the placebo group. The safety profile of *Moderna* among adolescents from the study by Ali et al. is summarized in the table below.

*Long term safety outcomes*

***Description of evidence***
One randomized, double blind Phase I/II study reported on the safety and immunogenicity of *CoronaVac* (Han et al. 2021). In addition, one ongoing Phase III trial was detected by the NCPG. Please refer to the description of evidence in the effectiveness section for the study characteristics.

***Key Findings***
*Quality of the study*
The risk of bias (RoB) was high due to incomplete outcome data considering that the published result of the Phase I/II trial was an interim analysis, thus, full assessment could not be made. The allocation concealment was also unclear. Details of the RoB assessment of Han et al. (2021) is presented in Appendix 2.

*Results on Safety*
Incidences of adverse reactions were generally similar across the treatment groups with no dose-related concerns on safety. Only pain at the injection site was noted to occur more frequently in the vaccine group. No case of hypersensitivity was observed in both vaccine groups (1 case was noted in the control group). The GRADE table is presented in Appendix 2, which generally shows a very low level of certainty of evidence. The table below shows the safety outcomes within 28 days after dose 1 and 2 in the Han et al., 2021 study.

| | 1.5ug (n=219) | 3.0ug (n=217) | Placebo (n=114) | p-value |
|---|---|---|---|---|
| **ARs within 0-7d** | | | | |

Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported in v-safe, which is a smartphone-based safety surveillance system.

The table below describe the population examined in the other six pediatric studies that focused on myocarditis:

| Study | Design | Population |
|---|---|---|
| CDC- ACIP (Gargano et al, 2021) | Cohort review | 323 cases* of VAERS reported cases meeting the CDC diagnosis of myocarditis/pericarditis, aged 12-29 years (US) |
| Das, et al, 2021 | Review of case reports in the literature as of Jun 2021 | 29 cases of vaccine-related myocarditis, 13 were aged 16-18 years (Italy and US) |
| Pepe et al, 2021 | Cohort review | Review of myocarditis reports from the regulatory agencies of five countries (Australia, Israel, the UK, Europe, Canada) across all eligible age groups, including pediatric population. **No disaggregation of cases per age were reported.* |
| Schauer, et al, 2021 | Retrospective case review | 13 patients younger than 18 year old with chest pain and signs of pericarditis within 1 week of receiving the 2nd dose of BNT162b2 (US) |

At the time of the report, no anaphylactic reaction, SAEs with fatal outcome or deaths were reported. No cases of myocarditis have been reported, although 3 participants who received the vaccine reported symptoms that could be consistent with myocarditis or pericarditis.

| | Vaccine Group (N=2,485) | Placebo (N=1,1240) | Risk Ratio (95% CI) | Certainty of Evidence |
|---|---|---|---|---|
| **Solicited Local AE** | 2,431 (97.8%) | 602 (48.5%) | 2.2. (1.9, 2.13) | High |
| **Solicited Systemic AE** | 2,284 (91.8%) | 830 (66.9%) | 1.37 (1.32, 1.43) | High |
| **Unsolicited AE** | 510 (20.5%) | 197 (15.9%) | 1.17 (1.12, 1.22) | Moderate |
| **Severe unsolicited AE** | 4* (0.2%) | 1 (<0.1%) | 2.0 (0.22, 17.83) | Low |
| **Any Serious AE** | 2 (<0.1%) | 1 (<0.1%) | 0.54 (0.03, 8.67) | Low |
| Related | 0 | 0 | 0 | NA |
| **Death** | 0 | 0 | 0 | NA |

*NA - not assessed*
* appendicitis, diarrhea, vomiting, drug-induced liver injury, testicular torsion, concussion in 4 participants

***Safety from Real World Evidence***

***Description of evidence***

The study detected in the LCPG review by Pepe et al, 2021 is a review of the safety monitoring data of national regulatory agencies and ministries of health covering the pediatric and adult populations eligible per brand in five countries/regions [i,e. Israel, UK, Europe, Canada, and USA]. However, the review of Pepe et al, 2021 did not present their data on the events of myocarditis and pericarditis in the pediatric population.

***Key findings***

*Quality of the study*

| | | | | |
|---|---|---|---|---|
| Any | 51 (23%) | 59 (27%) | 22 (19%) | 0.28 |
| Pain at injection site | 36 (16%) | 35 (16%) | 2 (2%) | <0.0001 |
| **Systemic ARs** | | | | |
| Fever | 9 (4%) | 11 (5%) | 5 (4%) | 0.93 |
| Hypersensitivity | 0 | 0 | 1 (1%) | 0.21 |
| **Unsolicited AR within 0-28 days** | | | | |
| Any | 11 (5%) | 15 (7%) | 9 (8%) | 0.52 |
| **Overall AR within 0-28 days** | | | | |
| Any | 56 (26%) | 63 (29%) | 27 (24%) | 0.55 |
| Grade 3 (severe) | 2 (1%) | 0 | 0 | 0.39 |

***Safety from Real World Evidence***

There is currently no evidence detected by the NCPG (refer to Appendix 2, Part 2) or internal targeted search in implementing countries (Chile, Indonesia, China) on the safety (from real world data) of *CoronaVac* in children and adolescents aged 17 years and younger.

| | | |
|---|---|---|
| Snapiri, et al, 2021 | Retrospective case series | 7 patients aged 16-17 year old with chest pain after vaccination (Israel) |
| Tano, et al, 2021 | Retrospective case series | 8 adolescents with perimyocarditis within 4 days of receiving a dose of BNT162b2 |
| Lane et al, 2021 | Surveillance reports | Incidence of myocarditis and pericarditis among individuals aged 12 and above after receiving the first or second dose of mRNA vaccine from the United Kingdom, United States, and European Economic Area from December 2020 to August 2021. |

*The US CDC reported cases also include those who received *Moderna.*

***Key Findings***

*Quality of studies*

Bickel et al, Revon-Riviere et al; and Jain et al. based on the appraisal of HTAU had 'very serious' RoB due to lack of randomization, allocation concealment, blinding of participants, investigators and assessors, and low control for confounders. Meanwhile, the RoB assessment for Hause et al., Gargano et al., Pepe et al.,Lane et al., and Boehmer et al. were not performed as these are surveillance studies and reports from NRAs. The RoB assessment of Das et al., Snapiri et al., Schauer et al., and Tano et al. were also not performed as these are case series and case reports.

*Safety results*

**Reactogenicity and adverse events**

The Bickel, et al, 2021 study reported that the majority of the 31 participants did not report any side effects.

RoB for Pepe et al. and Lane et al. was not performed as these are surveillance studies.

*Results on safety*

The study of Pepe et al. (2021) which reviewed regulatory agency reports of post-COVID-19 vaccination myocarditis or pericarditis cases from different countries cites incidence rates ranging from 1.6 to 13.5 per million doses for different vaccine brands or platforms . The number of cases of myocarditis or pericarditis following *Moderna* included in the review are detailed in the table below.

| Country | Regulatory agency | # cases of myocarditis/ pericarditis | Incidence rate |
|---|---|---|---|
| UK | UK Medicines and Healthcare Products Regulatory Agency | 9 cases of myocarditis<br>9 cases of pericarditis<br>1 case of endocarditis | mRNA: 5.0 per million doses<br><br>AstraZeneca: 3.7 per million doses |
| EU | European Medicines Agency | 16 cases of myocarditis<br>18 cases of pericarditis | mRNA: 1.6 per million doses<br><br>viral vectors: 2.0 per million doses |
| Canada | Public Health Agency of Canada (PHAC), Health Canada | 40 cases of myocarditis/pericarditis | from mRNA vaccines and AstraZeneca: 3.9 per million doses |

Another study by Lane et al. (2021) looked into surveillance reports on the incidence of myocarditis and pericarditis among individuals aged 12 and above after receiving the first or second dose of mRNA vaccine. Reports were obtained from the United Kingdom, United States, and European Economic Area from December 2020 to August 2021. The table below summarizes the study findings specifically for the pediatric population:

| Country | Reporting syste | Age group | Number of cases of myocarditis or pericarditis | Incidence rate |
|---|---|---|---|---|

However, the duration of follow-up was not mentioned in the study. The following are the reported safety outcomes in the study:

- Proportion with no reported adverse events:
  - 26 out of 31 (83.9%) after dose 1
  - 23 out of 31 (74.2%) after dose 2
- Agitation or discomfort - *most common*
  - 3 out of 31 (9.7%) after dose 1
  - 4 out of 31 (12.9%) after dose 2
- Nausea
  - 2 out of 31 (6.5%) after dose 1
  - 1 out of 31 (3.2%) after dose 2
- Fever
  - 0 out of 31 (0.0%) after dose 1
  - 2 out of 31 (6.5%) after dose 2

Additionally, the study of Revon-Riviere et al, 2021 reported the following safety outcomes:

- Proportion with no reported side effects:
  - 5 out of 13 after dose 1
  - 4 out of 11 after dose 2
- At least one systemic reaction/s:
  - 3 out of 13 after dose 1
  - 5 out of 11 after dose 2
- At least one local reaction/s:
  - 6 out of 13 after dose 1
  - 2 out of 11 after dose 2

**Myocarditis and Pericarditis**

On August 6, the CDC-ACIP (Hause, et al, 2021) published its review of adverse events reported in two US databases, namely, US FDA's Vaccine Adverse Event Reporting System (VAERS) and US CDC's 'v-safe' (a smartphone-based safety surveillance system). As of July 16, 2021, the VAERS received 9,246 reports of adverse events (AEs) out of 8.9 million adolescents (12-17 years old) vaccinated with *Pfizer-BioNTech*. A total of 90.7% of these reports were for non-serious adverse events and 9.3% were for serious adverse events, including myocarditis (4.3%). Meanwhile, out of the 129,000 adolescents enrolled in the 'v-safe', 63.9% reported local AEs after dose 1 and 62.4% after dose 2 and 48.9% reported systemic AEs after dose 1 and 63.4% after dose 2. CDC-ACIP noted that this frequency is similar to that reported in preauthorization clinical

| | m | | Myocarditis | Pericarditis | Myocarditis | Pericarditis |
|---|---|---|---|---|---|---|
| UK<br><br>As of 04 Aug 2021 | Yellow Card scheme | Not disaggregated | 29 cases | 25 cases | 2.07 cases per million vaccine recipients who received at least 1 dose) | 1.79 cases per million vaccine recipients who received at least 1 dose |
| US<br><br>As of 06 Aug 2021 | Vaccine Adverse Event Reporting System [VAERS] | 6-17 years (all ages for incidence rates) | 3 cases | 1 case | 3.65 cases per million fully vaccinated individuals | 2.69 cases per million fully vaccinated individuals |
| EU<br><br>As of 04 Aug 2021 | European Economic Area [EEA] EudraVigilance | 12-17 years (all ages for incidence rates) | 1 case | 0 case | 6.15 cases per million vaccees who received at least 1 dose | 3.84 cases per million vaccine recipients who received at least 1 dose |

***Safety Reports from NRAs***

Two national regulatory agencies (NRAs) were noted to have reports about the safety of mRNA vaccines.

The Government of Canada (2021) indicated that *Moderna* is considered safe and effective in preventing COVID-19 symptomatic infection among adolescents aged 12 to 17, as evidenced by Phase III clinical trials. Common AEs include injection site inflammation and flu-like symptoms (chills, fatigue, joint pain, headache, mild fever, muscle aches). Rare adverse events include myocarditis, pericarditis, Bell's palsy, and anaphylactic reaction. Its safety and effectiveness in people younger than 12 years of age have not yet been established.

In addition, the Health Service Authority of Singapore (2021) stated that among individuals aged 12 to 18 years, the most common AEs include rash, hives, angioedema

trials. Systemic events were also more common after dose 2. Overall, ACIP conducted a risk-benefit assessment and continues to recommend the *Pfizer-BioNTech* for all persons aged ≥12 years.

In terms of mRNA-vaccine related myocarditis, the US CDC database review estimated a rate of 40.6 cases per million second doses in males 12-29 years old and 4.2 for females. The highest rate was found with males 12-17 years old at 62.8 cases per million doses of either *Pfizer-BioNTech* and *Moderna*. However, the ACIP concluded that the benefit of mRNA vaccination still outweigh the risks, including the risk of myocarditis after vaccination, for all age groups. This conclusion was based on evidence that 5,700 COVID-19 cases per million vaccines in males and 8,500 in females can be prevented with mRNA vaccination.

The surveillance study of Lane et al, 2021 which looked at the 6 August 2021 data for VAERS and EudraVigilance; and 4 August 2021 data for Yellow Card scheme reported the incidence of myocarditis and pericarditis. The table below summarizes the results of the study.

| Country | Reporting system | Age group | Number of cases of myocarditis or pericarditis | | Incidence rate | |
|---|---|---|---|---|---|---|
| | | | Myocarditis | Pericarditis | Myocarditis | Pericarditis |
| UK<br><br>As of 04 Aug 2021 | Yellow Card scheme | Not disaggregated | 29 cases | 25 cases | 2.07 cases per million vaccine recipients who received at least 1 dose) | 1.79 cases per million vaccine recipients who received at least 1 dose |
| US<br><br>As of 06 Aug 2021 | Vaccine Adverse Event Reporting System [VAERS] | 6-17 years (all ages for incidence rates) | 3 cases | 1 case | 3.65 cases per million fully vaccinated | 2.69 cases per million fully vaccinated |

(swelling of the eyelids, face and lips), shortness of breath, fever, dizziness, lightheadedness and syncope. Cases of Bell's Palsy (facial muscle weakness caused by inflammation of the facial nerve) have also been observed. Although there is a small increased risk of myocarditis and pericarditis in the younger age groups (30 years and below), the local incidence rate remains low.

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | individuals | individuals |
| EU<br><br>As of 04 Aug 2021 | European Economic Area [EEA] EudraVigilance | 12-17 years (all ages for incidence rates) | 1 case | 0 case | 6.15 cases per million vaccees who received at least 1 dose | 3.84 cases per million vaccine recipients who received at least 1 dose |

The study of Pepe et al, 2021 reviewed regulatory agency reports of post-COVID 19 vaccination myocarditis or pericarditis cases from four countries (Australia, Israel, UK, and Canada) and the European Union. Incidence rates ranged from 1.6 to 13.5 per million doses, as detailed in the table below. The reports, however, were not limited to events in children.

| Country | Regulatory Agency | Number of Cases | Incidence |
|---|---|---|---|
| Australia | Department of Health Therapeutic Goods Administration | 50 myocarditis or pericarditis | *Pfizer-BioNTech:* 13.5 per million doses |
| Israel | Ministry of Health | 62 myocarditis | *Pfizer-BioNTech:* 12.4 per million patients |
| UK | UK Medicines and Healthcare Products Regulatory Agency | 81 myocarditis, 63 pericarditis | mRNA vaccines: 5.0 per million doses<br><br>*AstraZeneca*: 3.7 per million doses |
| EU | European Medicines Agency | 122 myocarditis, 126 pericarditis | mRNA vaccines: 1.6 per million doses<br><br>viral vectors: 2.0 |

| | | | |
|---|---|---|---|
| | | | per million doses |
| Canada | Public Health Agency of Canada (PHAC), Health Canada | 111 myocarditis/pericarditis | three-brands combined (*Pfizer-BioNTech:, Moderna, and AstraZeneca* ):<br><br>3.9 per million doses |

The clinical presentation of the mRNA vaccine-associated myocarditis/pericarditis in children and adolescents is consistent across the case reports, case series, and the CDC review examined by the LCPG. Majority were males (>90%) and nearly all presented after the second dose, commonly within 7 days after vaccination. The common symptoms included chest pain, fever, palpitation, shortness of breath, fatigue, nausea, vomiting, often transient and self limiting. Median interval of the symptoms was 2 days. All reported cases had elevated troponin and C-reactive protein. The most common abnormal ECG changes included ST-segment elevation and diffuse ST changes. On echocardiography, left ventricular function was normal The clinical course was mild and all patients recovered and discharged home in less than a week. No deaths have been reported.

