Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

RESEARCH QUESTION: Among children aged 6 months to 4 years old, what is the clinical and immunologic efficacy and effectiveness and safety of the primary series COVID-19 vaccine?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of monovalent **mRNA-1273 (Moderna)** vaccine in children 6 months to 4 years to prevent SARS-CoV-2 infection.	Very Low	Weak
We suggest the use of **CoronaVac (Sinovac)** vaccine in children 3 to 5 years to prevent SARS-CoV-2 infection.	Very Low	Weak
There is no recommendation on the use of the following vaccines in children 6 months to 2 years to prevent SARS-CoV-2 infection due to lack of evidence. a. **CoronaVac (Sinovac)** b. **BBIBP-CorV (Sinopharm-Beijing)** c. **WIBP-CorV (Sinopharm-Wuhan)**	No evidence	None
There is no recommendation on the use of the following vaccines in children 3 to 5 years to prevent SARS-CoV-2 infection due to insufficient evidence. a. **BBIBP-CorV (Sinopharm-Beijing)** b. **WIBP-CorV (Sinopharm-Wuhan)**	Low	None
There is no recommendation on the use of **BNT162b2 (Pfizer-BioNTech)** in children 6 months to 4 years to prevent SARS-CoV-2 infection due to insufficient evidence.	Very Low	None

Consensus Issues

The evidence on children 3 to 5 years old for each vaccine, BBIBP-CorV (Sinopharm-Beijing) & WIBP-CorV (Sinopharm-Wuhan) came from a single Phase 1-2 randomized controlled trial with small sample size only and the Consensus Panel decided this lowered the certainty of evidence from Moderate to Low Certainty.

KEY FINDINGS

- There were six published studies on the primary series of COVID-19 vaccines in children 6 months to 4 years compared to placebo or non-vaccinated children or non-COVID vaccines. There was one study each on BNT162b2 (Pfizer-BioNTech), WIBP-CorV (Sinopharm-Wuhan) and two on CoronaVac (Sinovac). Data on mRNA-1273 (Moderna) & WIBP-CorV (Sinopharm-Wuhan) are from published interim or preliminary results. The three studies on inactivated vaccines did not include younger children less than 2 years old. None of the studies used a bivalent vaccine.
- There were no studies on ChAdOx1 (AstraZeneca), Ad26-CoV2-S (Janssen/Johnson&Johnson), Gam-COVID-Vac (Sputnik V).

- A large randomized controlled trial (RCT) on mRNA-1273 (Moderna) vaccine showed significant decrease in risk for COVID-19 infection regardless of symptom for children 6 months to 5 years old. Immunogenicity results showed geometric mean ratios (GMRs) that are non-inferior to young adults. Solicited adverse reactions, mostly mild to moderate severity, were significantly higher in the vaccine group compared to placebo within seven days of vaccination. Risk of serious adverse events (SAE) related to vaccination between the two comparisons was not significantly different. There is one study withdrawal due to the vaccine. (Very Low certainty of evidence)
- A large population-based cohort study on CoronaVac (Sinovac) vaccine in children 3 to 5 years old showed protection against symptomatic laboratory-confirmed COVID-19 infection and hospitalization. A clinical trial (n=143) showed significantly higher immunogenicity response than placebo. Incidence of adverse reactions within 28 days after receiving the vaccine was comparable to placebo, with mild to moderate local and systemic adverse reactions. There was no reported SAE. (Very Low certainty of evidence)
- No study on clinical efficacy and immunogenicity of BNT162b2 (Pfizer-BioNTech) in children less than 5 years old is available. For safety, a large retrospective cohort study showed that off-label BNT162b2 vaccination has increased risk for local adverse reactions but decreased risk for systemic adverse reactions compared to on-label non-COVID-19 vaccination (i.e., influenza, MMR, etc.).
- No clinical efficacy data is available for BBIBP-CorV (Sinopharm-Beijing). A small study in children 3 to 5 years old showed significantly higher neutralizing antibody geometric mean titers (GMT) after the second BBIBP-CorV vaccine as compared to the control group. Incidence of adverse reaction (local and systemic) within 30 days after the second vaccination was not significantly different from placebo. All local and systemic adverse reactions were mild to moderate in severity. (Moderate certainty of evidence)
- A published interim analysis of a double blind RCT (n=336) on WIBP-CorV (Sinopharm-Wuhan) showed significant increase of 47- to 76-fold in GMT of neutralizing antibodies and 56- to 66-fold in specific IgG-binding antibodies after vaccination compared to placebo in children 3 to 5 years old. Only mild to moderate adverse events were observed and the incidence within 30 days after the primary series was not significantly different from placebo. (Moderate certainty of evidence)
- No study reported adverse events of myocarditis, pericarditis, MIS-C, and deaths although the studies had a short duration of follow-up.

INTRODUCTION

COVID-19 infection affects people of all ages. With the emergence of new variants, pediatric COVID-19 cases are increasing [1,2]. COVID-19 infection in children is believed to be milder compared to adults, but there are still a proportion of children that can develop severe disease [3,4]. Children of all ages are susceptible to COVID-19 and they can be important in the transmission of infection [3-5].

Vaccination in children more than 5 years old has started in our country. In the background of vaccine supply shortage, there is a need to evaluate studies on risks and benefits of primary vaccination of children six months to four years old and base the recommendations on sound evidence.

REVIEW METHODS

Search Strategy

A systematic search was done on October 24, 2022, on the following electronic databases: MEDLINE, CENTRAL, L.OVE Platform for COVID-19 Evidence, COVID-NMA, clinicaltrials.gov, Chinese Clinical Trial Registry, EU Clinical Trials Register, medRVIx.org, and bioRXiv.org using MeSH combined with free text terms related to “COVID-19 vaccine,” “SARS-Cov-2,” “COVID-19,” “child,” “infant,” “toddler,” “pediatric,” “COVID-19 vaccination” with no language limits or method filters. The references sections of the included studies were reviewed for relevant articles. (Appendix 2,3)

Eligibility Criteria
This review prioritized clinical trials and observational studies that evaluated the clinical and immunologic efficacy and effectiveness and safety of the primary series COVID-19 vaccine among children aged 6 months to 4 years old. This review focused only on the primary series of any type of COVID-19 vaccine compared to non-vaccination or placebo or an active comparator. Articles that had no available full-text reports or with insufficient data on the vaccination of children aged 6 months to 4 years were excluded.

Methodological Quality Assessment of Included Studies
Studies were appraised using Cochrane Risk of Bias tool (ver. 1) for RCTs and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool for non-randomized studies [6,7].

RESULTS

Characteristics of Included Studies

Six published studies: four clinical trials [4,5,8,9], one population-based cohort [2], and one retrospective cohort [10], were included. Two ongoing trials on mRNA-1273 and WIBP-CorV (Sinopharm-Wuhan) published the interim results [8,9]. There were two studies on mRNA vaccines (one each on mRNA-1273 (Moderna) [8] and on BNT162b2 (Pfizer-BioNTech) [10] and four on inactivated vaccines: one on BBIBP-CorV (Sinopharm-Beijing) [5], one on WIBP-CorV (Sinopharm-Wuhan) [9], two studies on CoronaVac (Sinovac) vaccine [2,4]. The BBIBP-CorV (Sinopharm-Beijing) and WIBP-CorV (Sinopharm-Wuhan) are considered as different vaccine products since they were developed from two different strains [5,9]. None of the studies used a bivalent vaccine. There are no studies found on ChAdOx1 (AstraZeneca), Ad26-CoV2-S (Janssen/Johnson&Johnson), Gam-COVID-Vac (Sputnik V) vaccine for children 6 months to 4 years old. (Appendix 4)

Risk of bias assessment showed that the RCTs have low risk of bias. Observational studies showed serious risk of bias due to possible bias from confounding, bias in classification of interventions and outcome measurement. (Appendix 5)

mRNA-1273 (Moderna) vaccine

One ongoing phase 2-3 trial [8] published their interim results. Part 1 of the trial (n=374) is an open-label dose-escalation phase while Part 2 (n=6403) is an observer-blind, randomized, placebo-controlled expansion. Included were healthy children and children with stable chronic conditions (i.e., asthma, diabetes) aged 6 months to 5 years. They were randomly assigned to receive 2 doses of 25µg monovalent vaccine or the placebo (saline), 28 days apart. The median duration of follow-up after the second dose of vaccination for those 6 to 23 months old was 68 days and for those 2 to 5 years old was 71 days. The predominant variant was B.1.1.529 (Omicron) during the study period. (Appendix 4)

Efficacy Outcomes
There was a significant decrease in risk of COVID-19 infection, regardless of symptoms for both age groups at 14 or more days after the second dose of mRNA-1273 vaccination. [(6 to 23 months: RR 0.61, 95% CI 0.43-0.87); (2 to 5 years: RR 0.70, 95% CI 0.56-0.89)] and for symptomatic laboratory-confirmed COVID-19 infection [(6 to 23 months: RR 0.51, 95% CI 0.33-0.78); (2 to 5 years: RR 0.65, 95% CI 0.48-0.87)] (High certainty). However, there is no significant reduction in the risk of asymptomatic COVID-19 infection for both age groups [(6 to 23 months: RR 0.99, 95% CI 0.50-1.94); (2 to 5 years: RR 0.79, 95% CI 0.53-1.18)] (Moderate certainty). Participants' follow–up was a median of 68 to 71 days after the second vaccination.