According to the report by Boehmer et al. (2021), there is an elevated risk for myocarditis among mRNA COVID-19 vaccine recipients, particularly among males in the younger age group including children aged 12 and above. In males aged 12 to 29 years old, 39–47 cases of myocarditis, pericarditis, and myopericarditis per million second mRNA COVID-19 vaccine doses administered are expected.

Lastly, in the study by Jain et al. 2021, there were 63 cases of acute myocarditis reports in individuals aged <21 years old in the US from March to June 2021.

| | | | |
|---|---|---|---|
| ***Safety Reports from NRAs***<br>Government of Canada (2021): This agency officially states that mRNA vaccines *Pfizer-BioNTech* and *Moderna* are considered safe and effective in preventing COVID-19 symptomatic infection among adolescents aged 12 to 17, as evidenced by Phase III clinical trials. Common AEs include injection site inflammation and flu-like symptoms (chills, fatigue, joint pain, headache, mild fever, muscle aches). Rare adverse events include myocarditis, pericarditis, Bell's palsy, and anaphylactic reaction. Its safety and effectiveness in people younger than 12 years of age have not yet been established.<br><br>HSA, Singapore (2021): In 12 to 18 years, most common AEs include rash, hives, angioedema (swelling of the eyelids, face and lips), shortness of breath, fever, dizziness, lightheadedness and syncope. Cases of Bell's Palsy (facial muscle weakness caused by inflammation of the facial nerve) have also been observed. Although there is a small increased risk of myocarditis and pericarditis in the younger age groups (30 years and below), the local incidence rate remains low | | | |
| **HTAC judgment for *Pfizer-BioNTech*:** Based on the current evidence from the phase III clinical trials and real world safety reports, short-term safety of Pfizer-BioNTech is acceptable. However, further follow-up data is needed to establish longer-term safety. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the Pfizer-BioNTech vaccine, the benefits still outweigh the risks for vaccination in this population. | **HTAC judgment for *Moderna*:** Based on the current evidence from the phase III clinical trial with high certainty of evidence (Ali et al), short-term safety of Moderna for the pediatric population (12 to 17 years old) is acceptable. However, further follow-up data is needed to establish longer-term safety. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the Moderna (Pepe et al, Lane et al.), the benefits still outweigh the risks for vaccination in this population. | **HTAC judgment for *AstraZeneca and Janssen*:** Currently, there is limited evidence on the efficacy and effectiveness of *AstraZeneca and Janssen* against variants of concern in the pediatric population aged 18 years and below. | **HTAC judgment for *CoronaVac*:** Currently, there is limited evidence on the safety of *CoronaVac* for the pediatric population. Current available evidence from the Phase I/II trial shows that short term safety in children and adolescents aged 3 to 17 years old were found to be similar to the adult population.<br><br>Further studies are anticipated to strongly conclude on its safety for this age group. |
| ***RQ.2.4: Does the COVID-19 vaccines provide a highly favorable benefit/risk profile in the context of observed vaccine effectiveness in the pediatric population?***<br><br>***HTAC Specifications:***<br>*Favorable benefit/risk profile* | | | |
| **Pfizer-BioNTech** | **Moderna** | **AstraZeneca** | **Janssen** | **CoronaVac** |

| | | |
|---|---|---|
| Trial evidence on adolescents aged 12-15 years old shows that the clinical benefits of *Pfizer-BioNTech* in terms of decreased occurrence of symptomatic COVID-19 outweigh the known short-term risks.<br><br>Efficacy and effectiveness against symptomatic hospitalization due to COVID-19, death due to COVID-19, asymptomatic COVID-19, and against new variants were not reported in the detected studies. Thus, the benefit/risk profile specifically for these pediatric subgroups cannot be determined. | Current available evidence from Phase II/III trial (Ali et al, 2021) covering adolescents aged 12-17 years old shows that the clinical benefits of *Moderna* in terms of decreased occurrence of symptomatic COVID-19 outweigh the known short-term risks based on data available at the time of evaluation. One real world evidence study on the general population which includes the pediatric population also shows that *Moderna* is capable of decreasing the incidence of symptomatic and severe COVID-19 caused by both the Alpha and Delta variants. Studies and reports on safety reveal that the benefits of this vaccine outweigh risks associated with AEs (i.e. rare cases of myocarditis or pericarditis).<br><br>Trial evidence on adolescents aged 12-15 years old with regard to VEs against symptomatic COVID-19 among individuals with comorbidities, hospitalization due to COVID-19, death due to COVID-19, asymptomatic COVID-19 were not reported in the trial. Thus, the benefit/risk profile specifically for these subgroups cannot be determined for this population. | The efficacy, effectiveness and safety in the pediatric population below 18 years old is yet to be established , thus, the benefit risk profile in this age group cannot be assessed at the moment. |
| **HTAC judgment for *Pfizer-BioNTech*:** *Pfizer-BioNTech* passed the benefit risk profile assessment in adolescents aged below 12 years and older based on efficacy and short term safety data. | **HTAC judgment for *Moderna*:** *Moderna* passed the benefit risk profile assessment in adolescents aged 12 to 17 years based on efficacy and short term safety data. | **HTAC judgment for *AstraZeneca, Janssen, and CoronaVac*:** The benefit risk profile cannot be assessed due to current limited evidence. |

## Criterion 3: Affordability and Viability

***RQ3.1: What are the current implementation experiences, challenges and strengths related to the use of COVID-19 Vaccines, specifically on the following?***

- ***delays in supply delivery with implications on capacities of manufacturers***
- ***incidents of errors in preparation and administration using specific vaccine brands***
- ***implementation advantage or benefit in using specific vaccine brands***
- ***variations in implementing the COVID-19 vaccination program in LGUs***
- ***handling serious AEFIs and challenges in the management of serious AEFIs***
- ***any other implementation barriers***

***HTAC Specifications***
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.

Based on a consultation with the National Vaccine Operations Center (NVOC), the following are the common challenges encountered in the implementation of the COVID-19 Vaccination Program:

- delays in the delivery of some vaccine brands to the country;
- wastage of COVID-19 vaccines due to temperature excursions during storage
- requirement of intricate techniques among personnel in the preparation of vaccines which are prone to error;
- inadvertent administration of a different vaccine brand for the second dose;
- lack of mechanism to track vaccine recipients to ensure that they receive the appropriate vaccination regimen (i.e., same brands for both doses and correct number of dose/s); and
- longer time required from the time of delivery up to its actual roll-out in the site for vaccines needing more tedious assessment of readiness of vaccination sites prior implementation i.e., those requiring storage temperatures below 2 to 8 degrees Celsius.

The NVOC has noted the following observed measures to address these challenges:

- Despite delays in delivery of vaccines, proper training and preparations for the rollout of vaccines are ensured through alignment of BIHC and NVOC on vaccine brands that will be available.
- Development Management Officers (DMOs) report to the vaccination sites to monitor compliance to the standard vaccination process.
- To assess quality and compliance to the vaccination process, the DOH regional offices (Centers for Health Development) use supportive supervision tools. This is discussed weekly by the Regional Vaccines Operation Centers (RVOCs).
- Inadvertent administration of a different vaccine brand is addressed by conducting re-trainings and reassessment of the vaccination sites. Future incidents are prevented by highlighting the importance of checking vaccination cards. Additionally, the simultaneous implementation of two vaccine brands in one vaccination site is also minimized.
- Mechanisms to track vaccine recipients are being developed in coordination with the Department of Information and Communications Technology (DICT) to ensure that they receive the appropriate vaccination regimen.

The NVOC noted that it is easier and faster to roll out vaccines with storage temperature requirements of 2 to 8 degrees Celsius. These vaccines can be rolled out within the same day of delivery to the site. Meanwhile, vaccines with lower storage temperature requirements are harder to roll out since limited areas have the required equipment. Further, longer preparation time is needed for these vaccines, thus the rollout cannot be initiated right after the vaccine delivery to the site.

In terms of management of Adverse Events Following Immunization (AEFIs), the DOH-Epidemiology Bureau (EB) cited the following challenges:

- Insufficient financial risk protection for individuals who experienced AEFIs based on reports from regional offices which shows that allowable national health insurance and other fundings are being maxed out;
- Uneven capacity in clinical detection, diagnostic evaluation and management across different areas;
- Inadequacy of reporting or on-reporting of AEFIs among vaccinated individuals experiencing AEFIs. In most cases, individuals experiencing AEFIs seek services directly from hospitals. However, vaccination history is not integrated in the routine questions during full history and physical examination in most hospitals leading to loss of capture of potential AEFI cases;
- Passive nature of AEFI surveillance which includes surveillance of breakthrough infections both at the local and international setting; and

- Limited capacity to conduct individual and population-level causality assessment, signal management, and risk-benefit assessment.

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| Aside from the aforementioned challenges above, the NVOC also noted specific challenges on the current implementation of *Pfizer-BioNTech*:<br>● ***Vaccine preparation:*** *Pfizer-BioNTech* requires intricate vaccine preparation which is prone to error (i.e., a special inverting and extraction technique is needed to be performed which increases the risk of puncturing the rubber stopper).<br>● ***Manpower*****:** *Pfizer-BioNTech* requires pharmacists designated for vaccine preparation as compared to other vaccine brands which can be prepared by the vaccinators.<br>● ***Storage temperature requirement*****:** *Pfizer-BioNTech* requires ultra-low temperature freezers (ULTF), thus the vaccine can only be allocated to vaccination sites with the required logistical facilities.<br>● ***Site temperature requirement:*** *Pfizer-BioNTech* requires an ambient temperature of not more than 25ºC during administration, thus requiring an air conditioning system to tailor fit the vaccination sites.<br>● ***Longer waiting time for patients:*** Since *Pfizer-BioNTech* is available as a multi-dose preparation, the vaccine's requirement of a certain viable number of vaccine recipients prior to vaccine preparation may result in longer waiting time.<br>● ***Longer preparation time before rollout:*** Initiation of *Pfizer-BioNTech* rollout takes a longer period of time as it needs more tedious site readiness assessment to ensure that the site meets the above mentioned requirements. | Aside from the aforementioned challenges above, the NVOC also noted specific challenges on the current implementation of *Moderna*:<br>● ***Vaccine preparation:*** *Moderna* requires intricate vaccine preparation which is prone to error (i.e., swirling and observing figure 8 motion).<br>● ***Longer waiting time:*** Since *Moderna* is available as a multi-dose preparation, the vaccine's requirement of a certain viable number of vaccine recipients prior to vaccine preparation may result in longer waiting time.<br>● ***Decreased viability due to ambient air requirement***: An unopened vial of the *Moderna* can only be viable for use up to 12 hours in an area with temperature of 2°C to 25°C. Meanwhile, once the vial is punctured, its viability decreases to 6 hours if stored at 2°C to 8°C.Thus, careful planning of the timing of vaccine preparation should be done to avoid wastage.<br>● ***Longer preparation time before rollout:*** Initiation of *Moderna* rollout takes a longer period of time as it needs more tedious site readiness assessment to ensure that the site meets the above mentioned requirements. | Aside from the aforementioned challenges above, the NVOC also noted specific advantages and challenges on the current implementation of *AstraZeneca:*<br>● ***Storage Temperature Requirement:*** The rollout for this vaccine required less preparations with a storage temperature requirement of 2°C to 8°C.<br>● ***Supply delivery delays*****:** There were delays in the supply delivery of *AstraZeneca* due to production-related challenges in India where supplies in our region are manufactured.<br>● ***Logistical challenges involving administering the 2nd dose:*** *AstraZeneca* requires a longer dosing interval and there were cases of change in residence of vaccine recipients prior to their second dose. This resulted in challenges in securing vaccine supply and tracking of vaccine recipients for their second dose.<br>● ***Time- sensitive rollout:*** The rollout of *AstraZeneca* has been time-sensitive due to the following considerations:<br>○ donated supplies are delivered 2-3 months after manufacture<br>○ the shelf-life of *AstraZeneca* is 6 months<br>○ the dosing interval of *AstraZeneca* is 8 to 12 weeks<br><br>Despite the manageable cold chain | Aside from the aforementioned challenges above, the NVOC also noted specific advantages and challenges on the implementation of *Janssen*:<br>● ***Storage temperature requirement:*** The rollout for this vaccine required less preparations with a storage temperature requirement of 2°C to 8°C.<br>● ***One-dose vaccine:*** As a one-dose vaccine, it also offers implementation advantages in terms of the vaccination rollout.<br>● ***Longer waiting time for patients:*** Since *Janssen* is available as a multi-dose preparation, the vaccine's requirement of a certain viable number of vaccinees prior to vaccine preparation may result in longer waiting time. | Aside from the aforementioned challenges above, the NVOC also noted specific advantages and challenges on the current implementation of *CoronaVac*:<br>● ***Storage Temperature Requirement:*** The rollout for this vaccine required less preparations with a storage temperature requirement of 2°C to 8°C.<br>● ***Single Dose Vial Preparation:*** Since *CoronaVac* is available as a single dose vial, preparation is easier and waiting time for vaccinees is minimized.<br>● ***Delays in Delivery:*** There were noted delays in deliveries as supply of *CoronaVac* is expected to arrive once a week. The NVOC detailed that in July 2021, there was a 2-week period wherein no vaccines of this brand were delivered. |

| | | | | |
|---|---|---|---|---|
| | | requirement, the lack of a centralized database for the vaccination program as mechanism to track vaccine recipients and the longer dosing interval of 8 to 12 weeks have made the *AstraZeneca* less viable to implement compared to other vaccines with the same storage temperature requirement such as *CoronaVac* with a 4-week dosing interval or the single-dose *Janssen*. | | |
| **HTAC judgment for *Pfizer-BioNTech*:** Based on the current experience in the COVID-19 Vaccination Program, the vaccine implementation with *Pfizer-BioNTech* was generally challenging due to the intricacies in the storage, handling, and preparation of these vaccines, the NVOC implemented measures and ensures proper training and preparation prior to the rollout to mitigate these challenges. | **HTAC judgment for *Moderna:*** Based on the current experience in the COVID-19 Vaccination Program, the vaccine implementation with Moderna was generally challenging due to the intricacies in the storage, handling, and preparation of these vaccines, the NVOC implemented measures and ensures proper training and preparation prior to the rollout to mitigate these challenges. | **HTAC judgment for *Astrazeneca*:** Based on the current experience in the COVID-19 Vaccination Program, the implementation of *AstraZeneca* in the Philippine COVID-19 Vaccination Program was generally manageable to roll out despite logistical issues involving its requirement of a longer interval of 8 to 12 weeks between doses. However, despite its manageable cold chain requirement, this longer dosing interval and the lack of a centralized database for the vaccination program as a mechanism to track vaccine recipients have made the vaccine less viable to implement compared to other vaccines with the same storage temperature requirement. | **HTAC judgment for *Janssen*:** Based on the current experience in the COVID-19 Vaccination Program, the implementation of *Janssen* in the Philippine COVID-19 Vaccination Program was generally manageable to roll out due to its single-dose regimen and storage temperature requirement. A longer waiting time for vaccinees as a result of it being a multi-dose vial preparation was noted. | **HTAC judgment for *Sinovac*:** Based on the current experience in the COVID-19 Vaccination Program, the implementation of *CoronaVac* in the Philippine COVID-19 Vaccination Program was generally manageable to roll out due to its temperature requirement and single-dose vial presentation. |
| ***RQ3.2.: Are COVID-19 Vaccines affordable for pediatric vaccination?***<br><br>***HTAC Specifications***<br>Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets.<br><br>**The vaccine unit cost is comparable with those in other ASEAN countries.*<br><br>**The vaccine implementation cost is a reasonable and acceptable allocation of resources.* | | | | |
| **Pfizer-BioNTech** | **Moderna** | **AstraZeneca** | **Janssen** | **CoronaVac** |

According to the Department of Finance (DOF), the unit price of the *Pfizer-BioNTech and Moderna* offered to the Philippine government is within the price range at which the *Pfizer-BioNTech and Moderna* is available in various markets globally.

Based on clinical evidence, *Pfizer-BioNTech* along with *Moderna* can be used for pediatric vaccination for ages 12 to 17 years old. Further, both vaccine brands currently hold an EUA by the Philippine FDA for this population.

As disclosed by the DOF, the 2021 supplies of *Pfizer-BioNTech* and *Moderna* are sufficient to cover the 12 to 17 years age group, should vaccination be extended to this subpopulation in 2022. Hence, it will not incur cost for the 2022 budget. The unit costs of vaccines used in the analyses were based on the January 2021 price offer to the government as disclosed in confidence by DOF. The additional cost of consumables, logistics, and other operations cost were sourced from the DOH National Immunization Program.

The table below compares the number of vaccinees that can be still covered with the computed remaining supplies of *Pfizer-BioNTech* and *Moderna* which supports the assumption that 2021 supplies of *Pfizer-BioNTech and Moderna* are sufficient for the vaccination of the 12 to 17 years age group. Details of the costing assumptions are provided in Appendix 5.

| **Supply** | | **Demand** | | **Supply** | |
|---|---|---|---|---|---|
| **Source** | **Number of Vaccinees that can be vaccinated with the remaining supply** *(Based on the national vaccine coverage as of Sept 6)* | **PSA Target** *(10-19 year olds)* | **DPCB-NVOC Target** *(12-18 year olds)* | **Source** | **Number of Vaccinees that can be vaccinated with the remaining supply** *(Based on the national vaccine coverage as of Sept 6)* |
| **Scenario 1: Procured and Donated Doses** | | | | **Scenario 1: Procured and Donated Doses** | |
| **Procured** *(January 15 NVOC Allocation)* + **Donated** Supplies *(BIHC report)* | **32,767,361** | **21,185,343** | **10,000,000** | **Procured** *(January 15 NVOC Allocation)* + **Donated** Supplies *(BIHC report)* | **32,767,361** |

Affordability was not assessed for this brand due to limited clinical evidence in the pediatric population. Further, these vaccines currently do not have EUA for the pediatric population.

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| **HTAC judgment for *Pfizer-BioNTech and Moderna*:** According to the DOF, the supply of *Pfizer-BioNTech and Moderna* procured in 2021 are sufficient to vaccinate the pediatric population aged 12 to 17 years, thus, its implementation will not incur additional cost from the 2022 budget. | **HTAC judgment for *AstraZeneca, Janssen, and CoronaVac*:** Cannot be assessed |

***RQ3.3.:*** *What are the budget implications of using the COVID-19 vaccines for the pediatric population?*

***HTAC Specifications***
*Proportionality of the size of the population to be vaccinated versus the cost.*

*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.*

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| According to the DOF, the supply of *Pfizer-BioNTech* and *Moderna* procured in 2021 are sufficient to vaccinate the pediatric population aged 12 to 17 years, thus, its implementation will not incur additional cost from the 2022 budget. Hence, the pediatric vaccination strategy with *Pfizer-BioNTech* is considered affordable. | | Budget implications were not assessed for this brand due to limited clinical evidence in the pediatric population. Further, these vaccines currently do not have EUA for the pediatric population. | | |

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| **HTAC judgment for *Pfizer-BioNTech and Moderna*:** The share of the cost of the *Pfizer-BioNTech* to the total 2021 vaccine budget is considered commensurate to the share of the population to be vaccinated using the said vaccine. | **HTAC judgment for *AstraZeneca, Janssen, and CoronaVac*:** Cannot be assessed |

***RQ3.4.: Do COVID-19 vaccines represent good value for money in terms of preventing COVID-19 morbidity and mortality?***

***HTAC Specifications***
*The HTAC deems that the health, economic, and social benefits of the vaccination program outweigh the costs.*

*The vaccine is a cost-effective/ efficient allocation of resources.*

- *Formal cost-effectiveness analysis (CEA) will be done (not under EUA). It will be performed when enough evidence is available at the time of full marketing authorization*
- *Societal perspective will be taken due to the observed social and economic impacts of COVID-19*
- *CEA currently not done in rapid reviews under pandemic situation because of emergency nature.*

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
|---|---|---|---|---|
| *Pfizer-BioNTech* represents good value for money in terms of lowering symptomatic COVID-19 and severe COVID-19 for the pediatric population aged 12-15 years old (Frenck et al., 2021), based on moderate certainty of evidence. Immunogenicity data on adolescents aged 12 to 15 years also demonstrated noninferiority when compared with young adults aged | *Moderna* represents good value for money in terms of reducing the risk of symptomatic COVID-19 caused by the original strain in patients aged 12-17 years old (Ali et al., 2021). It also represents good value for money in terms of reducing the risk of symptomatic COVID-19, severe COVID-19 caused by the Alpha, and Delta variants in a population | Value for money was not assessed for this brand due to limited clinical evidence in the pediatric population. Further, these vaccines currently do not have EUA for the pediatric population. | | |

| | | |
|---|---|---|
| 16 to 25 years old. Current real world studies also suggest its potential clinical benefits in terms of symptomatic COVID-19, moderate to severe COVID-19, and hospitalization due to COVID-19.<br><br>It also represents good value for money in terms of lowering symptomatic COVID-19 caused by Delta, Alpha, Beta, and Gamma based on 5 real world studies in individuals aged 16 and older. However, an Israel MOH report showed that it did not pass the minimum VE for symptomatic COVID-19 caused by the Delta variant.<br><br>*Pfizer-BioNTech* also represents good value for money, in terms of lowering severe COVID-19 caused by the Delta variant based on one study by the Israel MOH. However, another real world study in Canada (Nasreen et al. 2021) reported a VE against severe Delta infection below HTAC threshold (i.e., at least 80% VE) but passed the threshold against severe Alpha variant infection. | including 16 years and older (Nasreen et al, 2021). | |
| **HTAC judgment for *Pfizer-BioNTech*:** The use of *Pfizer-BioNTech* in the pediatric population aged 12 years and older represents good value for money in terms of preventing symptomatic infections, severe infections and hospitalizations associated with COVID-19 and variants of concern. | **HTAC judgment for *Moderna*:** The use of *Moderna* in the pediatric population represents good value for money in terms of preventing symptomatic infections caused by the original strain for 12-17 year-olds, and in preventing symptomatic and severe COVID-19 caused by variants of concern in ages 16 years and older. | **HTAC judgment for *AstraZeneca, Janssen, and CoronaVac*:** Cannot be assessed |

# Criterion 4: Household Financial Impact

## *RQ 4.1: Will the vaccine reduce or not add further to the out-of-pocket expenses of Filipino households?*

***HTAC Specifications***
The adoption of the vaccine can reduce out-of-pocket spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

As mandated by Philhealth Circular 2021-0014 and Philhealth Circular 2020-0009, the following benefit packages with corresponding case rates related to COVID-19 are available for the general population. Note that these also cover the pediatric population as there are no separate benefit packages for this subgroup.

1. Isolation Package for asymptomatic and mild cases (C19CI): Case rate = Php 22,499.00
2. Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Case rate= Php 43,997.00
3. Moderate COVID-19 pneumonia (C19IP2): Case rate= Php 143, 267.00
4. Severe COVID-19 pneumonia (C19IP3): Case rate= Php 333,519.00
5. Critical COVID-19 pneumonia (C19IP4): Case rate= Php 786,384.00

Meanwhile, children of healthcare workers are eligible to the full financial risk protection (i.e. no cap in terms of case rate) for hospitalization due to COVID-19 (C19FRP) as mandated by PhilHealth Circular 2020-0011.

Based on Philhealth data, there were a total of 1,554 hospitalization claims from April 15, 2020 to August 10, 2021 for the pediatric population aged 0-17 years old. The table below summarizes the cost of COVID-19 illness (inferred from total hospital bill) and out-of-pocket-expenses incurred by patients belonging to the pediatric population at different levels of severity. The mean financial coverage ranged from 82.49% to 98.35%.

| **Severity** *[Benefit package]* | **Total Number of Paid Claims** | **Total Hospital Bill** | | **Out-of-Pocket Payment (Median)** *[PHP]* | **Average % Coverage** *[proportion of financial coverage out of the total bill]* |
|---|---|---|---|---|---|
| | | **Range of Hospitalization Cost** *[PHP]* | **Median Hospitalization Cost** *[PHP]* | | |
| **Community Isolation** *[C19CI]* | 1,054 | ₱0 to ₱130,357.95 | ₱18,343.15 | ₱0 | 98.35% |
| **Full Financial Risk Protection** *[C19FRP]* | 23 | ₱0 to ₱3,236,743.07 | ₱133,806.06 | ₱9,771.52 | 82.49% |
| **Mild COVID-19** *[C19IP1]* | 166 | ₱8,191.50 to ₱1,751,629.51 | ₱59,353.22 | ₱15,356.22 | 69.20% |
| **Moderate COVID-19** *[C19IP2]* | 252 | ₱0 to ₱789,847.46 | ₱142,827.31 | ₱0 | 86.99% |
| **Severe COVID-19** *[C19IP3]* | 46 | ₱33,360.70 to ₱890,834.30 | ₱333,549.00 | ₱30.00 | 84.72% |
| **Critical COVID-19** *[C19IP4]* | 13 | ₱354,987.89 to ₱1,679,694.96 | ₱786,383.03 | ₱0 | 88.45% |

The cost of COVID-19 illness (based on hospital bills) is generally lower in the pediatric population than in the general population across all severity. Further, the mean financial coverage across severity (excluding community isolation cost and claims in the full financial risk protection) ranged from 69.20% to 88.45% which is higher than the coverage for the general population. Meanwhile, financial coverage was also seen to follow the same trend as the general population where financial coverage increases with severity of the COVID-19 disease.

| | |
|---|---|
| **HTAC judgment for *Pfizer-BioNTech and Moderna*:** Based on current evidence *Pfizer-BioNTech and Moderna* all have the potential to reduce out-of-pocket expenses in the pediatric population due to averted costs of isolation and treatment of mild, moderate, and severe COVID-19. | **HTAC judgment *AstraZeneca, Janssen, CoronaVac*:** Cannot be assessed due to current limited evidence |

## Criterion 5: Social Impact

***RQ5.1: Do the vaccines 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 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***

***HTAC Specifications:*** 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.

### Pfizer-BioNTech

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 specific for the use of*Pfizer-BioNTech* to the pediatric population:

1) **Safe and efficacious**
   - Evidence:
   - *Pfizer-BioNTech* is efficacious in preventing symptomatic and severe COVID-19 in the pediatric population (aged 12-17 years old). Current real world studies suggest that it has potential clinical benefit against moderate to severe/critical COVID-19, COVID-19 hospitalization and deaths for this population. Meanwhile, *Pfizer-BioNTech* shows effectiveness in preventing symptomatic COVID-19 caused by Delta, Alpha, Beta, and Gamma variants. Short-term safety of *Pfizer-BioNTech* in children and adolescents aged 16 and below is acceptable. Further follow-up data is needed to establish longer-term safety. Further real world safety data are also anticipated to support evidence on its overall safety in the pediatric population. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the *Pfizer-BioNTech*, the clinical benefits still outweigh the risks for vaccination in this population. Currently, the EUA issued by the FDA Philippines has recommended its use among individuals aged 12 years and older.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
   - Evidence: The Philippine FDA has issued an amended Emergency Use Authorization for *Pfizer-BioNTech* on 28 May 2021 to expand the population to adolescents 12-15 years old from its previously approved indication for 16 years and older (14 January 2021).

3) **Potential for high and equitable coverage across the population**
   - Evidence: Due to stringent logistical requirements, the *Pfizer-BioNTech* can only be deployed in tertiary hospitals where special freezers are available. The *Pfizer-BioNTech* has low potential to be distributed to

isolated geographic locations.

- In the updated recommendation by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) released last 06 September 2021, the PPS and PIDSP maintained its recommendation to prioritize older and more vulnerable age groups in the vaccination roll-out and proceed with vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. They noted that vaccine roll out in children should be initiated in high transmission areas and should prioritize in children with comorbidities and children of healthcare frontliners.
- Meanwhile, according to the Inter-Agency Task Force for the Management of Emerging Diseases (IATF) Resolution 141 dated 30 September 2021, the IATF approved the commencement of COVID-19 vaccination in the pediatric population aged 12 to 17 years old with comorbidities starting 15 October 2021. This resulted in the DOH Department Memorandum 2021-0464, dated 14 October 2021, recommending the vaccination of the pediatric population ages 12 to 17 years old with comorbidities.

4) **Ease in logistics and administration**

- Evidence: The *Pfizer-BioNTech* 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* is required to ensure product integrity across an uninterrupted cold chain. Based on current experience, the implementation of *Pfizer-BioNTech (BNT162b2)* in the Philippine COVID-19 Vaccination Program was generally challenging due to the intricate vaccine preparation which is prone to error and temperature requirement for storage and handling.
- According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will pose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

5) **Cost-effective**

- Evidence: The health, economic, and social benefits of implementing the vaccination program with *Pfizer-BioNTech* in the pediatric vaccination 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:

**General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population**

The DOH-Health Promotion Bureau (HPB) conducted a survey on the acceptability of COVID-19 Vaccines to adolescents aged 12 to 17 years old (N = 13, 376) and parents (N = 25,872) on September 21 to 29, 2021. Majority of the adolescent respondents were in Junior High School (55.36%) followed by Senior High school students (42.33%), College students (1.27%) and Elementary students (1.04%). Parent respondents had a mean age of 42 years old. Most of the parent respondents were college graduates (70.67%).

Results of the survey showed that a high proportion of adolescents respondents are willing to get vaccinated (76.50%). Adolescents' willingness increased given that vaccination will be required to attend face to face classes (85.33%). Willingness further increased given that the vaccine is deemed safe and effective and is approved by the Philippine FDA (86.57%). The survey further indicated that adolescents are more likely to be willing get vaccinated for the following reasons: (1) they want to protect themselves and their family against COVID-19, (2) they want to resume to physical classes soon, (3) their family members were already vaccinated, encouraging them to get the vaccine as well. On the other hand, adolescents are unlikely to get vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust of brands and (3) mistrust in the results of studies.

Meanwhile, results of the survey with parents showed that the majority (89.92%) of the respondents would have their children vaccinated when available. There is an increased willingness among parents when the COVID-19 vaccine is deemed to be safe and effective and when vaccination is mandatory prior to face-to-face classes (93.04% and 90.33%, respectively). The survey further indicated that parents are more likely to allow their children to get vaccinated for the following reasons: (1) they themselves or any family member got vaccinated, (2) they want to resume face-to-face classes for their children, (3) they deem COVID-19 as a risk. On the other hand, parents are unlikely to have their children vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust in the results of the studies, and (3) mistrust of brands.

Moreover, another ongoing online survey by Johns Hopkins Center on the acceptability of pediatric vaccination across different countries was found. Survey results are available from May to September 2021 with respondents ranging from 13,824 to 23,063 Filipinos aged 18 years and older. Respondents who declared to have children were asked if they will choose to get a COVID-19 vaccine for their children when they become eligible. Results across different time points suggests that vaccinating children against COVID-19 is acceptable (at least 80% acceptability). However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines.

**Program Implementers' Perception on COVID-19 Vaccination for the Pediatric Population**

According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

**Economic and Educational Impact of School Closures due to COVID-19**

The Asian Development Bank (ADB) published a study by Gayares et al 2021 which estimated the learning and earning losses due to school closures in Asia during the COVID-19 pandemic. Based on the results, assuming that Filipino children and adolescents in the pre primary to secondary level of education stand to lose approximately 0.61 years worth of quality education due to the school closures out of the baseline 7.49 learning adjusted school years (LAYS) or 8.11% learning loss. This translates to an estimated earning loss per student per year 131 USD or 3.9% decline in earning per student per year. In total, this results in an aggregated lifetime earning loss of 30.7B USD assuming that pre primary to secondary education students affected by school closures will remain in the workforce for 45 years.