Immunogenicity Outcomes
Antibody testing one month after the second injection (day 57) was compared to those of young adults given 100µg in another trial. Neutralizing antibody geometric mean concentration (GMC) for all age groups

showed an increase from baseline. The GMC of both age cohorts (6 to 23 months: GMC 1781; 2 to 5 years: GMC 1410) were comparable with the GMC of young adults. The geometric mean ratios (GMR) of both age groups were found to be non-inferior with the young adult age group [(6 to 23 months: GMR 1.3, 95% CI 1.1-1.5); (2 to 5 years: GMR 1.0, 95% CI 0.9-1.2)]. (Very Low certainty)

Safety Outcomes
Any solicited adverse reactions (ARs) within seven days of vaccination were noted to be significantly higher in the vaccine group compared to the placebo [(6 to 23 months: post-Dose 1 RR 1.06, 95% CI 1.02-1.12; post-Dose 2 RR 1.15, 95% CI 1.09-1.22); (2 to 5 years: post-Dose 1 RR 1.19, 95% CI 1.14-1.25; post-Dose 2 RR 1.34, 95% CI 1.27-1.41)]. (High certainty) Solicited local ARs were higher after the second dose of injection in both age groups.

Most local and systemic ARs were mild to moderate with a median duration 1 to 3 days. The most common solicited local AR was injection site pain. Severe local ARs are uncommon (0.5% - 1.4%) and were mostly severe injection site pain that interfered with daily activity, erythema and swelling. The most common systemic AR for children 6 to 36 months was irritability or crying while fatigue is the most common for participants aged 37 months to 5 years old. Severe systemic ARs were few (2.2% - 4.4%), mostly high fever, irritability or crying or fatigue that prevents daily activity. Although risk for unsolicited ARs were higher in the vaccine group compared to placebo in both age groups, this was not significant [(6 to 23 months: RR 1.27, 95% CI 0.99-1.62); (2 to 5 years: RR 1.19, 95% CI 0.94-1.51)].

There was one SAE related to the study vaccination, a case of a concomitant viral infection in a 1-year-old presenting as fever and febrile convulsion (RR 0.93, 95% CI 0.04-22.69). (Moderate certainty) This event was also tagged as an adverse event of special interest (AESI). Other AESIs were erythema multiforme, chest pain, and a liver injury in a 9-month-old participant. One participant withdrew from the study due to a vaccine-related adverse event. There were no reports of myocarditis, pericarditis, multisystem inflammatory syndrome in children (MIS-C), and deaths.

Certainty of evidence
For both age cohorts, the certainty of evidence for the efficacy asymptomatic COVID-19 infection was downgraded to Moderate due to imprecision. Likewise, the certainty of evidence for the risk of serious adverse events were downgraded to Moderate due to imprecision. In both age cohorts, the immunogenicity outcome was downgraded to very low due to indirectness (immunogenicity as indirect evidence of vaccine efficacy) and for the historical cohort study design for that particular outcome. These led to an overall Certainty of Evidence of Very Low. (Appendix 6)

CoronaVac (Sinovac) vaccine

A clinical trial [4] reported immunogenicity and safety of the vaccine, and a population-based cohort showed vaccine effectiveness in children 3 to 5 years old [2]. No studies were found on children ≤ 2 years old.

Efficacy Outcomes
The population-based cohort study (n=490694) was done in Chile during the Omicron outbreak. Some (9.7%) participants have co-morbidities, with asthma as the most common (77.3%). Two doses, 28 days apart of the CoronaVac (Sinovac) vaccine were given but the dosage used was not mentioned [2]. However, the only commercially available dose was 3µg. (Appendix 4)

CoronaVac vaccination significantly reduced the risk of symptomatic laboratory confirmed-COVID-19 infection (RR 0.59, 95% CI 0.57-0.61) and COVID-19 related hospitalization (RR 0.36, 95% CI 0.22-0.58) but not for COVID-19 related ICU admission (RR 0.32, 95% CI 0.09-1.20). (Very Low certainty)

Immunogenicity Outcomes
Immunogenicity of CoronaVac was studied in a double-blind placebo-controlled Phase 1-2 RCT in China [4]. The sub-group of 3 to 5 years subjects (Phase 1 n=24, Phase 2 n=119) randomly received either 1.5μg and 3μg of the CoronaVac (Sinovac) vaccine given 28 days apart. (Appendix 4)

In both phases of the trial, the neutralizing antibody geometric mean titers (GMT) of the vaccine group (both 1.5μg and 3μg) were significantly higher than the placebo 28 days after the second dose [(1.5μg post-Dose 2: Mean Difference (MD) 92.1, 95% CI 66.31-117.89); (3μg post-Dose 2: MD 138.5, 95% CI 109.03-167.97)]. The GMT of antibodies in the 3μg level was significantly higher than the 1.5μg level. Both dose levels produced a 100% seroconversion rate by 28 days after the second vaccination. (Moderate certainty)

Safety Outcomes
In the clinical trial [4], no significant risk in the overall adverse reactions within 28 days after receiving both dose levels compared to placebo was noted [(1.5μg: RR 0.76, 95% CI 0.37-1.57); (3μg: RR 0.89, 95% CI 0.44-1.79)]. (Moderate certainty). Most solicited adverse reactions (ARs) were mild to moderate while unsolicited ARs were of moderate severity. One case of severe high fever (Grade 3) was solicited.

Injection site pain was the most common local AR with swelling, and pruritus also reported. For systemic reactions, fever is the most common with cough, anorexia, diarrhea, nausea, and vomiting noted within 7 days. No serious adverse reaction was reported in the 3 to 5 years old age group.

Certainty of Evidence
The certainty of evidence for immunogenicity outcome was downgraded for indirectness while the safety outcomes were downgraded for imprecision. Efficacy outcomes were downgraded to very low due to serious risk of bias in an observational study. The Overall Certainty of Evidence for CoronaVac vaccine is Very Low. (Appendix 5)

BNT162b2 (Pfizer-BioNTech)

One investigator-initiated retrospective cohort study (n=7806) done in Germany during the Omicron outbreak showed the safety of off-label use of BNT162b2 vaccine on children less than 5 years old. The median age of the participants is 3 years old with an interquartile range of 2 to 4 years old [10]. An online survey was done on post-vaccination symptoms of subjects who received at least one dose of BNT162b2 vaccine of varying dosage levels (3μg, 5μg, 10μg) and after vaccination of on-label non-COVID-19 vaccines (i.e., influenza, meningococcal, MMR, etc.) in the same group of participants. There were no clinical and immunogenicity outcomes for this study. (Appendix 4)

There is a study cited by the US-FDA on the clinical efficacy, immunogenicity, and safety of BNT162b2 in this age group [11]. However, it will not be discussed in this review because as of this writing, it contains unpublished interim analysis data.

Safety Outcomes
There was an increased risk for overall ARs (RR 1.34, 95% CI 1.25-1.44) and local ARs (RR 1.57, 95% CI 1.43-1.72) after BNT162b2 vaccination compared to non-COVID-19 vaccines. However, a significantly lower risk of systemic ARs (RR 0.75, 95% CI 0.67-0.83) was seen. Risk of developing adverse reactions requiring inpatient care was not significantly increased after vaccination (RR 3.59, 95% CI 0.20-64.89). (Very Low certainty) Ten children reported SAEs at the higher doses. There were no reported myocarditis, pericarditis, MIS-C, and deaths in the study.

Certainty of Evidence
The Overall Certainty of Evidence for BNT162b2 (Pfizer-BioNTech) vaccine is very low due to very serious risk of bias in an observational study. (Appendix 6)

BBIBP-CorV (Sinopharm-Beijing)

BBIBP-CorV was developed by Beijing Institute of Biological Products from the 19nCoV-CDC-Tan-HB02 strain. A double blind RCT on the safety and immunogenicity of the BBIBP-CorV vaccine given as primary series on healthy children 3 to 17 years old was done [5]. There is no data for younger children 6 months to 2 years old. There were no clinical efficacy outcomes available for this vaccine.