Where COVID-19 outbreaks are sufficiently contained, the decision on reopening schools should be made based on the following considerations: local transmission, vaccination rates, size of the student body, ability to divide students into smaller cohorts, and physical condition of school buildings.

Results of an online survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable. However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines. Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need for additional human and logistical resources to accommodate the pediatric population.

The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools.

**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. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package)", aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program.

**8) Appropriateness of the vaccine to the pediatric population**

- Evidence: The interim results from the Phase III clinical trials enrolled individuals aged 16 years and above (Thomas et al. 2021) and 12-15 years old (Frenck et al, 2021). The current evidence for special populations allow it to be used in special at-risk groups such as adolescents aged 12-17 years old.The updated WHO interim recommendations (15 June 2021) on the use of the vaccine in the pediatric population, and on certain conditions which may also be experienced by the pediatric population are detailed below.

*For children and adolescents below the age of 18 years ( 12 to 15 yo - 100% of the Frenck et al. population; 16 to 17 o - 1.5% of the Thomas et al. population).*

- According to WHO, COVID-19 is rarely severe in children and adolescents. However, evidence suggests that adolescents, particularly older adolescents are as likely to transmit SARS-CoV-2 as adults. With this, WHO recommends vaccination using *Pfizer-BioNTech* in children aged 12-15 years old only when high vaccination coverage has been achieved in high priority groups. Meanwhile, individuals in this age group with comorbidities may be offered vaccination as they are at significantly higher risk of serious COVID-19 disease. Currently, no efficacy or safety data are available for children below 12 years old.
- In the WHO SAGE Roadmap for Prioritizing use of COVID-19 Vaccines in the Context of Limited Supply (13 November 2020), they stated that children are not directly prioritized for vaccination as they have lower risk of severe COVID-19 and death.

*For populations with comorbidities (20.5% of the Polack et al.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 II/III RCT. The trial included the following comorbidities: hypertension, diabetes, asthma, pulmonary, liver, and kidney disease as well as chronic (stable and controlled) infection with HIV, hepatitis C, and hepatitis B virus. Hence, the WHO recommends it for persons with comorbidities.

*For persons who have previously had SARS-CoV-2 infection*

- 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. The optimal minimum interval between a natural infection and vaccination is not yet known.

*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 for *Pfizer-BioNTech*:** Based on short-term outcomes, *Pfizer-BioNTech* possesses most of the characteristics desired by key stakeholders for its use among the pediatric population aged 12 to 17 years old.

## Moderna

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 specific for the use of the *Moderna* to the pediatric population:

1) **Safe and efficacious**
- Evidence:
- As shown in a Phase III trial with moderate certainty of evidence, *Moderna* is efficacious in preventing symptomatic COVID-19 in the pediatric population (aged 12-17 years old). One real world-study which included both pediatric and adult populations showed that *Moderna* passed vaccine effectiveness against symptomatic and severe COVID-19 caused by both Alpha and Delta variants. Short-term safety for the pediatric population is acceptable. However, further follow-up data is needed to establish longer-term safety. Despite the rare cases of myocarditis and pericarditis that have been reported following vaccination of young adults with the Moderna (Pepe et al., Lane et al.), the benefits still outweigh the risks for vaccination in this population. 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
- Evidence: *Moderna* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA issued an EUA for the vaccine on 05 May 2021 for its use among 18 years old and above. This EUA was then amended on 03 September 2021 to expand its use among aged 12 to 17 years. Currently, *Moderna* does not have an EUA for the pediatric population from the US FDA.

3) **Potential for high and equitable coverage across the population**
- Evidence: *Moderna* has a lower storage temperature requirement which makes it harder to roll out since limited areas and RHUs have the required equipment for storage and handling.
- In the updated recommendation by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) released last 06 September 2021, the PPS and PIDSP maintained its recommendation to prioritize older and more vulnerable age groups in the vaccination roll-out and proceed with vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. They noted that vaccine roll out in children should be initiated in high transmission areas and should prioritize in children with comorbidities and children of healthcare frontliners.
- Meanwhile, according to the Inter-Agency Task Force for the Management of Emerging Diseases (IATF) Resolution 141 dated 30 September 2021, the IATF approved the commencement of COVID-19 vaccination in the pediatric population aged 12 to 17 years old with comorbidities starting 15 October 2021. This resulted in the DOH Department Memorandum 2021-0464, dated 14 October 2021, recommending the vaccination of the pediatric population ages 12 to 17 years old with comorbidities.

4) **Ease in logistics and administration**

- Evidence: *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. Based on current experience, the implementation of *Moderna* in the Philippine COVID-19 Vaccination Program was generally challenging due to the intricate vaccine preparation which is prone to error and temperature requirement for storage and handling.
- According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

5) **Cost-effective**

- Evidence: The health, economic, and social benefits of using *Moderna* in the pediatric vaccination 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:

**General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population**

The DOH-Health Promotion Bureau (HPB) conducted a survey on the acceptability of COVID-19 Vaccines to adolescents aged 12 to 17 years old (N = 13, 376) and parents (N = 25,872) on September 21 to 29, 2021. Majority of the adolescent respondents were in Junior High School (55.36%) followed by Senior High school students (42.33%), College students (1.27%) and Elementary students (1.04%). Parent respondents had a mean age of 42 years old. Most of the parent respondents were college graduates (70.67%).

Results of the survey showed that a high proportion of adolescents respondents are willing to get vaccinated (76.50%). Adolescents' willingness increased given that vaccination will be required to attend face to face classes (85.33%). Willingness further increased given that the vaccine is deemed safe and effective and is approved by the Philippine FDA (86.57%). The survey further indicated that adolescents are more likely to be willing get vaccinated for the following reasons: (1) they want to protect themselves and their family against COVID-19, (2) they want to resume to physical classes soon, (3) their family members were already vaccinated, encouraging them to get the vaccine as well. On the other hand, adolescents are unlikely to get vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust of brands and (3) mistrust in the results of studies.

Meanwhile, results of the survey with parents showed that the majority (89.92%) of the respondents would have their children vaccinated when available. There is an increased willingness among parents when the COVID-19 vaccine is deemed to be safe and effective and when vaccination is mandatory prior to face-to-face classes (93.04% and 90.33%, respectively). The survey further indicated that parents are more likely to allow their children to get vaccinated for the following reasons: (1) they themselves or any family member got vaccinated, (2) they want to resume face-to-face classes for their children, (3) they deem COVID-19 as a risk. On the other hand, parents are unlikely to have their children vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust in the results of the studies, and (3) mistrust of brands.

Moreover, another ongoing online survey by Johns Hopkins Center on the acceptability of pediatric vaccination across different countries was found. Survey results are available from May to September 2021 with respondents ranging from 13,824 to 23,063 Filipinos aged 18 years and older. Respondents who declared to have children were asked if they will choose to get a COVID-19 vaccine for their children when they become eligible. Results across different time points suggests that vaccinating children against COVID-19 is acceptable (at least 80% acceptability). However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines.

**Program Implementers' Perception on COVID-19 Vaccination for the Pediatric Population**

According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

**Economic and Educational Impact of School Closures due to COVID-19**

The Asian Development Bank (ADB) published a study by Gayares et al 2021 which estimated the learning and earning losses due to school closures in Asia during the COVID-19 pandemic. Based on the results, assuming that Filipino children and adolescents in the pre primary to secondary level of education stand to lose approximately 0.61 years worth of quality education due to the school closures out of the baseline 7.49 learning adjusted school years (LAYS) or 8.11% learning loss. This translates to an estimated earning loss per student per year 131 USD or 3.9% decline in earning per student per year. In total, this results in an aggregated lifetime earning loss of 30.7B USD assuming that pre primary to secondary education students affected by school closures will remain in the workforce for 45 years.

Where COVID-19 outbreaks are sufficiently contained, the decision on reopening schools should be made based on the following considerations: local transmission, vaccination rates, size of the student body, ability to divide students into smaller cohorts, and physical condition of school buildings.

Results of an online survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable. However, given the limitations of this survey, the result of the DOH-HPB

survey is essential to confirm acceptability of pediatric vaccination in the Philippines. Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need for additional human and logistical resources to accommodate the pediatric population.

The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools.

**7) Availability of mechanisms to manage any untoward serious adverse reactions following vaccination**

- Evidence: 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. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package), aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program.

**8) Appropriateness of the vaccine to the pediatric population**

- Evidence: The interim results from the Phase II/III clinical trials enrolled individuals aged 12 to 17 years old (Ali et al. 2021). The current evidence for special populations allow it to be used in special at-risk groups such as adolescents aged 12-17 years old. The WHO recommendations (15 June 2021) on the pediatric population, and on certain conditions which may also be experienced by the pediatric population are detailed below.

*For children and adolescents below the age of 18 years (12 to 17 years old: 100% of Ali et al. population)*

- Currently, no efficacy or safety data for children and adolescents below the age of 18 years are available. Hence, at present, individuals below 18 years of age should not be routinely vaccinated with this vaccine.

*For populations with comorbidities (27.2% of the Baden et al. 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 persons who have previously had SARS-CoV-2 infection*

- 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 for *Moderna*:** Based on short-term outcomes, *Moderna* possesses most of the characteristics desired by key stakeholders for its use among the pediatric population aged 12 to 17 years old.

## AstraZeneca

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 specific on the use *AstraZeneca* to the pediatric population:

1) **Safe and efficacious**
- Evidence:

Currently, there is limited evidence on efficacy, effectiveness, and safety that support the use of *AstraZeneca* in children and adolescents below 18 years.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: *AstraZeneca* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA issued an EUA for the vaccine on 28 January 2021. No changes to the EUA have been implemented since the date of issuance but the product insert was updated to include major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine as a contraindication. Currently, *AstraZeneca* does not have an EUA from the Philippine FDA for the pediatric population.

3) **Potential for high and equitable coverage across the population**
- Evidence: *AstraZeneca* can be made more available since vaccine handling and storage are within the capacity of the RHUs.
- In the updated recommendation by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) released last 06 September 2021, the PPS and PIDSP maintained its recommendation to prioritize older and more vulnerable age groups in the vaccination roll-out and proceed with vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. They noted that vaccine roll out in children should be initiated in high transmission areas and should prioritize in children with comorbidities and children of healthcare frontliners.
- Meanwhile, according to the Inter-Agency Task Force for the Management of Emerging Diseases (IATF) Resolution 141 dated 30 September 2021, the IATF approved the commencement of COVID-19 vaccination in the pediatric population aged 12 to 17 years old with comorbidities starting 15 October 2021. This resulted in the DOH Department Memorandum 2021-0464, dated 14 October 2021, recommending the vaccination of the pediatric population ages 12 to 17 years old with comorbidities.

4) **Ease in logistics and administration**
- Evidence: *AstraZeneca* can be stored at 2-8 degrees Celsius which is present in most RHUs. However, according to the NVOC, despite its manageable cold chain requirement, the lack of a centralized database for the vaccination program as mechanism to track vaccine recipients and the longer dosing interval of *AstraZeneca* have made the vaccine less viable to implement compared to other vaccines with the same storage temperature requirement.
- According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

5) **Cost-effective**
- Evidence: The health, economic, and social benefits of using *AstraZeneca* in the pediatric population cannot be assessed due to currently limited clinical evidence.

6) **Public acceptability**
- Evidence:

**General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population**

The DOH-Health Promotion Bureau (HPB) conducted a survey on the acceptability of COVID-19 Vaccines to adolescents aged 12 to 17 years old (N = 13, 376) and parents (N = 25,872) on September 21 to 29, 2021. Majority of the adolescent respondents were in Junior High School (55.36%) followed by Senior High school students (42.33%), College students (1.27%) and Elementary students (1.04%). Parent respondents had a mean age of 42 years old. Most of the parent respondents were college graduates (70.67%).

Results of the survey showed that a high proportion of adolescents respondents are willing to get vaccinated (76.50%). Adolescents' willingness increased given that vaccination will be required to attend face to face classes (85.33%). Willingness further increased given that the vaccine is deemed safe and effective and is approved by the Philippine FDA (86.57%). The survey further indicated that adolescents are more likely to be willing get vaccinated for the following reasons: (1) they want to protect themselves and their family against COVID-19, (2) they want to resume to physical classes soon, (3) their family members were already vaccinated, encouraging them to get the vaccine as well. On the other hand, adolescents are unlikely to get vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust of brands and (3) mistrust in the results of studies.

Meanwhile, results of the survey with parents showed that the majority (89.92%) of the respondents would have their children vaccinated when available. There is an increased willingness among parents when

the COVID-19 vaccine is deemed to be safe and effective and when vaccination is mandatory prior to face-to-face classes (93.04% and 90.33%, respectively). The survey further indicated that parents are more likely to allow their children to get vaccinated for the following reasons: (1) they themselves or any family member got vaccinated, (2) they want to resume face-to-face classes for their children, (3) they deem COVID-19 as a risk. On the other hand, parents are unlikely to have their children vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust in the results of the studies, and (3) mistrust of brands.

Moreover, another ongoing online survey by Johns Hopkins Center on the acceptability of pediatric vaccination across different countries was found. Survey results are available from May to September 2021 with respondents ranging from 13,824 to 23,063 Filipinos aged 18 years and older. Respondents who declared to have children were asked if they will choose to get a COVID-19 vaccine for their children when they become eligible. Results across different time points suggests that vaccinating children against COVID-19 is acceptable (at least 80% acceptability). However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines.

**Program Implementers' Perception on COVID-19 Vaccination for the Pediatric Population**

According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

**Economic and Educational Impact of School Closures due to COVID-19**
The Asian Development Bank (ADB) published a study by Gayares et al 2021 which estimated the learning and earning losses due to school closures in Asia during the COVID-19 pandemic. Based on the results, assuming that Filipino children and adolescents in the pre primary to secondary level of education stand to lose approximately 0.61 years worth of quality education due to the school closures out of the baseline 7.49 learning adjusted school years (LAYS) or 8.11% learning loss. This translates to an estimated earning loss per student per year 131 USD or 3.9% decline in earning per student per year. In total, this results in an aggregated lifetime earning loss of 30.7B USD assuming that pre primary to secondary education students affected by school closures will remain in the workforce for 45 years.

Where COVID-19 outbreaks are sufficiently contained, the decision on reopening schools should be made based on the following considerations: local transmission, vaccination rates, size of the student body, ability to divide students into smaller cohorts, and physical condition of school buildings.

Results of an online survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable. However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines. Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need for additional human and logistical resources to accommodate the pediatric population.

The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools.

**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.In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package), aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program. 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.

**8) Appropriateness of the vaccine to the pediatric population**

- Evidence: There are currently no trials evaluating the use of *AstraZeneca* in the pediatric population. The WHO recommendations (30 July 2021) on the pediatric population, and on certain conditions which may also be experienced by the pediatric population are detailed below.

  *Children and adolescents below the age of 18 years:*
  - Currently, there is no data on the safety and efficacy of the vaccine in children or adolescents below the age of 18 years.

- In the current WHO recommendation for *AstraZeneca,* vaccination of individuals below 18 years old is not recommended.

*Persons with comorbidities*
- Trials demonstrated similar vaccine efficacy and safety in persons with various underlying medical conditions, including those that increase the risk for severe COVID-19.
- Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19 such as obesity, cardiovascular disease, respiratory disease and diabetes among others.

*For persons who have previously had SARS-CoV-2 infection*
- 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 in the context of limited supply, they have noted additional recommendations that in settings where variants of concern are circulating, earlier immunization (e.g., 90 days after natural infection) may be advisable due to higher risk of symptomatic reinfection. When more data become available, the interval period between natural infection and vaccination may be updated.
- The 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, including occurrence in between doses, should not be vaccinated until after full recovery from the acute illness and meeting the criteria for discontinuation of isolation. The optimal minimum interval between a natural infection and vaccination is not yet known.

*For persons who previously received passive antibody therapy for COVID-19*
- Currently, there is 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 for *AstraZeneca*:** Not assessed for this theme due to limited clinical evidence on *AstraZeneca* for the pediatric population. Further, this vaccine does not have an EUA for the pediatric population.

## Janssen

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 specific on the use of *Janssen* to the pediatric population:

1) **Safe and efficacious** .
- Evidence: Currently, there is limited evidence on efficacy, effectiveness, and safety that support the use of *Janssen* in children and adolescents below 18 years.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The *Janssen* underwent the usual regulatory process of the FDA Philippines and issued an EUA for the vaccine on 07 May 2021. As of 27 February 2021, the US FDA issued an EUA for *Janssen* while the EMA issued a conditional marketing authorization for the product across the European Union on 11 March 2021. The vaccine was included in the WHO emergency use listing on 12 March 2021. Currently, *Janssen* does not have an EUA from the Philippine FDA for the pediatric population.

3) **Potential for high and equitable coverage across the population**
- Evidence: The one-dose vaccination requirement with *Janssen* can facilitate utility in a wider setting especially for those experiencing difficulty with completing their second dose required in other vaccines, thereby improving compliance. In addition, this can be made more available since vaccine handling and storage are within the capacity of the RHUs.

- In the updated recommendation by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) released last 06 September 2021, the PPS and PIDSP maintained its recommendation to prioritize older and more vulnerable age groups in the vaccination roll-out and proceed with vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. They noted that vaccine roll out in children should be initiated in high transmission areas and should prioritize in children with comorbidities and children of healthcare frontliners.
- Meanwhile, according to the Inter-Agency Task Force for the Management of Emerging Diseases (IATF) Resolution 141 dated 30 September 2021, the IATF approved the commencement of COVID-19 vaccination in the pediatric population aged 12 to 17 years old with comorbidities starting 15 October 2021. This resulted in the DOH Department Memorandum 2021-0464, dated 14 October 2021, recommending the vaccination of the pediatric population ages 12 to 17 years old with comorbidities.

4) **Ease in logistics and administration**

- Evidence: *Janssen* can be stored for 3 months at 2-8 degrees Celsius in a refrigerator which is present in most RHUs. The vaccine also does not require dilution at the vaccination site which may simplify implementation of the vaccine especially in community settings.
- According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

5) **Cost-effective**

- Evidence:The health, economic, and social benefits of using *Janssen* in the pediatric population cannot be assessed due to currently limited clinical evidence.

6) **Public acceptability**

Evidence:

**General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population**

The DOH-Health Promotion Bureau (HPB) conducted a survey on the acceptability of COVID-19 Vaccines to adolescents aged 12 to 17 years old (N = 13, 376) and parents (N = 25,872) on September 21 to 29, 2021. Majority of the adolescent respondents were in Junior High School (55.36%) followed by Senior High school students (42.33%), College students (1.27%) and Elementary students (1.04%). Parent respondents had a mean age of 42 years old. Most of the parent respondents were college graduates (70.67%).

Results of the survey showed that a high proportion of adolescents respondents are willing to get vaccinated (76.50%). Adolescents' willingness increased given that vaccination will be required to attend face to face classes (85.33%). Willingness further increased given that the vaccine is deemed safe and effective and is approved by the Philippine FDA (86.57%). The survey further indicated that adolescents are more likely to be willing get vaccinated for the following reasons: (1) they want to protect themselves and their family against COVID-19, (2) they want to resume to physical classes soon, (3) their family members were already vaccinated, encouraging them to get the vaccine as well. On the other hand, adolescents are unlikely to get vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust of brands and (3) mistrust in the results of studies.

Meanwhile, results of the survey with parents showed that the majority (89.92%) of the respondents would have their children vaccinated when available. There is an increased willingness among parents when the COVID-19 vaccine is deemed to be safe and effective and when vaccination is mandatory prior to face-to-face classes (93.04% and 90.33%, respectively). The survey further indicated that parents are more likely to allow their children to get vaccinated for the following reasons: (1) they themselves or any family member got vaccinated, (2) they want to resume face-to-face classes for their children, (3) they deem COVID-19 as a risk. On the other hand, parents are unlikely to have their children vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust in the results of the studies, and (3) mistrust of brands.

Moreover, another ongoing online survey by Johns Hopkins Center on the acceptability of pediatric vaccination across different countries was found. Survey results are available from May to September 2021 with respondents ranging from 13,824 to 23,063 Filipinos aged 18 years and older. Respondents who declared to have children were asked if they will choose to get a COVID-19 vaccine for their children when they become eligible. Results across different time points suggests that vaccinating children against COVID-19 is acceptable (at least 80% acceptability). However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines.

**Program Implementers' Perception on COVID-19 Vaccination for the Pediatric Population**

According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

**Economic and Educational Impact of School Closures due to COVID-19**
The Asian Development Bank (ADB) published a study by Gayares et al 2021 which estimated the learning and earning losses due to school closures in Asia during the COVID-19 pandemic. Based on the results, assuming that Filipino children and adolescents in the pre primary to secondary level of education stand to lose approximately 0.61 years worth of quality education due to the school closures out of the baseline 7.49 learning adjusted school years (LAYS) or 8.11% learning loss. This translates to an estimated earning loss per student per year 131 USD or 3.9% decline in earning per student per year. In total, this results in an aggregated lifetime earning loss of 30.7B USD assuming that pre primary to secondary education students affected by school closures will remain in the workforce for 45 years.

Where COVID-19 outbreaks are sufficiently contained, the decision on reopening schools should be made based on the following considerations: local transmission, vaccination rates, size of the student body, ability to divide students into smaller cohorts, and physical condition of school buildings.

Results of an online survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable. However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines. Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need for additional human and logistical resources to accommodate the pediatric population.

The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools.

**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. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package), aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program.

**8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities**

- Evidence: There are currently no trials evaluating the use of *Janssen* in the pediatric population. The WHO recommendations (15 June 2021) on the pediatric population, and on certain conditions which may also be experienced by the pediatric population are detailed below.

*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 routinely recommended at the moment.
-

*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 persons who have previously had SARS-CoV-2 infection*

- 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.
- 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 is 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 for *Janssen*:** Not assessed for this theme due to limited clinical evidence on *Janssen* for the pediatric population. Further, this vaccine does not have an EUA for the pediatric population.

## CoronaVac

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 specific on the use of *CoronaVac* in the pediatric population:

1) **Safe and efficacious**
- Evidence: Currently, there is limited evidence on efficacy, effectiveness, and safety that support the use of *Sinovac* in children and adolescents below 18 years. However, interim results from clinical trials showed that the vaccine is highly immunogenic in children and adolescents aged 3 to 17 years old and the safety profile in this age group is similar to the adult population. Further studies are anticipated to provide stronger evidence on its efficacy and safety for the pediatric age group.

2) Underwent a **transparent regulatory process** of being evaluated and approved by health authorities
- Evidence: The *CoronaVac* underwent the usual regulatory process of the FDA Philippines. The Philippine FDA does not object to the expansion of its target population to include individuals aged 60 years and older as stated in a letter dated 07 April 2021. According to the Philippine FDA, *CoronaVac* has a pending EUA application for its use in the pediatric population.

3) **Potential for high and equitable coverage across the population**
- Evidence: *CoronaVac* can be made more available since vaccine handling and storage are within the capacity of the RHUs.
- In the updated recommendation by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the Philippines (PIDSP) released last 06 September 2021, the PPS and PIDSP maintained its recommendation to prioritize older and more vulnerable age groups in the vaccination roll-out and proceed with vaccinating children aged 12 years old and above once there is sufficient coverage in the adult priority groups. They noted that vaccine roll out in children should be initiated in high transmission areas and should prioritize in children with comorbidities and children of healthcare frontliners.
- Meanwhile, according to the Inter-Agency Task Force for the Management of Emerging Diseases (IATF) Resolution 141 dated 30 September 2021, the IATF approved the commencement of COVID-19 vaccination in the pediatric population aged 12 to 17 years old with comorbidities starting 15 October 2021. This resulted in the DOH Department Memorandum 2021-0464, dated 14 October 2021, recommending the vaccination of the pediatric population ages 12 to 17 years old with comorbidities.

4) **Ease in logistics and administration**
- Evidence: *CoronaVac* can be stored at 2 to 8 degrees Celsius which is present in most RHUs.
- According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

5) **Cost-effective**
- Evidence: The health, economic, and social benefits of using *CoronaVac* in the pediatric population cannot be assessed due to currently limited clinical evidence.

6) **Public acceptability**
- Evidence:
  **General Public's Acceptability of Administration of COVID-19 Vaccination for the Pediatric Population**

The DOH-Health Promotion Bureau (HPB) conducted a survey on the acceptability of COVID-19 Vaccines to adolescents aged 12 to 17 years old (N = 13, 376) and parents (N = 25,872) on September 21 to 29, 2021. Majority of the adolescent respondents were in Junior High School (55.36%) followed by Senior High school students (42.33%), College students (1.27%) and Elementary students (1.04%). Parent respondents had a mean age of 42 years old. Most of the parent respondents were college graduates (70.67%).

Results of the survey showed that a high proportion of adolescents respondents are willing to get vaccinated (76.50%). Adolescents' willingness increased given that vaccination will be required to attend face to face classes (85.33%). Willingness further increased given that the vaccine is deemed safe and effective and is approved by the Philippine FDA (86.57%). The survey further indicated that adolescents are more likely to be willing get vaccinated for the following reasons: (1) they want to protect themselves and their family against COVID-19, (2) they want to resume to physical classes soon, (3) their family members were already vaccinated, encouraging them to get the vaccine as well. On the other hand, adolescents are unlikely to get vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust of brands and (3) mistrust in the results of studies.

Meanwhile, results of the survey with parents showed that the majority (89.92%) of the respondents would have their children vaccinated when available. There is an increased willingness among parents when the COVID-19 vaccine is deemed to be safe and effective and when vaccination is mandatory prior to face-to-face classes (93.04% and 90.33%, respectively). The survey further indicated that parents are more likely to allow their children to get vaccinated for the following reasons: (1) they themselves or any family member got vaccinated, (2) they want to resume face-to-face classes for their children, (3) they deem COVID-19 as a risk. On the other hand, parents are unlikely to have their children vaccinated for these reasons: (1) insufficient addressing of safety concerns about vaccines, (2) mistrust in the results of the studies, and (3) mistrust of brands.

Moreover, another ongoing online survey by Johns Hopkins Center on the acceptability of pediatric vaccination across different countries was found. Survey results are available from May to September 2021 with respondents ranging from 13,824 to 23,063 Filipinos aged 18 years and older. Respondents who declared to have children were asked if they will choose to get a COVID-19 vaccine for their children when they become eligible. Results across different time points suggests that vaccinating children against COVID-19 is acceptable (at least 80% acceptability). However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines.

**Program Implementers' Perception on COVID-19 Vaccination for the Pediatric Population**

According to the NVOC, expanding the eligible population to include children and adolescents aged below 18 years old will impose additional challenges and complexity to the existing program. Further training and increase in capacity will be needed to effectively implement the vaccination program for the pediatric population.

**Economic and Educational Impact of School Closures due to COVID-19**

The Asian Development Bank (ADB) published a study by Gayares et al 2021 which estimated the learning and earning losses due to school closures in Asia during the COVID-19 pandemic. Based on the results, assuming that Filipino children and adolescents in the pre primary to secondary level of education stand to lose approximately 0.61 years worth of quality education due to the school closures out of the baseline 7.49 learning adjusted school years (LAYS) or 8.11% learning loss. This translates to an estimated earning loss per student per year 131 USD or 3.9% decline in earning per student per year. In total, this results in an aggregated lifetime earning loss of 30.7B USD assuming that pre primary to secondary education students affected by school closures will remain in the workforce for 45 years.

Where COVID-19 outbreaks are sufficiently contained, the decision on reopening schools should be made based on the following considerations: local transmission, vaccination rates, size of the student body, ability to divide students into smaller cohorts, and physical condition of school buildings.

Results of an online survey administered by a US-based University suggests that vaccinating children against COVID-19 is acceptable. However, given the limitations of this survey, the result of the DOH-HPB survey is essential to confirm acceptability of pediatric vaccination in the Philippines. Meanwhile, we noted that the program implementers foresee additional challenges and complexity to the current COVID-19 vaccination implementation by expanding it to the pediatric population, i.e. the need for additional human and logistical resources to accommodate the pediatric population.

The assurance of meeting all public health measures to students, teachers, and other school personnel is an important consideration in the reopening of schools.

**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. In response to RA 11525, PhilHealth released PhilHealth Circular No. 2021-0007 last 17 June 2021. The circular, otherwise known as the "Implementing Guidelines on the Coverage of COVID-19 Vaccine Injury due to Serious Adverse Effects (SAEs) following immunization resulting in hospitalization, permanent

disability or death under the COVID-19 National Vaccine Indemnity Fund (The COVID-19 Vaccine Injury Compensation Package), aims to provide coverage for cases of hospital confinement, permanent disability, or death due to SAEs from the use of COVID-19 vaccines administered through the COVID-19 vaccination program.

**8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities**

- Evidence: The currently available trial on the use of *CoronaVac* in the pediatric population is limited to a Phase I/II trial evaluating its immunogenicity and safety. The WHO recommendations (15 June 2021) on the pediatric population, and on certain conditions which may also be experienced by the pediatric population are detailed below.

*Children and adolescents below the age 18 years:*

- For most children and adolescents the disease profile is less severe.
  There is currently no efficacy or safety data for children or adolescents below the age of 18 years, although a phase 2 paediatric study is under way. Until such data are available, vaccination of individuals below 18 years of age is not routinely recommended.
-

*Persons with comorbidities:*

- Vaccine efficacy has been demonstrated among trial participants with obesity and hypertension while the number of participants with other comorbidities are too small to draw firm conclusions. Considering the favourable benefit-risk assessment, vaccination with *CoronaVac* is recommended for this special population.

*Persons who have previously had SARS-CoV-2 infection:*

- 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.
- In the context of limited vaccine supply, 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. However, 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.

*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. The optimal minimum interval between a natural infection and vaccination is not yet known.

*Persons who previously received passive antibody therapy for COVID-19:*

- Currently, there is 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 for *CoronaVac*:** Not assessed for this theme due to limited clinical evidence on *CoronaVac* for the pediatric population. Further, this vaccine does not have an EUA for the pediatric population.

## Criterion 6: Responsiveness to Equity

***RQ6: How will COVID-19 Vaccines and its use impact pre-COVID-19 and COVID-generated health and socioeconomic inequities? Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of COVID-19 Vaccines?***

***HTAC Specifications:*** Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health inequities especially for vulnerable sectors of our society.

Out of the 77,139,058 target population for 2021 (i.e. 70% of the total population), a total of 14,650,065 individuals have already received the full regimen of COVID-19 vaccines, which translates as 18.99% full vaccination coverage among the eligible populations. Meanwhile, 9,388,338 individuals (or 12.17%) are yet to receive their second dose COVID-19 vaccine as of 03 September 2021.

**Vaccination coverage by priority group**

Among the priority groups A1, A2, and A3 included in the roll-out in March 2021, complete vaccine coverage for senior citizens (A2) lags at 48.29% (n=3,993,308/8,269,178) compared to A1 at 98.49% (n=1,614,141/1,638,917), and A3 at 60.29% (n=5,239,911/8,691,541); despite the senior citizens having the highest number of cases at 233,171 cases (as of 11 August 2021) and highest CFR among the priority groups at 8.08% (as of 11 August 2021).

Full vaccination coverage in other priority groups which started to roll-out in June 2021 were also noted: frontline personnel in essential sectors, including uniformed personnel (A4) (10.07%); and, indigent population (A5) (4.40%).