There were 96 participants in phase 1 and 240 participants in phase 2, aged 3 to 5 years old, randomly assigned to three different dose levels: 2μg, 4μg, and 8μg given in 3 doses, 28 days apart. (Appendix 4)

Immunogenicity Outcomes
Neutralizing antibody GMT were measured at baseline and 28 days after each BBIBP-CorV vaccination. After the first dose (day 28), antibody GMTs of all three dose levels were significantly higher than the control group. This trend was seen 28 days after the second (day 56) and third vaccination (day 84) [(2μg post-Dose 2: MD 103.3, 95% CI 87.98-118.62); (4μg post-Dose 2: MD 178.23, 95% CI 161.09-195.39); (8μg post-Dose 2: MD 168.96, 95% CI 153.34-184.58)]. Seroconversion rates for all vaccine dose levels ranged from 75% to 91% after the first vaccination and became 100% after the second vaccination. (Moderate certainty of evidence)

Safety Outcomes
Incidence of any adverse reaction (local and systemic) within 30 days after the second BBIBP-CorV vaccination in all dose levels was not significantly different from placebo (RR 0.82, 95% CI 0.33-2.05). (Moderate certainty of evidence)

After second dose vaccination, all reactions were mild to moderate severity. Local adverse reactions were all mild (1.61%). Systemic reactions were mostly moderate in severity (moderate 4.02% vs mild 0.40%). The most common local adverse reactions were injection site pain and redness. For systemic adverse reactions, fever was the most common. No events of myocarditis, pericarditis, MIS-C, and deaths were noted.

Certainty of Evidence
The Overall Certainty of Evidence for BBIBP-CorV (Sinopharm-Beijing) vaccine is Moderate. The certainty of evidence for immunogenicity outcome was downgraded for indirectness while the safety outcomes were downgraded for imprecision. (Appendix 6)

WIBP-CorV (Sinopharm-Wuhan)

WIBP-Corv (Sinopharm-Wuhan) is developed by Wuhan Institute of Biological Products from the WIV04 strain. Interim analysis of a double blind RCT on only the safety and immunogenicity of the WIBP-CorV vaccine reported results of healthy children 3 to 17 years old [9]. Only data from the age cohort of 3 to 5 years old was available and none for younger children 6 months to 2 years old.

A total of 336 participants aged 3 to 5 years cohort (96 participants in phase 1 and 240 participants in phase 2) were given three doses of WIBP-CorV vaccine 28 days apart. Participants were randomly assigned to three different dose levels: 2.5μg, 5μg, and 10μg. (Appendix 4)

Immunogenicity Outcomes
The GMT of the neutralizing antibodies and specific IgG-binding antibodies were measured at baseline and at different time frames after the vaccinations. An increase of 47- to 76-fold in the neutralizing antibody titers from the baseline was seen 28 days after the second vaccination (day 56). At the same time point (day 56), the specific IgG-binding antibody titers increased for about 56- to 66-fold from baseline.

The GMT of the neutralizing antibodies of all dose levels of the vaccine at 28 days after second vaccination (day 56) were significantly higher than placebo for all dose levels [(2.5µg: MD 232.8, 95% CI 192.29-273.31); (5µg: MD 263.4, 95% CI 217.43-309.37); (10µg: MD 378.40, 95% CI 311.54-445.26)]. Similarly, the GMT of the specific IgG-binding antibodies in all dose levels of the vaccine at 28 days after second vaccination (day 56) were significantly higher compared to the placebo group. (Moderate certainty)
Seroconversion rates of neutralizing antibodies in all dose levels ranged from 97.6% to 100% after the second vaccination. Specific IgG-binding antibodies seroconversion rate in all dose levels was also at 100% after the second vaccination.

Safety Outcomes
Incidence of total ARs (local and systemic) within 30 days after the whole course of WIBP-CorV vaccination regardless of dose levels was not significantly different from placebo [(2.5µg: RR 1.13, 95%CI 0.62-2.05); (5µg: RR 0.88, 95% CI 0.46-1.68); (10µg: RR 0.81, 95% CI 0.42-1.58)]. (Moderate certainty)

The highest incidence of total ARs was seen in the 2.5µg dose level (2.5µg: 21.4% vs. 5µg: 16.7% vs. 10µg: 15.5%; placebo: 19%). This was also true for local ARs (2.5µg: 8.3% vs. 5µg 4.8% vs. 10µg: 3.6%). Systemic reaction rates in all vaccine dose levels were, however, similar between 11.9% to 13.1%. ARs were mild to moderate in severity, most commonly injection site pain for local and fever for systemic reaction. There were no observed severe ARs and SAEs related to the vaccine.

Certainty of Evidence
The certainty of evidence for immunogenicity outcome was downgraded for indirectness while the safety outcomes were downgraded for imprecision leading to a Moderate Overall Certainty of Evidence. (Appendix 6)

RECOMMENDATIONS FROM OTHER GROUPS

Regulatory agencies from different countries have recommendations on the vaccination of children 6 months to 4 years old [12-18]. Two groups [Australian Technical Advisory Group on Immunization (ATAGI) & Ministry of Health Singapore] recommend the use of Moderna vaccine only. Four groups [CDC-Advisory Committee on Immunization Practice (ACIP), Public Health Agency of Canada (PHAC) – National Advisory Committee on Immunization (NACI), European Medicines Agency (EMA), WHO-Strategic Advisory Group of Experts (SAGE)] recommend both Moderna and Pfizer vaccine. However, PHAC-NACI prefers Moderna over Pfizer in the severely immunocompromised.

The ATAGI group recommends vaccination only for those with severe immunocompromise, disability, and those who have complex and/or multiple health conditions which increase the risk of severe COVID-19. The CDC-ACIP and PHAC-NACI have specific recommendations on the dosing schedule for the immunocompromised.

There were no recommendations/authorizations from other groups on the use of other vaccine brands as primary series in children 6 months to 4 years old.

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Recommendation	Strength of Recommendation
Center for Disease Control & Prevention (CDC) Advisory Committee on Immunization Practice (ACIP) [12] As of June 18, 2022	**Moderna**: 6 months to 5 years Concentration of mRNA per primary dose: 25µg; Not moderately or severely immunocompromised - Primary Series: 2 doses; 4-8 weeks between doses 1 & 2 Moderately or severely immunocompromised - Primary Series: 3 doses; 4 weeks between doses 1 & 2; ≥ 4 weeks between dose 2 & 3	Not reported

	Pfizer-BioNTech: 6 months to 4 years Concentration of mRNA per primary dose: 3 µg Not moderately or severely immunocompromised - Primary Series: 3 doses; 3 weeks between doses 1 & 2; ≥ 8 weeks between dose 2 & 3 Moderately or severely immunocompromised – Primary series: 3 doses; 3 weeks between doses 1 & 2; ≥ 8 weeks between dose 2 & 3 Once a primary series is started, the same mRNA vaccine product should be used for all doses in the series.	
Public Health Agency of Canada (PHAC) – National Advisory Committee on Immunization (NACI) [13] As of October 21, 2022 July 14, 2022 – Moderna authorized by Health Canada for children 6 months to 5 years September 9, 2022 – Pfizer authorized by Health Canada for children 6 months to 4 years	**Primary series with mRNA COVID-19 vaccine:** 6 months to 4 years A primary series with an mRNA COVID-19 vaccine may be offered to children 6 months to 4 years of age who are not moderately to severely immunocompromised, with an interval of at least 8 weeks between doses. (*Discretionary NACI recommendation*) A primary series plus an additional dose of an mRNA COVID-19 vaccine may be offered to children 6 months to 4 years of age who are moderately to severely immunocompromised. *(Discretionary NACI recommendation)* ● NACI preferentially recommends a 3-dose primary series of the Moderna Spikevax (25mcg) vaccine for children who are moderately to severely immunocompromised, with an interval of 4 to 8 weeks between each dose. *(Strong NACI Recommendation)* If the Moderna Spikevax (25mcg) vaccine is not readily available, a 4-dose primary series with the Pfizer-BioNTech Comirnaty (3mcg) vaccine may be offered, with an interval of 4 to 8 weeks between each dose. *(Discretionary NACI Recommendation)*	Discretionary NACI recommendation
Australian Government Department of Health and Aged Care – Australian Technical Advisory Group on Immunization (ATAGI) [14] As of August 3, 2022	● COVID-19 vaccination for children aged 6 months to <5 years with severe immunocompromise, disability, and those who have complex and/or multiple health conditions which increase the risk of severe COVID-19: ● Recommendation: 2 primary doses, except for those with severe immunocompromise who require 3 primary doses with intervals between each dose is 8 weeks. ● Moderna COVID-19 vaccine (Spikevax) was provisionally approved by the Therapeutic Goods Administration (TGA) on 19 July 2022 for use in children aged 6 months to 5 years NOT currently recommend vaccination for children aged 6 months to < 5 years who are not in the risk categories for severe COVID-19.	Not reported
European Medicines Agency (EMA) [15] As of October 19, 2022	**Comirnaty:** 6 months to 4 years of age ● primary vaccination consisting of three doses (of 3mcg each); the first two doses are given three weeks apart, followed by a third dose given at least 8 weeks after the second dose. **Spikevax:** 6 months to 5 years of age	Not reported