The vaccination coverage per priority group are as follows:

- Workers in Frontline Health Services (A1):
  - Of the 1,638,917 eligible A1 population, 98.49% (1,614,141) have received a full dose of COVID-19 vaccines. This group has the highest coverage across all priority groups, to date.
- Senior Citizen (A2):
  - Of the 8,269,178 eligible A2 population, 48.29% (3,993,308) have received a full dose of COVID-19 vaccines.
- Persons with Comorbidities (A3):
  - Of the 8,691,541 eligible A3 population, 60.29% (5,239,911) have received a full dose of COVID-19 vaccines.
- Frontline personnel in essential sectors, including uniformed personnel (A4):
  - Of the 28,300,410 eligible A4 population, 10.07% (2,850,281) have received a full dose of COVID-19 vaccines.
- Indigent Population (A5):
  - Of the 12,911,193 eligible A5 population, 4.40% (568,297) have received a full dose of COVID-19 vaccines.

**Vaccination coverage by region**

There is an observed disparity in the vaccination coverage across all regions, both for the vaccination coverage of at least one dose and the full regimen. As of September 3, 2021, NCR reported the highest vaccination coverage (full regimen: 48.81%; at least one dose: 84.14% of the total target population i.e. 70% of the population) while the Bangsamoro Autonomous Region in Muslim Mindanao (BARMM) recorded the lowest vaccination coverage (full regimen: 7.07%; at least one dose: 9.30% of the total target population i.e. 70% of the population). According to the NVOC, the observed disparity between regions is greatly impacted by the allocation-based (regional prioritization) strategy of the government. Currently, NCR is given higher priority due to the relatively higher incidence of COVID-19 in the region. The NVOC also acknowledges that there are logistical problems in BARMM that might also have led to its low coverage.

| Pfizer-BioNTech | Moderna | AstraZeneca | Janssen | CoronaVac |
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| As *Pfizer-BioNTech* requires ultra-low temperatures of -90 °C to -60 °C, the | Based on current experience in the Philippine COVID-19 Vaccination | *AstraZeneca* can be stored at normal cold storage conditions (2 to 8 degrees | *Janssen* can be stored at normal cold storage conditions (2 to 8 degrees | *CoronaVac* can be stored at normal cold storage conditions (2 to 8 degrees |

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| existing cold chain infrastructure of the Department of Health can only allow the distribution to areas with the required logistical facility (i.e., NCR, Region VII, and Region XI) resulting in inequities for rural areas with no specialized freezers and capacity to handle the vaccine. In hospitals where refrigeration units are commonly available, the vaccine can be stored for five days in such refrigerators at 2–8 °C. With this, vaccination sites must ensure efficient roll out of the vaccines to avoid wastage. 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.<br><br>Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 1,300,688 individuals (2.17%) received a full regimen of *Pfizer-BioNTech.* The relatively lower utilization of the *Pfizer-BioNTech* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to supply issues.<br><br>The vaccination coverage per priority group are as follows:<br>● Workers in Frontline Health Services (A1):<br>○ Of those individuals eligible under A1, 3.10% or 50,866 individuals received a full dose of *Pfizer-BioNTech.* Further, there are 15,567 individuals under A1 who are about to receive their second dose of the vaccine.<br>● Senior Citizen (A2):<br>○ Of the 8,269,178 eligible A2 population, 48.29% (3,993,308) | Program, due to the lower temperature requirement of *Moderna,* the vaccine is harder to roll out since limited areas have the required equipment for storage and handling.<br><br>Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 65,507 individuals (0.11%) received a full regimen of *Moderna.* The relatively lower utilization of the *Pfizer-BioNTech* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to supply issues.<br><br>The vaccination coverage per priority group are as follows:<br>● Workers in Frontline Health Services (A1):<br>○ Of those individuals eligible under A1, 0.28% or 4,594 individuals received a full dose of *Moderna.* Further, there are 20,653 individuals under A1 who are about to receive their second dose of the vaccine.<br>● Senior Citizen (A2):<br>○ Of those individuals eligible under A2, 0.11% or 9,171 individuals received a full dose of *Moderna.* Further, there are 109,095 individuals under A2 who are about to receive their second dose of the vaccine.<br>● Persons with Comorbidities (A3):<br>○ Of those individuals eligible under A3, 0.15% or 12,700 individuals received a full dose of *Moderna.* Further, there are 460,254 individuals under A3 who are about to receive their second dose of the vaccine.<br>● Frontline personnel in essential | Celsius). This made vaccine distribution in geographically isolated and disadvantaged areas possible.<br><br>Compared to other new vaccines, the price per dose and the logistical and operational cost of *AstraZeneca* allow it to be utilized widely.<br><br>Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 2,006,587 individuals (3.35%) received a full regimen of *AstraZeneca.* The relatively lower utilization of the *AstraZeneca* compared to the *CoronaVac* and *Janssen* which were the two most utilized vaccines in the Philippines can be attributed to longer dosing interval.<br><br>The vaccination coverage per priority group are as follows:<br>● Workers in Frontline Health Services (A1):<br>○ Of those individuals eligible under A1, 31.63% or 518,321 individuals received a full dose of *AstraZeneca.* Further, there are 105,718 individuals under A1 who are about to receive their second dose of the vaccine.<br>● Senior Citizen (A2):<br>○ Of those individuals eligible under A2, 9.78% or 808,328 individuals received a full dose of *AstraZeneca.* Further, there are 203,588 individuals under A2 who are about to receive their second dose of the vaccine.<br>● Persons with Comorbidities (A3):<br>○ Of those individuals eligible under A3, 6.75% or 586,828 individuals received a full dose of *AstraZeneca.* Further, there are 442,654 individuals under A3 | Celsius) for 3 months and protected from light. This made vaccine distribution in geographically isolated and disadvantaged areas possible.<br><br>Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 3,479,899 individuals (5.82%) received a full regimen of *Janssen.* The vaccination coverage per priority group are as follows:<br><br>The vaccination coverage per priority group are as follows:<br>● Workers in Frontline Health Services (A1):<br>○ Of those individuals eligible under A1, 5.92% or 97,061 individuals received a full dose of *Janssen.*<br>● Senior Citizen (A2):<br>○ Of those individuals eligible under A2, 15.95% or 1,318,607 individuals received a full dose of *Janssen.*<br>● Persons with Comorbidities (A3):<br>○ Of those individuals eligible under A3, 21.14% or 1,837,174 individuals received a full dose of *Janssen.*<br>● Frontline personnel in essential sectors, including uniformed personnel (A4):<br>○ Of those individuals eligible under A4, 0.56% or 158,894 individuals received a full dose of *Janssen.*<br>● Indigent Population (A5):<br>○ Of those individuals eligible under A5, 0.53% or 68,163 individuals received a full dose of *Janssen* | Celsius). This made vaccine distribution in geographically isolated and disadvantaged areas possible. Compared to other new vaccines, the price per dose and the logistical and operational cost of *CoronaVac* allow it to be utilized widely.<br><br>Of the 59,811,239 individuals eligible in the A1 to A5 priority group, 7,353,005 individuals (12.29%) received a full regimen of *CoronaVac.* The vaccination coverage per priority group are as follows:<br><br>The vaccination coverage per priority group are as follows:<br>● Workers in Frontline Health Services (A1):<br>○ Of those individuals eligible under A1, 57.44% or 941,475 individuals received a full dose of *CoronaVac.* Further, there are 105,929 individuals under A1 who are about to receive their second dose of the vaccine.<br>● Senior Citizen (A2):<br>○ Of those individuals eligible under A2, 19.07% or 1,577,152 individuals received a full dose of *CoronaVac.* Further, there are 360,708 individuals under A2 who are about to receive their second dose of the vaccine.<br>● Persons with Comorbidities (A3):<br>○ Of those individuals eligible under A3, 24.79% or 2,154,718 individuals received a full dose of *CoronaVac.* Further, there are 1,064,915 individuals under A3 who are about to receive their second dose of the vaccine.<br>● Frontline personnel in essential sectors, including uniformed |

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| have received a full dose of COVID-19 vaccines.<br>● Persons with Comorbidities (A3):<br>○ Of those individuals eligible under A3, 7.12% or 618,677 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 139,529 individuals under A3 who are about to receive their second dose of the vaccine.<br>● Frontline personnel in essential sectors, including uniformed personnel (A4):<br>○ Of those individuals eligible under A4, 0.32% or 91,039 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 303,469 individuals under A4 who are about to receive their second dose of the vaccine.<br>● Indigent Population (A5):<br>○ Of those individuals eligible under A5, 2.11% or 272,188 individuals received a full dose of *Pfizer-BioNTech*. Further, there are 140,525 individuals under A5 who are about to receive their second dose of the vaccine. | sectors, including uniformed personnel (A4):<br>○ Of those individuals eligible under A4, 0.11% or 31,564 individuals received a full dose of *Moderna*. Further, there are 208,402 individuals under A4 who are about to receive their second dose of the vaccine.<br>● Indigent Population (A5):<br>○ Of those individuals eligible under A5, 0.08% or 10,478 individuals received a full dose of *Moderna*. Further, there are 767,701 individuals under A5 who are about to receive their second dose of the vaccine. | who are about to receive their second dose of the vaccine.<br>● Frontline personnel in essential sectors, including uniformed personnel (A4):<br>○ Of those individuals eligible under A4, 0.31% or 87,895 individuals received a full dose of *AstraZeneca*. Further, there are 940,289 individuals under A4 who are about to receive their second dose of the vaccine.<br>● Indigent Population (A5):<br>○ Of those individuals eligible under A5, 0.04% or 5,215 individuals received a full dose of *AstraZeneca*. Further, there are 200,966 individuals under A5 who are about to receive their second dose of the vaccine. | | personnel (A4):<br>○ Of those individuals eligible under A4, 8.72% or 2,467,469 individuals received a full dose of *CoronaVac*. Further, there are 2,689,476 individuals under A4 who are about to receive their second dose of the vaccine.<br>● Indigent Population (A5):<br>○ Of those individuals eligible under A5, 1.64% or 212,191 individuals received a full dose of *CoronaVac*. Further, there are 450,397 individuals under A5 who are about to receive their second dose of the vaccine. |
| **HTAC Judgement for *Pfizer-BioNTech*:**<br>Vaccination coverage showed that there is a disparity in distribution of vaccines across priority groups and regions.<br><br>The stringent logistic requirements (i.e., -90 °C to -60 °C) and intricate vaccine storage, handling and preparation of *Pfizer-BioNTech* have made the distribution more challenging. This is supported by the observed relatively lower vaccination coverage compared to other vaccines across priority groups and regions, although this may be a result of its later rollout compared to other brands. | **HTAC Judgement for *Moderna*:**<br>Vaccination coverage showed that there is a disparity in distribution of vaccines across priority groups and regions.<br><br>The stringent logistic requirements (i.e., -25 to -15 degrees Celsius) and intricate vaccine storage, handling and preparation of *Moderna* have made the distribution more challenging. This is supported by the relatively lower vaccination coverage compared to other vaccines across priority groups and regions, although this may be a result of its later rollout compared to other brands. | **HTAC Judgement *AstraZeneca*:** Because of non-stringent logistic requirements, *AstraZeneca* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. Despite this, the ' full vaccination coverage of this vaccine is low due to a longer dosing interval required.New evidence based on real world studies demonstrate the clinical benefits of *AstraZeneca* in terms of safety and effectiveness against hospitalization due to COVID-19 in older adults ≥ 56 years.<br><br>There is insufficient data from clinical trials and real world studies on the safety | **HTAC Judgement for *Janssen*:** The non-stringent logistic requirements (i.e., 2 to 8 degrees Celsius) allows it to be utilized widely. However, in spite of its non-stringent logistic requirements and its advantage as a one-dose vaccine, the vaccination coverage of *Janssen* has been low due to supply issues.<br><br>Further, we recommend that the DOH devise an efficient supply chain management that would take into account the three-month shelf life of the vaccine especially in ensuring the stability of the vaccines, from distribution up to the administration to all target areas especially geographically isolated | **HTAC Judgement for *CoronaVac*:**<br>Because of non-stringent logistic requirements, *CoronaVac* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations.<br><br>New evidence based on real-world effectiveness data demonstrated clinical benefits in reducing risk of symptomatic COVID-19, hospitalization due to COVID-19, death due to COVID-19, in older adults (≥60 years old). In terms of safety, trials which included both 18 to 59 and ≥60 age groups generally showed that adverse event rates are lower in older adults compared to the young adult |

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| However, the use of *Pfizer-BioNTech* in the pediatric population will reduce inequities in the health system, assuming that the decision to vaccinate children is made in consultation with stakeholders, and pediatric vaccination shall be rolled out following the country's prioritization criteria, cognizant of the following:<br>● Burden of COVID-19 to the pediatric population, especially those with comorbidities;<br>● Sufficient supply to cover the pediatric population per DOF. | However, the use of *Moderna* in the pediatric population will reduce inequities in the health system, assuming that the decision to vaccinate children is made in consultation with stakeholders, and pediatric vaccination shall be rolled out following the country's prioritization criteria, cognizant of the following:<br>● Burden of COVID-19 to the pediatric population, especially those with comorbidities;<br>● Sufficient supply to cover the pediatric population per DOF. | and efficacy if *AstraZeneca* in important vulnerable groups such as children and adolescents below 18 years, individuals with any confirmed or suspected immunosuppressive or immunodeficient state, including people with HIV infection, pregnant and lactating women.<br><br>However, its ability to reduce health equities in terms of its use in the pediatric population was not assessed due to limited clinical evidence in the pediatric population. Further, this vaccine currently does not have EUA for the pediatric population. | and disadvantaged areas (GIDA).<br><br>The trial excluded or has limited to no data on pregnant and breastfeeding women, and persons who were immunocompromised (WHO SAGE Background Document, 2021; EMA Public Assessment Report, 2021). 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 considerations will be on a case by case basis.<br><br>Meanwhile, the efficacy and effectiveness of *Janssen* in the pediatric population have yet to be established.<br><br>However, its ability to reduce health equities in terms of its use in the pediatric population was not assessed due to limited clinical evidence in the pediatric population. Further, this vaccine currently does not have EUA for the pediatric population. | population.<br><br>Meanwhile, the efficacy and effectiveness of CoronaVac in the pediatric population have yet to be established.<br><br>Vaccination coverage showed that there is a disparity in distribution of vaccines across priority groups and regions.<br><br>However, its ability to reduce health equities in terms of its use in the pediatric population was not assessed due to limited clinical evidence in the pediatric population. Further, this vaccine currently does not have EUA for the pediatric population. |

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## Section 5. Acknowledgments


- DOH-Bureau of International Health Cooperation (BIHC)
- DOH-Disease Prevention and Control Bureau (DPCB)
- DOH-Epidemiology Bureau (EB)
- DOH-Health Promotion Bureau (HPB)
- Department of Foreign Affairs (DFA)
- Department of Finance (DOF)
- National Center for Vaccines Operation (NVOC)
- Philippine Living Clinical Practice Guidelines Group (LCPG Group)
- Philippine Insurance Corporation (PhilHealth)

# Section 6. Appendix

## Appendix 1. HTAC Evidence Summaries

### Pfizer-BioNTech

Version 1 dated 02 February 2021: http://bit.ly/ESbiontechC19Pfizer

Version 2 dated 25 June 2021**:** https://bit.ly/HTAC-PfizerC19_JuneReassessment

### Moderna

Version 1 dated 28 May 2021: *http://bit.ly/ES-ModernaC19*

### AstraZeneca

Version 1 dated 08 February 2021: http://bit.ly/2YZwIqo

Version 2 dated 25 June 2021: https://bit.ly/HTAC-AstraZenecaC19_JuneReassessment

### Janssen

Version 1 dated 30 April 2021: https://drive.google.com/file/d/1nRFx0I2ReUFmWjuiIGAFdyiIcbikjjLU/view

Version 2 dated 25 June 2021: https://drive.google.com/file/d/1PDNXU7x8Ror4jxc7HTthdje7LxsidSJ5/view

### CoronaVac

Version 1 dated 09 April 2021: http://bit.ly/ES-SinovacC19

Version 2 dated 30 July 2021: https://bit.ly/HTAC-SinovacC19_JulyReassessment

## Appendix 2. LCPG Reports

**COVID-19 Vaccines in Children v. August 16, 2021:**
https://docs.google.com/document/d/16tWGW6HmXUqcBKUof4vm6Gr1QznkJvyJ/edit

**COVID-19 Vaccines in Children v. August 18, 2021:**
https://docs.google.com/document/d/1e5N97MrtIiw0IbwBbAZxNOTgWV5tXAgh/edit

**COVID-19 Vaccines in Children v. September 8, 2021:**
https://docs.google.com/document/d/1805AlK1g844yPcHvx66S8VWYyY-le438/edit?usp=sharing&ouid=106609931003099584698&rtpof=true&sd=true

# Appendix 3. Risk of Bias Assessments

## A. LCPG APPRAISAL

Lopez-Bernal, et al., 2021 (*Pfizer-BioNTech*) and Nasreen, et al., 2021 (*Pfizer-BioNTech, Moderna*) controlled for all three confounders, namely age, exposure risk, and comorbidities.