	• primary vaccination consisting of two doses (of 25mcg each), four weeks apart. For children within these age groups, both vaccines are given as injections in the muscles of the upper arm or the thigh	
Ministry of Health Singapore – Expert Committee on COVID-19 Vaccination (EC19V) [16] As of October 7, 2022	**Moderna/Spikevax**: 6 months to 5 years • primary vaccination of children aged 6 months to 5 years recommended to receive two 25mcg doses of the Moderna/Spikevax vaccine, given 8 weeks apart.	Not reported
World Health Organization/ Strategic Advisory Group of Experts (SAGE) recommendations [17,18] As of August 18, 2022	**Moderna**: 6 months to 5 years The schedule, as per manufacturer specification, is 2 doses (25µg [0.25ml each]), 4 weeks apart. WHO recommends that the second dose should be administered 4 to 8 weeks after the first dose; an interval of 8 weeks between doses is preferred as this interval is associated with higher vaccine effectiveness and lower risk of myocarditis. However, these considerations should be balanced against the need to achieve quick protection, in particular for high-risk groups, in settings of high transmission intensity and circulating variants of concern. **Pfizer-BioNTech**: 6 months to 4 years The recommended schedule is three doses (3µg, 0.2ml each): a schedule of two doses 3 weeks apart followed by a third dose at least 8 weeks after the second dose are according to the label. However, countries could consider extending the interval between the first and second dose up to 8 weeks.	Not reported

ONGOING STUDIES AND RESEARCH GAPS

As of October 24, 2022, there are nine ongoing trials on the COVID-19 vaccine in children at clinicaltrials.gov. There is one registered trial in the Chinese Clinical Registry and 6 trials in EU Clinical trials register. Among those that have started recruitment and are ongoing, the earliest estimated completion date is October 31, 2023. (Appendix 7)

The following are identified research gaps regarding COVID-19 vaccination for children 6 months to 4 years

1. Effectiveness, efficacy, and safety of other COVID-19 vaccines in children 6 months to 4 years
2. Duration of protection in children 6 months to 4 years
3. Efficacy, effectiveness, and safety of the bivalent vaccine in children 6 months to 4 years

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

Based on a European purchase agreement in August 2021, Pfizer vaccine costs $25.15 a dose while Moderna vaccine costs $25.50 [19]. As per DOH statement dated March 18, 2021, the Philippine government estimates an average composite cost of around PHP 1,300.00 per person for the vaccination program (inclusive of a two-dose requirement and ancillary) [20]. Cost-effectiveness study done locally is not yet available. As per Department of Health (DOH) statement dated March 18, 2021, a full-blown cost-

effectiveness analysis is not done under a pandemic situation. Cost-effectiveness is not a priority during this time. However, cost and resource analysis of the COVID vaccination program will be done [21].

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Values: A 2022 study in the Philippines showed that there are complex reasons for refusing or delaying COVID-19 vaccination. Individual perception influenced by (mis)information from the media, the community and the health systems is a big factor in the vaccine hesitancy of Filipinos [22]. In a 2022 study done prior to the start of the nationwide COVID-19 vaccination in our country, 37.4% of the respondents were hesitant on vaccination. Among the vaccine hesitant, 48.9% were worried that the vaccines will make them sick [23].

Acceptability: A 2022 cross-sectional study done on the acceptance of COVID-19 vaccine among unvaccinated Filipinos have shown that 20.5% of the unvaccinated Filipinos are not accepting and are undecided about COVID-19 vaccines. Among the non-acceptance group, 59.7% are not sure of the safety of the vaccine, 56.5% do not accept COVID-19 vaccine because they do not trust the vaccine, and 40.9% were uncertain of the vaccine effectiveness. Only 23.4% refused the vaccine due to fear of side effects (i.e., fever and pain). [24]

No studies on equity and feasibility of vaccination in children 6 months to 4 years old were found.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)	Varies	Uncertain			• As new variants of COVID-19 virus, there is an increasing number of pediatric COVID-19 cases. Though most pediatric cases may be milder than adults, there are still a proportion of children that can develop severe disease [1,3]. A systematic review of the epidemiological characteristics of COVID-19 in children showed that 45% of the pediatric COVID cases would require admission and that 4% of the cases required intensive care management [3].
Benefits	Large (2)	Moderate (5)	Small	Trivial	Varies (1)	Uncertain	**mRNA-1273 (Moderna)** • Significant decrease in risk of both COVID-19 infection, regardless of symptom status (6 to 23 months: RR 0.61, 95% CI 0.43-0.87; 2 to 5 years: RR 0.70, 95% CI 0.56-0.89) and symptomatic laboratory confirmed COVID-19 infection (6 to 23 months: RR 0.61, 95% CI 0.43-0.87; 2 to 5 years: RR 0.70, 95% CI 0.56-0.89) • Reported neutralizing antibody geometric mean ratios (GMRs) are non-inferior to the GMR in young adults **BNT162b2 (Pfizer-BioNTech)** • No published clinical efficacy & immunogenicity data **BBIBP-CorV (Sinopharm)** • No published clinical efficacy data • Significant increase in neutralizing antibody titers after vaccination

							CoronaVac (Sinovac) • Significant decrease in risk of symptomatic laboratory-confirmed COVID-19 infection (RR 0.59, 95% CI 0.57-0.61) and COVID-19-related hospitalization (RR 0.36, 95% CI 0.22-0.58) • Significant increase in neutralizing antibody titers after vaccination
Harm	Large	Moderate (1)	Small (7)	Trivial	Varies	Uncertain	**mRNA-1273 (Moderna)** • Solicited adverse reactions within seven days of vaccination were noted to be significantly higher in the vaccine group compared to the placebo. [(6 to 23 months: post-Dose 1 RR 1.06, 95% CI 1.02-1.12, post-Dose 2 RR 1.15, 95% CI 1.09-1.22); (2 to 5 years: post-Dose 1 RR 1.19, 95% CI 1.14-1.25), post-Dose 2 RR 1.34, 95% CI 1.27-1.41)] • Local and systemic adverse reactions are mostly mild to moderate in severity • Severe local adverse reactions and systemic adverse reactions are few • No significant difference in serious adverse event between vaccine and placebo (RR 0.93, 95% CI 0.04-22.69) **BNT162b2 (Pfizer-BioNTech)** • Increase in risk of any post-vaccination symptom (RR 1.34, 95% CI 1.25-1.44)]and local adverse reaction compared (RR 1.57, 95% CI 1.43-1.72) to non-COVID-19 vaccines • Decrease in risk of systemic adverse reaction (RR 0.75, 95% CI 0.67-0.83) and fever (RR 0.39, 95%

							CI 0.33-0.45) compared to non-COVID-19 vaccines **BBIBP-CorV (Sinopharm)** • No significant difference in the overall incidence of any adverse reaction (local and systemic) 30 days after vaccination and in the placebo. (RR 1.31, 95% CI 0.85-2.00) • All recorded local and systemic are mild to moderate in severity **CoronaVac (Sinovac)** • Overall incidence of adverse reactions within 28 days after receiving the vaccine is not significantly different from placebo [1.5 µg: RR 0.76 (95% CI 0.37-1.57); 3 µg: RR 0.89 (95% CI 0.44-1.79)] • Local and systemic adverse reactions are mild to moderate in severity with only one case of a severe reaction
Certainty of Evidence	High	Moderate (2)	Low (6)	Very low			**mRNA-1273 (Moderna)** • Moderate **BNT162b2 (Pfizer-BioNTech)** • Very Low **BBIBP-CorV (Sinopharm)** • Moderate **CoronaVac (Sinovac)** • Very Low
Balance of effects	Favors vaccination (2)	Probably favors vaccination (6)	Does not favor vaccination	Probably favors no vaccination	Favors no intervention	Varies	**mRNA-1273 (Moderna)** • Reduces risk of symptomatic COVID-19 infection without significant increase in risk of serious adverse event **BNT162b2 (Pfizer-BioNTech)**

							• Insufficient evidence **<u>BBIBP-CorV (Sinopharm)</u>** • Insufficient evidence **<u>CoronaVac (Sinovac)</u>** • Reduces risk of symptomatic COVID-19 infection and COVID-19-related hospitalizations without significant increase in risk of adverse events
Values	Important uncertainty or variability (5)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			• A 2022 study showed that there are complex reasons for refusing or delaying COVID-19 vaccination. Individual perception influenced by (mis)information from the media, the community and the health systems is a big factor in the vaccine hesitancy of Filipinos [13]. In a study done prior to the start of the nationwide COVID-19 vaccination in our country, 37.4% of the respondents were hesitant on vaccination. Among the vaccine hesitant, 48.9% were worried that the vaccines will make them sick [14]. A cross-sectional study done on the acceptance of COVID-19 vaccine among unvaccinated Filipinos have shown that 20.5% of the unvaccinated Filipinos are not accepting and are undecided about COVID-19 vaccines. Among the non-acceptance group, 59.7% are not sure of the safety of the vaccine, 56.5% do not accept COVID vaccine because they do not trust the vaccine, and 40.9% were uncertain of the vaccine effectiveness. Only 23.4% refused the vaccine due to fear of side effects (i.e., fever and pain) [15].

Resources Required	Don't know	Varies	Large cost (4)	Moderate cost (2)	Negligible cost or savings (2)	Moderate savings	Large savings	• Based on a European purchase agreement in August 2021, Pfizer vaccine costs $25.15 a dose while Moderna vaccine costs $25.50 [16]. • As per DOH statement dated March 18, 2021, the Philippine government estimates an average composite cost of around ₱1,300.00 per person for the vaccination program (inclusive of a two-dose requirement and ancillary) [17].
Certainty of evidence of required resources	No included studies (2)		Very low	Low (3)	Moderate	High (1)		
Cost effectiveness	No included studies (4)	Varies (1)	Favors the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison	Probably favors the intervention (5)	Favors the intervention (2)	
Equity	Uncertain (4)	Varies	Reduced (1)	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased (2)	
Acceptability	Don't know (3)		Varies (2)	No (1)	Probably no	Probably yes (1)	Yes (1)	
Feasibility	Don't know (2)		Varies	No (1)	Probably no (1)	Probably yes (2)	Yes (2)	

Appendix 2: Search Strategy

Table 2. Database search strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE & TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	"prophyla*"[All Fields] OR "prevent*"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND ("pediatric"[MeSH Terms] OR "child"[All Fields] OR "infant"[All Fields] OR "toddler"[All Fields] OR "5 years old"[All Fields]) Filter: January 1 to October 24, 2022	October 24, 2022 10:00:00 GMT +8	1519	9
CENTRAL	[COVID-19] explode all trees and with qualifier(s): [prevention & control – PC] AND MeSH descriptor: [Pediatric] this term only Filter: January 1 to October 24, 2022	October 24, 2022 16:00:00 GMT +8	0	0
ClinicalTrials.gov	Condition or disease: “Covid19” Intervention/treatment: “Vaccine” Others: Pediatric, child, toddler, infant Age group (birth-17)	October 24, 2022 21:30:01 GMT +8	31	9
Chinese Clinical Trial Registry	Target Disease: “covid-19” Intervention: “vaccine” (multiple words not allowed)	October 24, 2022 22:00:00 GMT +8	60	1
EU Clinical Trials Register	“COVID-19 vaccine AND Infant OR Toddler OR Child OR Pediatric”	October 24, 2022 23:00:00 GMT +8	156	6
medRxiv.org/ bioRxiv.org	“COVID 19 vaccine pediatric” Filter: January 1, 2022 to October 24, 2022	October 24, 2022 16:10:00 GMT +8	813	6
COVID-NMA	Vaccines > Living Evidence Synthesis (Vaccines RCT)	October 24, 2022, 19:30:00 GMT +8	154	1
LOVE Platform for COVID-19 Evidence	“COVID 19 Vaccination” Filter keyword: pediatric OR infant OR toddler OR child OR adolescent	October 24, 2022 21:00:01 GMT +8	23	0

Appendix 3: PRISMA flow diagram

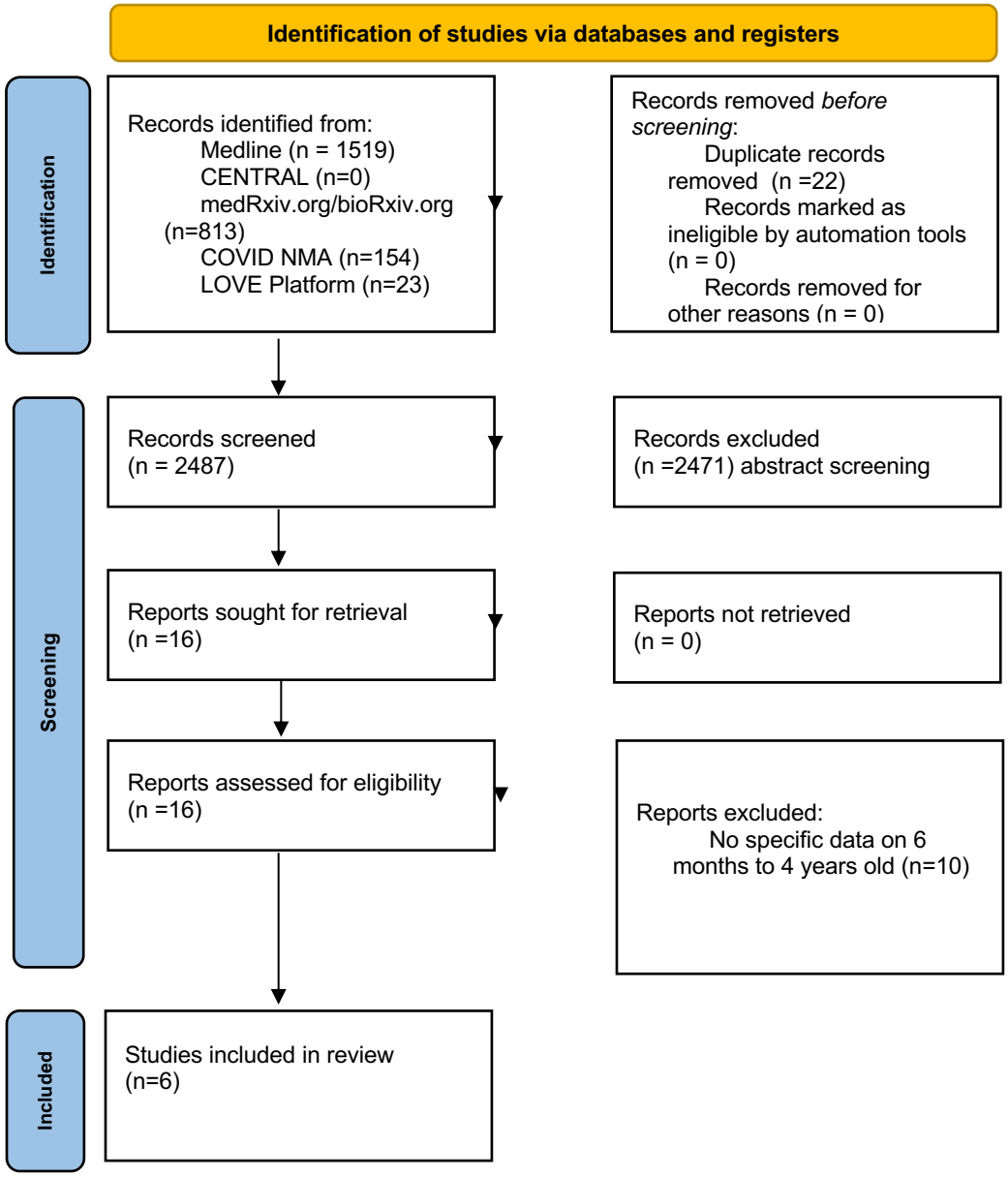


Figure 1. PRISMA flow diagram.