***Effectiveness against VOCs***

| STUDY ID | STUDY DESIGN | RANDOMIZA-TION | ALLOCATION CONCEALMENT | BLINDING OF PARTICIPANTS | BLINDING OF INVESTIGATORS | BLINDING OF ASSESSORS | MISSING OUTCOMES / FOLLOW UP | SELECTIVE REPORTING | ASSESSMENT OF CONFOUNDING FACTORS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | AGE | | | EXPOSURE RISK | | | COMORBIDITIES | | | OVERALL for CONTROL OF COUNFOUNDERS |
| | | | | | | | | | A | B | C | A | B | C | A | B | C | |
| Chia | Retrospective cohort | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | N | Y | N | NA | NA | Y | N | Y | LOW |
| Lopez Bernal | test negative case control | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | U | Y | Y | U | Y | Y | U | Y | LOW |
| Mlcochova | Crosssectional? | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | U | Y | N | NA | NA | N | NA | NA | HIGH |
| Nasreen | test negative case control | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | N | Y | Y | N | Y | Y | N | Y | LOW |
| Sheikh | test negative case control | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | U | Y | Y | N | Y | N | NA | NA | LOW |
| Stowe | test negative case control | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | U | U | U | U | U | U | U | U | U | HIGH |
| Thiruvengadem | test negative case control | HIGH | HIGH | HIGH | UNCLEAR | UNCLEAR | UNCLEAR | UNCLEAR | Y | Y | Y | Y | Y | Y | N | U | N | LOW |

LOW UNCLEAR HIGH NOT APPLICABLE

Y YES N NO U UNCLEAR NA NOT APPLICABLE

## B. COVID-NMA Appraisal

Thomas et al. 2021 *(Pfizer-BioNTech)*

| Bias | Author's judgement | Support for judgement |
|---|---|---|
| Randomization | Low | Quote: "Participants were randomized 1:1 by an interactive web based system."<br>Allocation sequence random<br>Allocation sequence concealed<br>Risk assessed to below for the outcomes: Confirmed symptomatic COVID. Severe COVID. Mortality. Adverse events. Withdrawals due to adverse events. Serious adverse events. |
| Deviations from intervention | Some concerns | Quote: "observer blinded"<br>Comment: Blinded study (participants and personnel/carers)<br>Data were analyzed using intention to treat analysis for the outcomes: Severe COVID. Mortality. Adverse events. Withdrawals due to adverse events. Serious adverse events This method was considered appropriate to estimate the effect of assignment to intervention.<br>Risk assessed as low for the outcomes: Severe COVID. Mortality. Adverse events. Withdrawals due to adverse events. Serious adverse events<br><br>Per protocol analysis was performed on the outcome: Confirmed symptomatic COVID.<br>Reasons for exclusion: Positive at baseline (689 Vs 716) not received 2 vaccinations as randomized (326 Vs 430)<br>Reasons foe exclusion in the 12-15 yo group not reported<br>As we are assessing the effect of assignment to intervention (intention to treat effect), we considered that the data were analyzed inappropriately.<br>Risk assessed as some concerns for the outcome: Confirmed symptomatic COVID. |
| Missing outcome data | Low | Comment: 46429 participants randomized (44165 participants aged ≥16 years randomized; 2264 participants aged 12-15 years randomized, previously reported, Frenck 2021) / 42094 participants aged ≥12 years analyzed for Confirmed symptomatic COVID / 46077 participants aged ≥12 years analyzed for Confirmed COVID severe or critical / 43847 participants aged ≥16 years analyzed for safety outcomes.<br>Data available for nearly all participants.<br>Risk assessed to be low for the outcomes: Confirmed symptomatic COVID. Confirmed COVID severe or critical. Adverse events. Withdrawals due to adverse events. Serious adverse events. |
| Measurement of the outcome | Low | Comment: Method of measuring the outcome probably appropriate.<br>Measurement or ascertainment of outcome probably does not differ between groups.<br>Blinded study (outcome assessor)<br>Risk assessed to be low for the outcomes: Confirmed symptomatic COVID. Severe COVID. Mortality. Adverse events. Withdrawals due to adverse events. Serious adverse events. |
| Selection of the reported results | Low | The propective registry is available (April 30, 2020)protocol and statistical plan are available<br>Outcomes pre-specified.<br>Results were not selected from multiple outcome measurements or analyses of the data.<br>Trial analyzed as pre-specified.<br>Risk assessed as low for the outcomes: Confirmed symptomatic COVID. Severe COVID. Mortality. Adverse events. Withdrawals due to adverse events. Serious adverse events. |
| Overall risk of bias | Some concerns | |

Barlow et al. 2021 *(Pfizer-BioNTech)*

| Bias | Author's judgement | Support for judgement |
|---|---|---|
| Confounding | Serious | The analysis matched and adjusted only for age and postcode. Our prespecified important confounding domains of comorbidity, geographic location, and COVID-19 symptoms at the time of potential vaccination were not controlled for, leading to a likelihood of uncontrolled confounding. |
| Selection of participants into the study | Moderate | The study used a test-negative design. This has the potential to suffer from selection bias by being restricted to individuals getting a test, although the issues are not yet well understood. |
| Clasification of interventions | Moderate | Information was recorded at the time of vaccination for everyone vaccinated in Oregon. However, anyone who was vaccinated outside of the state would not have their vaccination recorded in the state records and may be misclassified as unvaccinated. |
| Deviations from intervention | Low | No concerns in this domain - the study was observational. |
| Missing outcome data | Low | Data appear to be complete for vaccination status, measured confounders and outcomes. 72/1228 cases were excluded who had their +ve test from point-of-care information rather than electronic health records. |
| Measurement of the outcome | Low | No particular concerns in this domain - determination of infection unlikely to be biased. |
| Selection of the reported results | Moderate | There is no evidence of an analysis plan, and we have concerns that results could have been selected for reporting because of the findings. |
| Overall risk of bias | Serious | |
| Overall comment | | Concerns mainly about uncontrolled confounding. |

## C. HTAU Appraisal

Bicket et al. 2021 *(Pfizer-BioNTech)*

| **DOMAINS** | **REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)** | **SUPPORT FOR JUDGMENT** |
|---|---|---|
| **STUDY DESIGN** | Retrospective chart review | |
| **RANDOMIZATION** | HIGH | Patients are identified, no randomization done.<br><br>"Thirty-one patients ages 16 through 25 were identified as eligible for the vaccination based on age. Records were reviewed to determine subject's baseline medical conditions, vaccination status, and any documented side effects within 72 hours of administration. Vital signs, recorded routinely every 12 hours, were assessed." p.2 |
| **ALLOCATION CONCEALMENT** | HIGH | The study did not allocate participants as this is a retrospecitve cohort study. Consent was asked from patients' parents.<br><br>"All 31 eligible patients received the first dose of the Pfizer/BioNTech COVID-19 vaccine between January 11, 2021, and February 1, 2021, with a second vaccination 3 weeks later. *Consent from legal guardians was obtained in all patients."* p.2 |
| **BLINDING OF PARTICIPANTS** | HIGH | No blinding employed since records from the care facility were acquired.<br><br>"Records were reviewed to determine subject's baseline medical conditions, vaccination status, and any documented side effects within 72 hours of administration. Vital signs, recorded routinely every 12 hours, were assessed." p.2<br><br>"All 31 eligible patients received the first dose of the Pfizer/BioNTech COVID-19 vaccine between January 11, 2021, and February 1, 2021, with a second vaccination 3 weeks later." p.2 |
| **BLINDING OF INVESTIGATORS** | HIGH | "Records were reviewed to determine subject's baseline medical conditions, vaccination status, and any documented side effects within 72 hours of administration. Vital signs, recorded routinely every 12 hours, were assessed." p.22 |

| | | | |
|---|---|---|---|
| **BLINDING OF ASSESSORS** | | HIGH | "Records were reviewed to determine subject's baseline medical conditions, vaccination status, and any documented side effects within 72 hours of administration. Vital signs, recorded routinely every 12 hours, were assessed." p.22 |
| **MISSING OUTCOMES / FOLLOW-UP** | | Low | According to Table 1 which reported outcomes and characteristics of patients reviewed, all participants were accounted for |
| **SELECTIVE REPORTING** | | UNCLEAR | No protocol mentioning predetermined outcomes. |
| **Overall ROB** | | **HIGH** | |
| **ASSESSMENT OF CONFOUNDING FACTORS** | | | |
| *AGE* | A | YES | Refer Table 1 |
| | B | NO | No mention in the study of how balanced this confounder was in the intervention group. |
| | C | NO | No mention of any statistical adjustment done. |
| *EXPOSURE RISK* | A | UNCLEAR | No specific mention if exposure risk as a confounding factor is considered |
| | B | NO | No mention in the study of how balanced this confounder was in the intervention group. |
| | C | NO | No mention of any statistical adjustment done. |
| *COMORBIDITIES* | A | YES | Refer Table 1 |
| | B | NO | No mention in the study of how balanced this confounder was in the intervention group. |
| | C | NO | No mention of any statistical adjustment done. |
| **OVERALL FOR CONTROL OF CONFOUNDERS** | | **LOW** | |
| **OVERALL APPRAISAL** | | **VERY SERIOUS** | |

Revon-Reviere et al. 2021 (*Pfizer-BioNTech)*

| **DOMAINS** | **REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)** | **SUPPORT FOR JUDGMENT** |
|---|---|---|
| **STUDY DESIGN** | RETROSPECTIVE COHORT | |
| **RANDOMIZATION** | HIGH | The study did not randomize as this is a retrospective cohort study<br><br>Non-random sequence generation is indicated in the study because characteristics for each patient are identifiable, and each patient was given an identification number.<br><br>See Table 1 for details of characteristics per patient (p. 32) |
| **ALLOCATION CONCEALMENT** | HIGH | No explicit statement on allocation concealment prior to assignment but study is a retrospective cohort study. Participants are aware of where they are being assigned in.<br><br>"*This study includes a retrospective analysis of safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine administered to patients, ≥16 years old, under treatment for a solid tumour or within 6 months after treatment from 15th February 2021 to 15th April 2021*." (p. 30) |
| **BLINDING OF PARTICIPANTS** | HIGH | No statement on blinding of participants but the study indicates that participants are made aware of the treatment (Pfizer) being given to them.<br><br>"*Twenty-three patients were identified and proposed the BNT162b2 mRNA COVID-19 vaccine. Of these 23 patients, 9 refused to receive the vaccine. The reasons for refusal were the fear of developing side-effect, the lack of long-term knowledge about tolerance for 8 patients and living too far from the hospital for 1 patient.*" (pp. 31-32) |

| | | |
|---|---|---|
| **BLINDING OF INVESTIGATORS** | HIGH | The study involves retrospective observation of real-world data of select patients in a hospital. Hence, investigators are aware of the treatment being given to patients and cannot control these outcomes.<br><br>*"The study was approved by the AP-HM, and access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of Assistance Publique-Hoˆpitaux de Marseille (APHM PADS21-136). All patients signed informed consent."* (p. 31) |
| **BLINDING OF ASSESSORS** | HIGH | Results indicate that investigators, who assessed the outcomes themselves, have access to information regarding the reactogenicity outcomes for each patient (p. 32-33) |
| **MISSING OUTCOMES / FOLLOW-UP** | Low | Twenty-three patients were identified and proposed the BNT162b2 mRNA COVID-19 vaccine. Of these 23 patients, 9 refused to receive the vaccine. The reasons for refusal were the fear of developing side-effect, the lack of long-term knowledge about tolerance for 8 patients and living too far from the hospital for 1 patient. One patient did not receive the vaccine as he already had developed COVID-19 [[14]] and still displayed positive serology and positive virus neutralisation test. Therefore, 13 patients started vaccination (see Fig. 1).<br><br>Two patients did not receive the second injection because of tumour progression and also lived far away from our institution. They received palliative care only.<br><br>The outcomes in the remaining participants were reported |
| **SELECTIVE REPORTING** | LOW | Pre-specified outcomes (efficacy and safety) were reported (p. 33). |
| **Overall ROB** | **HIGH** | |
| **ASSESSMENT OF CONFOUNDING FACTORS** | | |
| *AGE* A | YES | Ages of each patient were known, and median age was also identified (p. 30). |
| *AGE* B | NO | This study notes that all participants have a comorbidity (cancer) (p. 30) |
| *AGE* C | NO | Age factors were not controlled upon analysis of results |
| *EXPOSURE RISK* A | YES | The study recognized that patients are immunocompromised |
| *EXPOSURE RISK* B | NO | Intervention groups were not subdivided as this is an observational study. |
| *EXPOSURE RISK* C | NO | Risk exposure factors were not controlled upon analysis of results |
| *COMORBIDITIES* A | YES | Ages of each patient were known, and median age was also identified (p. 30). |
| *COMORBIDITIES* B | NO | This study notes that all participants have a comorbidity (cancer) (p. 30) |
| *COMORBIDITIES* C | NO | Comorbidity factors were not controlled upon analysis of results |
| **OVERALL FOR CONTROL OF CONFOUNDERS** | **LOW** | |
| **OVERALL APPRAISAL** | **VERY SERIOUS** | |