Appendix 4: Characteristics of Included Studies

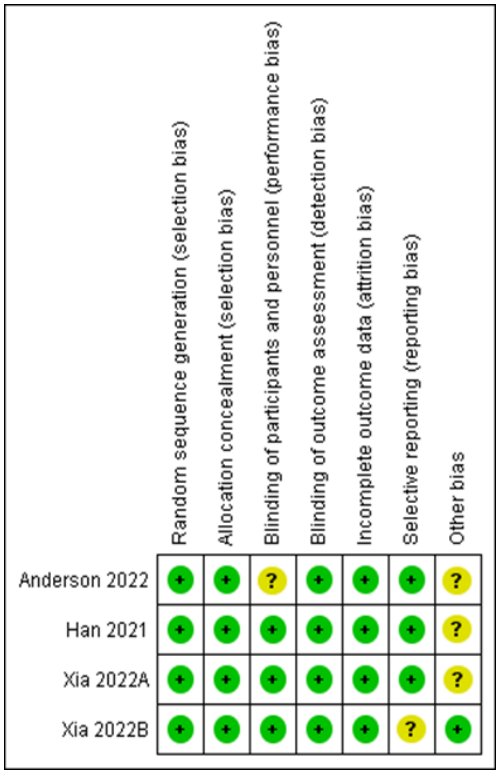
Table 3. Characteristics of included studies

Study ID	Study Design	Country	Population	Intervention	Comparator	Outcomes
Anderson et al., 2022 [8] *Published* *(Interim analysis)*	Ongoing Phase 2 -3 Clinical Trial Part 1 - open-label dose-escalation phase Part 2- observer-blinded, randomized, placebo-controlled expansion	North America (US & Canada)	healthy children plus children with stable chronic conditions (e.g., asthma, diabetes mellitus) aged 6 mos to 5 years Part 1 6 to 23 mos: N = 150 2 to 5 yrs: N = 224 Part 2 Total N= 6403 6 to 23 mos: Vaccine: N = 1762 Placebo: N = 593 2 to 5 yrs: Vaccine: N = 3040 Placebo: N = 1008 Predominant Variant: Omicron	mRNA vaccine: **mRNA-1273 (Moderna)** Dose: 25µg Number of Doses: 2 dose Schedule: 28 days apart	0.5ml Saline	INTERIM RESULTS Vaccine Efficacy - vs COVID infection, regardless of symptom - vs Symptomatic COVID infection - vs Asymptomatic COVID infection Immunogenicity (comparator: data of young adults) - GMC - GMR - Difference in serologic response Adverse Reaction - Solicited Local and Systemic Adverse Reactions within 7 days from vaccination - Unsolicited Adverse Reaction within 28 days from vaccination - Serious Adverse Reaction - Adverse event of special interest MEDIAN DURATION of FOLLOW-UP after the 2nd dose: 6 to 23 mos: 68 days and for the 2 to 5 yrs: 71 days
Han et al., 2021 [4] *Published*	Randomized, double-blinded, controlled Phase 1-2 trial Phase 1 – age de-escalation and dose-escalation	China	Healthy participants aged 3-17 years old (stratified: 3-5yrs, 6-12 yrs, 13-1 7 yrs) Total: Ph 1 N=72; Ph 2 N=480 For 3 – 5 years old Phase 1 Total N = 24 Vaccine: N = 18 (9 for each dose) Placebo: N = 6 Phase 2 Total N = 119 Vaccine: N = 95 - 1.5 µg N = 48 - 3 µg N = 47 Placebo: N = 24	Inactivated vaccine: **CoronaVac (Sinovac)** Adjuvant: aluminum hydroxide Dose: 1.5 µg, 3 µg Number of Doses: 2 doses Schedule: 28 days apart each dose (day 0, 28)	aluminum hydroxide adjuvant	Immunogenicity - GMT - Seroconversion Rate Adverse Reaction - Solicited Adverse events within 7 days after each vaccination - Unsolicited Adverse Events for 28 days - Serious adverse event throughout the study and continue 12 months after the 2nd dose - Laboratory Value Changes on day 3 after each vaccination (day 0, 28, 56 for phase 1; day 0, 56 for phase 2)
Jara et al., 2022 [2] *Published*	Population-based cohort	Chile	Children 3 to 5 years old N = 490694 Vaccine: N = 194427 Non-vaccinated: N = 189523 During Omicron Outbreak Predominant: Omicron BA.1.1	Inactivated vaccine: **CoronaVac (Sinovac)** Number of Doses: 2 doses Schedule: 28 days apart each dose (day 0, 28)	Non-vaccinated children	Vaccine Effectiveness - laboratory-confirmed symptomatic SARS-CoV-2 infection (COVID-19) - hospitalization admission associated with SARS-CoV-2 infection. - admission to the ICU associated with SARS-CoV-2 infection. Study Duration: 82 days

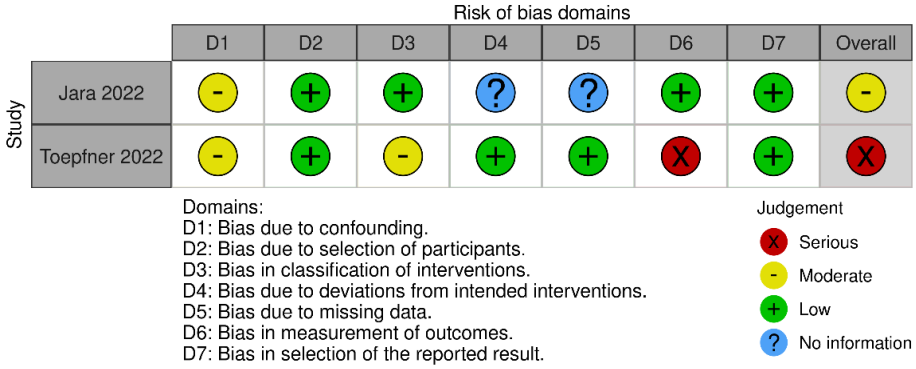
Toepfner et al, 2022 [10] *Published*	Investigator-initiated retrospective cohort	Germany	Children less than 5 years that received at least one dose of BNT162b2 that was administered before reaching the age of 5 years Total N = 7806 1st dose N = 7806 2nd dose N = 7102 3rd dose N = 846 Study period coincided with Omicron BA.1 and BA.2	mRNA vaccine: **BNT162b2 (Pfizer-BioNTech)** Dose: 3 µg, 5 µg, 10 µg Number of Doses: 3 dose Schedule: unclear OFF-LABEL USE *Off-label administration of SARS-CoV-2 vaccines to children younger than 5 years is permitted according to German law after obtaining written informed consent but remains at parents', legal guardians', or health care professionals' risk or liability.	On-label Non-COVID vaccinations of same group of participants (vaccines: Influenza, meningococcal, MMR, tetanus/diphteria/pertussis/ Hepatitis A & B, HPV)	Short-term safety data of 1 to 3 doses of 3 µg to 10 µg Frequencies of symptoms after vaccination MEAN DURATION OF FOLLOW – UP: 91.4 days
Xia et al., 2022A [5] *Published*	Randomized, double-blinded, controlled Phase 1-2 trial	China	Healthy participants aged 3-17 years old (stratified: 3-5yrs, 6-12 yrs, 13-17 yrs) Total: Ph1 N=288; Ph 2 N=720 For 3 – 5 years old Phase 1 Total N = 96 Vaccine: N = 72 (24 for each dose) Placebo: N = 24 Phase 2 Total N = 240 Vaccine: N = 180 (60 for each dose) Placebo: N = 60	Inactivated vaccine: **BBIBP-CorV** (Sinopharm-Beijing) Dose: 2 µg, 4 µg, 8 µg Number of Doses: 3 doses Schedule: 28 days apart each dose (day 0, 28, 56)	saline and aluminum hydroxide adjuvant	Immunogenicity - GMT - Seroconversion Rate Adverse Reaction - Solicited & Unsolicited Local and Systemic Adverse Reactions from 1st dose until 30 days after full course of vaccination - Laboratory Value Changes on day 4 after each vaccination
Xia et al., 2022B [9] *Published* *(Interim analysis)*	Randomized, double-blinded, controlled Phase 1-2 trial	China	Healthy participants aged 3-17 years old (stratified: 3-5yrs, 6-12 yrs, 13-17 yrs) Total: Ph 1 N=240;Ph 2 N=576 For 3 – 5 years old Phase 1 Total N = 96 Vaccine: N = 72 (24 for each dose) Placebo: N = 24 Phase 2 Total N = 240 Vaccine: N = 180 - N = 60 for each dose Placebo: N = 60	Inactivated vaccine: **WIBP-CorV** (Sinopharm-Wuhan) *developed by Wuhan Institute of Biological Products Dose: 2.5 µg, 5 µg, 10 µg Number of Doses: 3 doses Schedule: 28 days apart each dose (day 0, 28, 56)	aluminum hydroxide adjuvant	INTERIM RESULTS Immunogenicity - GMT of neutralizing antibodies and specific IgG-binding antibody - Seroconversion Rate Adverse Reaction - Occurrence of adverse reactions within 7 days after each vaccination. - Solicited & Unsolicited Local and Systemic Adverse Reactions from 1st dose until 30 days after full course of vaccination