**Reis et al, 2021** (*Pfizer-BioNTech)*

| **DOMAINS** | **REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)** | **SUPPORT FOR JUDGMENT** |
|---|---|---|
| **STUDY DESIGN** | Editor (Results of Matched Case C | |

| | | |
|---|---|---|
| **RANDOMIZATION** | HIGH | As this is an observational study, no randomization was performed.<br><br>"Of 184,905 vaccinated adolescents, 130,464 met the eligibility requirements, and 94,354 of these vaccine recipients were successfully matched with 94,354 unvaccinated controls " (Main study)<br>"We analyzed data from the electronic medical records of Clalit Health Services (CHS), an integrated healthcare payer-provider serving 52% of the Israeli population." p.5 (Supplementary file) |
| **ALLOCATION CONCEALMENT** | HIGH | As this is an observational study, no allocation concealment was performed.<br><br>"Each day of the study period, eligible adolescents vaccinated on that day were<br>individually matched to eligible adolescents who had not been vaccinated and who were not previously matched as controls. " p.6 (Supplementary file)<br><br>"If at a later date an unvaccinated control was vaccinated, he or she would be censored from the unexposed group together with his or her exposed match" P.7 (Supplementary file) |
| **BLINDING OF PARTICIPANTS** | HIGH | As this is an observational study which has a rolling cohort i.e. "Each day of the study, all newly vaccinated patients who met the inclusion criteria and did not meet the exclusion criteria were potential candidates for matching, including individuals who had previously been included as unvaccinated controls", it can be assumed that participants were aware that they are not blinded whether they were vaccinated or not. |
| **BLINDING OF INVESTIGATORS** | HIGH | Investigators were not blinded:<br><br>We analyzed data from the electronic medical records of Clalit Health Services (CHS), an integrated healthcare payer-provider serving 52% of the Israeli population |
| **BLINDING OF ASSESSORS** | HIGH | Assessors were not blinded:<br><br>The CHS data warehouse integrates data from multiple operational systems, with over 20 years of longitudinal history for most individuals. Every day, these data are combined with new data on COVID-19 vaccines, SARS-CoV-2 PCR test results, COVID-19 related hospitalizations, disease severity and death collected by the Israeli Ministry of Health. This enables integration of longitudinal medical information with real-time vaccination status and COVID-19 related outcomes for the entire CHS-covered population. |
| **MISSING OUTCOMES / FOLLOW-UP** | HIGH | Figure S1:<br>Vaccinated cohort: 94,354<br>Unvaccinated cohort: 94,354<br><br>Figure S2A: SARS-CoV-2 Infection<br>At risk vaccinated: 94,354<br>At risk unvaccinated: 94354<br><br>Figure S2B:<br>At risk vaccinated: 94,708<br>At risk unvaccinated: 94, 708 |
| **SELECTIVE REPORTING** | LOW | " We studied two outcomes: Documented SARS-CoV-2 infection (positive SARS-CoV-2 PCR test), and Symptomatic SARS-CoV-2 infection (infection with documented COVID-19 symptoms, or infection requiring hospitalization). The date of the first positive test was set as the outcome date." (Supplementary File)<br><br>"The estimated vaccine effectiveness against documented SARS-CoV-2 infection was 59% (95% confidence interval [CI], 52 to 65) on days 14 through 20 after the first dose, 66% (95% CI, 59 to 72) on days 21 to 27 after the first dose, and 90% (95% CI, 88 to 92) on days 7 to 21 after the second dose. The estimated vaccine effectiveness against symptomatic Covid-19 was 57% (95% CI, 39 to 71) on days 14 to 20 |

| | | | |
|---|---|---|---|
| | | | after the first dose, 82% (95% CI, 73 to 91) on days 21 to 27 after the first dose, and 93% (95% CI, 88 to 97) on days 7 to 21 after the second dose." (Main study) |
| **Overall ROB** | | **HIGH** | |
| **ASSESSMENT OF CONFOUNDING FACTORS** | | | |
| *AGE* | A | YES | Each day of the study period, eligible adolescents vaccinated on that day were individually matched to eligible adolescents who had not been vaccinated and who were not previously matched as controls. Matching factors included age (in 1 year bins), sex, population sector (General Jewish, Arab or Ultraorthodox Jewish), geostatistical living area (a small town or a neighborhood within a large city), whether or not the individual has at least one CDC risk factor for severe COVID-19,4 and the number of influenza vaccinations received in the last 5 years (in 2 bins |
| | B | YES | |
| | C | YES | |
| *EXPOSURE RISK* | A | YES | Despite detailed matching between cohorts, the potential for residual confounding remains. For example, individual behaviors that increase or decrease the risk of exposure to SARS-CoV-2 infection may be different between vaccinated and unvaccinated groups. That said, the similarity in cumulative incidence and in testing rates between the two groups during the initial days after the first dose suggests that residual confounding, if at all present, is minimal. |
| | B | YES | |
| | C | NO | |
| *COMORBIDITIES* | A | YES | See table S3 (controls for Cancer, CKD, COPD, Heart conditions, Immunocompromised, Obesity, severe obesity, pregnancy, Sickle Cell Disease, Smoking, Type 2 Diabetes Mellitus, Asthma, CVD, other respiratory disease, HTN, neurologic conditions, liver disease, overweight, Thalassemia, Type 1 diabetes mellitus, CDC risk factor count |
| | B | YES | |
| | C | YES | |
| **OVERALL FOR CONTROL OF CONFOUNDERS** | | **HIGH** | |
| | | | |
| **OVERALL APPRAISAL** | | **Serious** | |

**Jain et al. 2021** *(Pfizer-BioNTech)*

| **DOMAINS** | **REVIEWER JUDGMENT (HIGH / UNCLEAR / LOW / NA)** | **SUPPORT FOR JUDGMENT** |
|---|---|---|
| **STUDY DESIGN** | Retrospective multi-center study | |
| **RANDOMIZATION** | HIGH | No randomization was performed as this was a observational study<br><br>"The local research ethics boards of several of the participating centers issued an institutional review board exemption, and written informed consent was obtained from patients and/or their guardians at the others.<br>Patients >21 years of age with a diagnosis of acute myocarditis based on clinical presentation, abnormal biomarkers, and/or cardiovascular imaging findings within 2 weeks of COVID-19 vaccination were included."" p.2" |
| **ALLOCATION CONCEALMENT** | HIGH | No allocation was performed as this was an observational study<br><br>"Sixty-three patients with a mean age of 15.6 years were included; 92% were male. All had received a messenger RNA vaccine and, except for one, presented after the second dose." |
| **BLINDING OF PARTICIPANTS** | HIGH | Patients were aware of the intervention:<br><br>"Patients ≤21 years of age with a diagnosis of acute myocarditis based on clinical presentation, abnormal biomarkers, and/or cardiovascular imaging findings within 2 weeks of COVID-19 vaccination were included." |
| **BLINDING OF INVESTIGATORS** | HIGH | Investigators were aware of the intervention:<br><br>" Acall went out to physicians who specialize in cardiovascular imaging around the nation to report such cases from their |

| | | |
|---|---|---|
| | | institutions to this retrospective study. " |
| **BLINDING OF ASSESSORS** | HIGH | Outcome assessors were aware of the intervetion:<br><br>"a call went out to physicians who specialize in cardiovascular imaging around the nation to report such cases from their institutions to this retrospective study. " |
| **MISSING OUTCOMES / FOLLOW-UP** | LOW | "The length of stay in the hospital was 3.0 ± 1.4 days (range 1–7). Twenty-seven (43%) patients were supervised in the ICU during their hospitalization, mainly for arrhythmia monitoring, with a mean stay of 2.5 days. None of the patients required inotropic support, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). There were no deaths. Treatments included nonsteroidal antiinflammatory drugs in 54 patients (86%), intravenous immunoglobulin in 17 (27%), corticosteroids in 15 (24%), and colchicine in 4 (6%).<br><br>Forty-four patients (70%) had abnormal electrocardiogram (ECG) findings. Predominantly diffuse ST-segment elevations and/or T-wave inversion was noted (Fig 1). One patient (2%) presented with complete heart block but did not require pacing and regained normal conduction after admission. Three (5%) patients were noted to have nonsustained ventricular tachycardia, of whom one was treated with amiodarone (Fig 2) and another with an oral β-blocker." |
| **SELECTIVE REPORTING** | Low | Table 2 p.6<br><br>"From the CMR studies, ventricular volumes, and ejection fraction (EF) were obtained. The 2009 Lake Louise criteria4 or, when parametric mapping was available, the 2018 revised Lake Louise CMR criteria were used to test for a diagnosis of acute myocarditis5,6 (Supplemental Information). Evidence of myocardial edema was determined on the basis of abnormally high signal intensity on T2-weighted imaging or prolonged T2 relaxation time on T2 mapping. Hyperemia was determined by myocardial early gadolinium enhancement (EGE). Native T1 times, extracellular volume (ECV) fraction, and myocardial late gadolinium enhancement (LGE) imaging were collected as markers of cardiomyocyte injury and necrosis. Consistent with Society for Cardiovascular Magnetic Resonance guidelines, native T1 results were only used if institutional normal ranges were available and converted into categorical values.7 CMR image analysis and interpretation was done by the performing center to best reflect real-world practice. The study was not intended to identify and/or track pericarditis and was focused on the clinical and imaging characteristics of coronavirus disease 2019 vaccination–associated myocarditis (C-VAM)." p2 |
| **Overall ROB** | **HIGH** | |
| **ASSESSMENT OF CONFOUNDING FACTORS** | | |
| *AGE* | A | YES | Table 1 |
| | B | NO | AS there were no intervention and control groups, confounders were not balanced across groups |
| | C | NO | The study did not control for this confounder |
| *EXPOSURE RISK* | A | NO | Exposure risk of participants were not reported |
| | B | NO | AS there were no intervention and control groups, confounders were not balanced across groups |
| | C | NO | The study did not control for this confounder |
| *COMORBIDITIES* | A | NO | Comorbidities of participants were not reported |
| | B | NO | AS there were no intervention and control groups, confounders were not balanced across groups |
| | C | NO | The study did not control for this confounder |
| **OVERALL FOR CONTROL OF CONFOUNDERS** | | **LOW** | |
| | | | |
| **OVERALL APPRAISAL** | | **VERY SERIOUS** | |

# Appendix 4: GRADE Tables

## *Pfizer-BioNTech*

**Frenck et al. 2021 (GRADE), Phase III trial among 12-15 y/o, N= 2260**

### *Efficacy*

| OUTCOME | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Pfizer-BioNTech n/N | Placebo n/N | Effect Size (95% CI) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| Vaccine efficacy against symptomatic COVID-19 | Not serious | N/A | Not serious | Serious (CI not estimable) | None | 0/1001 (0%) | 16/972 (1.6%) | VE: 100% (Not estimable) | ⊕⊕⊕◯ MODERATE | CRITICAL |

### *Safety*

| OUTCOME | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Pfizer-BioN Tech n/N | Placebo n/N | Effect Size (95% CI) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| **1. Serious adverse events** | Not serious | N/A | Serious (needs longer follow up) | Serious (Wide CI) | None | 5/1131 (0.4%) | 2/1129 (0.1%) | RR: 2.50 (0.49 to 12.84) | ⊕⊕◯◯ **LOW** | CRITICAL |
| **2a. Systemic reactogenicity after dose 1** | Not serious | N/A | Not serious | Not serious | None | 877/1127 (77.8%) | 636/1127 (56.4%) | RR: 1.38 (1.30 to 1.46) | ⊕⊕⊕⊕ **HIGH** | CRITICAL |
| **2b. Systemic reactogenicity after dose 2** | Not serious | N/A | Not serious | Not serious | None | 904/1097 (82.4%) | 439/1078 (40.7%) | RR: 2.02 (1.87 to 2.19) | ⊕⊕⊕⊕ **HIGH** | CRITICAL |
| **3a. Local reactogenicity reactogenicity after dose 1** | Not serious | N/A | Not serious | Not serious | None | 976/1127 (86.6%) | 271/1127 (24.0%) | RR 3.60 (3.24 to 4.01) | ⊕⊕⊕⊕ **HIGH** | IMPORTANT |
| **3a. Local reactogenicity reactogenicity after dose 2** | Not serious | N/A | Not serious | Not serious | None | 872/1097 (79.5%) | 198/1078 (18.4%) | RR 4.33 (3.80 to 4.93) | ⊕⊕⊕⊕ **HIGH** | IMPORTANT |

## *Moderna*

**Ali et al. 2021 (GRADE), *N = 3,732***

### *Efficacy*

| **COMPARISON : mRNA-1273 vs placebo in Children (12 to <18years old)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Efficacy Outcome** (at >14days after dose2) | **Quality Assessment** | | | | | **Summary of Findings** | | | |
| | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Overall Assessment** | **Vaccine** | **Control** | **Vaccine Efficacy** | **Certainty** |
| ***1: Symptomatic COVID-19 infection*** | Not serious With concerns (interim report) | Not assessed | Not serious | Serious (wide CI) | Serious | 0/2163 | 4/1073 | 100 (28.9, NE) | Moderate |
| ***2 : Severe COVID-19 infection*** | Not serious With concerns (interim report) | Not assessed | Not serious | No cases | Not assessed | Na | Na | Na | Na |
| ***3 : COVID-19 infection, postD1, preD2*** | Not serious With concerns (interim report) | Not assessed | Not serious | No cases | Not assessed | Na | Na | Na | Na |
| ***4. Asymptomatic COVID-19 infection (mITT)*** | Not serious With concerns (interim report) | Not assessed | Not serious | Serious (wide CI) | Serious | 25/2163 | 29/1073 | 59.5% (28.4, 77.3) | Moderate |

### *Safety*

| **COMPARISON : mRNA-1273 vs placebo in Children (12 to <18years old)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Safety Outcome** | **Quality Assessment** | | | | | **Summary of Findings** | | | |
| | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Overall Assessment** | **Vaccine** | **Control** | **Relative Risk** | **Certainty** |
| ***1. Local adverse reaction*** | Not serious | Not assessed | Not serious | Not serious | Not serious | 2431/2485 | 602/1240 | 2.2 (1.9, 2.13) | ++++ high |
| ***2. Systemic adverse reaction*** | Not serious | Not assessed | Not serious | Not serious | Not serious | 2284/2485 | 830/1240 | 1.37 (1.32, 1.43) | ++++ high |
| ***3. Adverse event*** | Not serious With concerns (interim report) | Not assessed | Serious | Not serious | Serious | 510/2485 | 197/1240 | 1.17 (1.12, 1.22) | +++ Moderate |
| ***4. Severe adverse event*** | Not serious With concerns (interim report) | Not assessed | Serious | Serious | Serious | 4/2486 | 1/1240 | 2.0 (0.22, 17.83) | ++ Low |
| ***5. Serious adverse event*** | Not serious With concerns (interim report) | Not assessed | Serious | Serious | Serious | 2/2485 | 1/1240 | 0.54 (0.03, 8.67 | ++ Low |

## *CoronaVac*

**Han et al. 2021 (GRADE), *N = 558***

***Safety***

| COMPARISON : Coronavac (Sinovac) vs placebo in Children (3 to 17 years old) using 0.3ug | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Safety Outcome** | **Quality Assessment** | | | | | **Summary of Findings** | | | |
| | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Overall Assessment** | **Vaccine** | **Control** | **Relative Risk** | **Certainty** |
| ***1 : Adverse reaction*** *(reactogenicity)* | Serious (unclear concealment) | Not assessed | Not serious | Serious | Serious | 59/217 | 22/114 | 1.41 (0.91, 2.17) | ++ Low |
| ***2. Local adverse reaction*** | Not reported | Not assessed | Not assessed | Not assessed | Not assessed | na | na | na | na |
| ***3. Systemic adverse reaction*** | Not reported | Not assessed | Not assessed | Not assessed | Not assessed | na | na | na | na |
| ***4 : Adverse event*** *(long term adverse events)* | Serious (unclear concealment) (interim report) | Not assessed | Serious | Serious | Very Serious | 15/217 | 9/114 | 0.88 (0.40, 1.94) | + Very Low |

## Appendix 5: Costing analysis

**Comparison of Remaining Supply and Demand for Pediatric Vaccination with *Pfizer-BioNTech and Moderna* using the 2021 Budget**

| Description | Pfizer | Moderna | Assumptions/Notes | Source |
|---|---|---|---|---|
| ***Supply*** | | | | |
| **Vaccinees to be covered by DPCB Procurement [A]** | 20,000,000 | 6,500,000 | Based on Procurement Allocation as of January 15 , 2021 | DOF, DPCB |
| **Vaccinees to be covered by Donated supplies [B]** | 10,063,755 | - | Based on COVID-19 Vaccines Arrival Monitoring as of September 30, 2021 | BIHC |
| **Vaccination Coverage [C]** | 2,061,972 | 1,734,422 | These are the number of individuals vaccinated with at least one dose, based on the NVOC Report on Vaccination Coverage as of September 6, 2021. | DPCB- NVOC |
| **Vaccinees that can be catered by the remaining supplies from both donation and procurement [D]** | **28,001,783** | **4,765,578** | D= [A+B]-C | NA |
| **Vaccinees that can be catered by the remaining supplies from procurement only [E]** | **17,938,028** | **4,765,578** | E= A-C | NA |
| ***Demand*** | | | | |
| **PSA Projected 2021 Population (10-19 year olds)** | **21,185,343** | | Based the population projections of the PSA in the 2015 Census of Population | PSA |
| **DPCB Target (12-18 year olds)** | **10,000,000** | | Based on DPCB Presentation during the | DPCB |

Acronym: **DPCB:** Disease Prevention and Control Bureau | **NVOC:** National COVID-19 Vaccination Operations Center| **DOF:** Department of Finance | **PSA:** Philippine Statistics Authority