Appendix 5: Study Appraisal

Randomized Studies – Using Cochrane Risk of Bias Tool (RoB) [6]



Non-Randomized Studies - Using Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) [7]



Appendix 6: Grade Evidence Profile

mRNA-1273 (Moderna)

Table 4. Clinical Efficacy, Immunogenicity and Safety of the primary series of mRNA-1273 (Moderna) for children 6 to 23 months

Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD
Question: Primary series of mRNA-1273 compared to placebo in children 6 months to 23 months of age
Setting: community
Bibliography: Anderson EJ, Creech CB, Berthaud V, Piramzadian A, Johnson KA, Zervos M, et al. Evaluation of mRNA-1273 vaccine in children 6 months to 5 years of age. N Engl J Med [Internet]. 2022; Available from: http://dx.doi.org/10.1056/NEJMoa2209367

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	primary series of mRNA-1273	placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Efficacy - COVID-19 infection, regardless of symptoms - dose: 25 mcg												
1 (n=2024)	randomised trials	not serious	not serious	not serious	not serious	none	81/1511 (5.4%)	45/513 (8.8%)	**RR 0.61** (0.43 to 0.87)	**34 fewer per 1,000** (from 50 fewer to 11 fewer)	⊕⊕⊕⊕ High	CRITICAL
Clinical Efficacy - COVID-19 infection, Symptomatic - dose: 25 mcg												
1 (n=2024)	randomised trials	not serious	not serious	not serious	not serious	none	51/1511 (3.4%)	34/513 (6.6%)	**RR 0.51** (0.33 to 0.78)	**32 fewer per 1,000** (from 44 fewer to 15 fewer)	⊕⊕⊕⊕ High	CRITICAL
Clinical Efficacy - COVID-19 infection, Asymptomatic - dose: 25 mcg												
1 (n=2024)	randomised trials	not serious	not serious	not serious	serious[a,b]	none	32/1511 (2.1%)	11/513 (2.1%)	**RR 0.99** (0.50 to 1.94)	**0 fewer per 1,000** (from 11 fewer to 20 more)	⊕⊕⊕◯ Moderate	CRITICAL
Immunogenicity - Geometric Mean Ratio - dose: 25 mcg												
1 (n=525)	historical cohort	not serious	not serious	serious[c,d]	not serious	none	230	295	-	GMR **1.3 higher** (1.1 higher to 1.5 higher)	⊕◯◯◯ Very low	CRITICAL
Safety - Any Solicited Adverse Reaction Within 7 days After 1st Vaccination - dose: 25 mcg												
1 (n=2328)	randomised trials	not serious	not serious	not serious	not serious	none	1469/1746 (84.1%)	460/582 (79.0%)	**RR 1.06** (1.02 to 1.12)	**47 more per 1,000** (from 16 more to 95 more)	⊕⊕⊕⊕ High	CRITICAL
Safety - Any Solicited Adverse Reaction Within 7 days After 2nd Vaccination - dose: 25 mcg												
1 (n=2122)	randomised trials	not serious	not serious	not serious	not serious	none	1329/1596 (83.3%)	381/526 (72.4%)	**RR 1.15** (1.09 to 1.22)	**109 more per 1,000** (from 65 more to 159 more)	⊕⊕⊕⊕ High	CRITICAL
Safety - Serious Adverse Event related to vaccination - dose: 25 mcg												
1 (n=2500)	randomised trials	not serious	not serious	not serious	serious[b,e]	none	1/1911 (0.1%)	0/589 (0.0%)	**RR 0.93** (0.04 to 22.69)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio; **GMR**: Geometric Mean Ratio

Explanations

a. wide confidence intervals
b. straddles 1.0 threshold

c. GMR is an indirect evidence of vaccine efficacy
d. control group for this result are young adults that received mRNA-1273 vaccine
e. very wide confidence intervals

Table 5. Clinical Efficacy & Immunogenicity and Safety of the primary series of mRNA-1273 (Moderna) for children 2 to 5 years
Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD
Question: Primary series of mRNA -1273 compared to placebo in children 2 to 5 years of age
Setting: community
Bibliography: Anderson EJ, Creech CB, Berthaud V, Piramzadian A, Johnson KA, Zervos M, et al. Evaluation of mRNA-1273 vaccine in children 6 months to 5 years of age. N Engl J Med [Internet]. 2022; Available from: http://dx.doi.org/10.1056/NEJMoa2209367

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	primary series of mRNA -1273	placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Efficacy - COVID-19 infection, regardless of symptoms - dose: 25 mcg												
1 (n=3452)	randomised trials	not serious	not serious	not serious	not serious	none	198/2594 (7.6%)	93/858 (10.8%)	**RR 0.70** (0.56 to 0.89)	**33 fewer per 1,000** (from 48 fewer to 12 fewer)	⊕⊕⊕⊕ High	CRITICAL
Clinical Efficacy - COVID-19 infection, Symptomatic - dose: 25 mcg												
1 (n=3452)	randomised trials	not serious	not serious	not serious	not serious	none	119/2594 (4.6%)	61/858 (7.1%)	**RR 0.65** (0.48 to 0.87)	**25 fewer per 1,000** (from 37 fewer to 9 fewer)	⊕⊕⊕⊕ High	CRITICAL
Clinical Efficacy - COVID-19 infection, Asymptomatic - dose: 25 mcg												
1 (n=3452)	randomised trials	not serious	not serious	not serious	serious[a]	none	79/2594 (3.0%)	33/858 (3.8%)	**RR 0.79** (0.53 to 1.18)	**8 fewer per 1,000** (from 18 fewer to 7 more)	⊕⊕⊕◯ Moderate	CRITICAL
Immunogenicity - Geometric Mean Ratio - dose: 25 mcg												
1 (n=559)	historical cohort	not serious	not serious	serious[b,c]	not serious	none	264	295	-	GMR **1 higher** (0.9 higher to 1.2 higher)	⊕◯◯◯ Very low	CRITICAL
Safety - Any Solicited Adverse Reaction Within 7 days After 1st Vaccination - dose: 25 mcg												
1 (n=3927)	randomised trials	not serious	not serious	not serious	not serious	none	2332/2957 (78.9%)	641/970 (66.1%)	**RR 1.19** (1.14 to 1.25)	**126 more per 1,000** (from 93 more to 165 more)	⊕⊕⊕⊕ High	CRITICAL
Safety - Any Solicited Adverse Reaction Within 7 days After 2nd Vaccination - dose: 25 mcg												
1 (n=3897)	randomised trials	not serious	not serious	not serious	not serious	none	2478/2938 (84.3%)	603/959 (62.9%)	**RR 1.34** (1.27 to 1.41)	**214 more per 1,000** (from 170 more to 258 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio; **GMR:** Geometric Mean Ratio

Explanations
a. crosses 1.0 threshold
b. GMR is an indirect evidence of vaccine efficacy
c. control group for this result are young adults that received mRNA-1273 vaccine

CoronaVac (Sinovac)

Table 6. Effectiveness, Immunogenicity & Safety of the primary series of CoronaVac (Sinovac) for children 3 to 5 years

Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD

Question: Primary series of CoronaVac (Sinovac) compared to placebo in children 3 to 5 years

Setting: community

Bibliography: [1] Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis [Internet]. 2021;21(12):1645–53. Available from: http://dx.doi.org/10.1016/S1473-3099(21)00319-4; [2] Jara A, Undurraga EA, Zubizarreta JR, González C, Acevedo J, Pizarro A, et al. Effectiveness of CoronaVac in children 3-5 years of age during the SARS-CoV-2 Omicron outbreak in Chile. Nat Med [Internet]. 2022;28(7):1377–80. Available from: http://dx.doi.org/10.1038/s41591-022-01874-4

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	primary series of CoronaVac (Sinovac)	placebo	Relative (95% CI)	Absolute (95% CI)		
Real World Effectiveness - Symptomatic Laboratory Confirmed- COVID-19												
1 (n=383950) [2]	observational studies	serious[a]	not serious	not serious	not serious	none	4562/194427 (2.3%)	7555/189523 (4.0%)	**RR 0.59** (0.57 to 0.61)	**16 fewer per 1,000** (from 17 fewer to 16 fewer)	⨁◯◯◯ Very low	CRITICAL
Real World Effectiveness - COVID-19-related Hospital Admission												
1 (n=383950) [2]	observational studies	serious[a]	not serious	not serious	not serious	none	23/194427 (0.0%)	62/189523 (0.0%)	**RR 0.36** (0.22 to 0.58)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Real World Effectiveness - COVID-19-related ICU admission												
1 (n=383950) [2]	observational studies	serious[a]	not serious	not serious	serious[b,c]	none	3/194427 (0.0%)	9/189523 (0.0%)	**RR 0.32** (0.09 to 1.20)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Immunogenicity - Mean Difference of GMT at 28 days post 2nd vaccination - dose: 1.5 mcg												
1 (n=70) [1]	randomised trials	not serious	not serious	serious[d]	not serious	none	46	24	-	MD **92.1 higher** (66.31 higher to 117.89 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Immunogenicity - Mean Difference of GMT at 28 days post 2nd vaccination - dose: 3 mcg												
1 (n=70) [1]	randomised trials	not serious	not serious	serious[d]	not serious	none	45	24	-	MD **138.5 higher** (109.03 higher to 167.97 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Safety - Overall Adverse Reactions within 28 days of vaccination - dose: 1.5 mcg												
1 (n=87) [1]	randomised trials	not serious	not serious	not serious	serious[b,c]	none	13/57 (22.8%)	9/30 (30.0%)	**RR 0.76** (0.37 to 1.57)	**72 fewer per 1,000** (from 189 fewer to 171 more)	⨁⨁⨁◯ Moderate	CRITICAL
Safety - Overall Adverse Reactions within 28 days of vaccination - dose: 3 mcg												
1 (n=86) [1]	randomised trials	not serious	not serious	not serious	serious[b,c]	none	15/56 (26.8%)	9/30 (30.0%)	**RR 0.89** (0.44 to 1.79)	**33 fewer per 1,000** (from 168 fewer to 237 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. overall moderate risk of bias in ROBINS-I
b. wide confidence interval
c. crosses 1.0 threshold
d. GMT is an indirect evidence of vaccine efficacy

BNT162b2 (Pfizer-BioNTech)

Table 7. Safety of off-label use of BNT162b2 (Pfizer-BioNTech) vaccination versus non-COVID-19 vaccine in children less than 5 years old

Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD

Question: BNT162b2 (Pfizer-BioNTech) - off-label use compared to non-COVID-19 vaccine - on label use in children less than 5 years old

Setting: community

Bibliography: Toepfner N, von Meißner WCG, Strumann C, Drinka D, Stuppe D, Jorczyk M, et al. Comparative safety of the BNT162b2 messenger RNA COVID-19 vaccine vs other approved vaccines in children younger than 5 years. JAMA Netw Open [Internet]. 2022;5(10):e2237140. Available from: http://dx.doi.org/10.1001/jamanetworkopen.2022.37140

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNT162b2 (Pfizer-BioNTech) - off-label use	non-COVID-19 vaccine - on label use	Relative (95% CI)	Absolute (95% CI)		
Safety - Overall Adverse Reactions (Any Symptom)												
1 (n=6061)	observational studies	very serious[a]	not serious	not serious	not serious	none	2323/4570 (50.8%)	564/1491 (37.8%)	**RR 1.34** (1.25 to 1.44)	**129 more per 1,000** (from 95 more to 166 more)	⨁◯◯◯ Very low	CRITICAL
Safety - Local Adverse Reactions												
1 (n=6011)	observational studies	very serious[a]	not serious	not serious	not serious	none	1808/4520 (40.0%)	380/1491 (25.5%)	**RR 1.57** (1.43 to 1.72)	**145 more per 1,000** (from 110 more to 184 more)	⨁◯◯◯ Very low	CRITICAL
Safety - Systemic Adverse Reactions												
1 (n=5997)	observational studies	very serious[a]	not serious	not serious	not serious	none	874/4506 (19.4%)	388/1491 (26.0%)	**RR 0.75** (0.67 to 0.83)	**65 fewer per 1,000** (from 86 fewer to 44 fewer)	⨁◯◯◯ Very low	CRITICAL
Safety - Adverse Reaction Requiring Inpatient Treatment												
1 (n=6061)	observational studies	very serious[a]	not serious	not serious	serious[b]	none	5/4570 (0.1%)	0/1491 (0.0%)	**RR 3.59** (0.20 to 64.89)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. overall serious risk of bias in ROBINS-I

b. wide confidence intervals; crosses 1.0 threshold

BBIBP-CorV (Sinopharm-Beijing)

Table 8. Immunogenicity & Safety of the primary series of BBIBP-CorV (Sinopharm-Beijing) for children 3 to 5 years

Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD

Question: Primary series of BBIBP-CorV (Sinopharm-Beijing) compared to placebo in healthy children 3 to 5 years

Setting: community

Bibliography: Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial. Lancet Infect Dis [Internet]. 2022;22(2):196–208. Available from: http://dx.doi.org/10.1016/S1473-3099(21)00462-X

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	primary series of BBIBP-CorV (Sinopharm-Beijing)	placebo	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccination - dose: 2 mcg												
1 (n=111)	randomised trials	not serious	not serious	serious[a]	not serious	none	83	28	-	MD **103.3 higher** (87.98 higher to 118.62 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccination - dose: 4 mcg												
1 (n=112)	randomised trials	not serious	not serious	serious[a]	not serious	none	84	28	-	MD **178.24 higher** (161.09 higher to 195.39 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccinationn - dose: 8 mcg												
1 (n=112)	randomised trials	not serious	not serious	serious[a]	not serious	none	84	28	-	MD **168.96 higher** (153.34 higher to 184.58 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Safety - Local and Systemic Adverse Reaction within 30 days after 2nd vaccination - dose: 2 mcg												
1 (n=110)	randomised trials	not serious	not serious	not serious	serious[b]	none	2/83 (2.4%)	2/27 (7.4%)	**RR 0.33** (0.05 to 2.20)	**50 fewer per 1,000** (from 70 fewer to 89 more)	⊕⊕⊕◯ Moderate	CRITICAL
Safety - Local and Systemic Adverse Reaction within 30 days after 2nd vaccination - dose: 4 mcg												
1 (n=110)	randomised trials	not serious	not serious	not serious	serious[b]	none	7/83 (8.4%)	2/27 (7.4%)	**RR 1.14** (0.25 to 5.16)	**10 more per 1,000** (from 56 fewer to 308 more)	⊕⊕⊕◯ Moderate	CRITICAL
Safety - Local and Systemic Adverse Reaction within 30 days after 2nd vaccination - dose: 8 mcg												
1 (n=111)	randomised trials	not serious	not serious	not serious	serious[b]	none	6/83 (7.2%)	2/28 (7.1%)	**RR 1.01** (0.22 to 4.73)	**1 more per 1,000** (from 56 fewer to 266 more)	⊕⊕⊕◯ Moderate	CRITICAL
Safety - Local and Systemic Adverse Reaction within 30 days after 2nd vaccination - Overall												
1 (n=331)	randomised trials	not serious	not serious	not serious	serious[b]	none	15/249 (6.0%)	6/82 (7.3%)	**RR 0.82** (0.33 to 2.05)	**13 fewer per 1,000** (from 49 fewer to 77 more)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. GMT is an indirect evidence of vaccine efficacy; b. wide confidence intervals, crosses 1.0 threshold

WIBP-CorV (Sinopharm-Wuhan)

Table 9. Immunogenicity & Safety of the primary series of WIBP-CorV (Sinopharm-Wuhan) for children 3 to 5 years

Author(s): Giselle Anne Q. Adajar, MD, Ma. Lucila M. Perez, MD
Question: Primary series of WIBP-CorV (Sinopharm-Wuhan) compared to placebo in healthy children 3 to 5 years old
Setting: community
Bibliography: Xia S, Duan K, Zhang Y, Zeng X, Zhao D, Zhang H, et al. Safety and immunogenicity of an inactivated COVID-19 vaccine, WIBP-CorV, in healthy children: Interim analysis of a randomized, double-blind, controlled, phase 1/2 trial. Front Immunol [Internet]. 2022;13:898151. Available from: http://dx.doi.org/10.3389/fimmu.2022.898151

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	primary series of WIBP-CorV (Sinopharm-Wuhan)	placebo	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccination - dose: 2.5 mcg												
1 (n=163)	randomised trials	not serious	not serious	serious[a]	not serious	none	84	79	-	MD **232.8 higher** (192.29 higher to 273.31 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccination - dose: 5 mcg												
1 (n=162)	randomised trials	not serious	not serious	serious[a]	not serious	none	83	79	-	MD **263.4 higher** (217.43 higher to 309.37 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Immunogenicity - Mean Difference of GMT of neutralizing antibodies at 28 days post 2nd vaccination - dose: 10 mcg												
1 (n=159)	randomised trials	not serious	not serious	serious[a]	not serious	none	80	79	-	MD **378.4 higher** (311.54 higher to 445.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Safety - Total Adverse Reactions within 30 days after whole course of vaccination - dose: 2.5 mcg												
1 (n=168)	randomised trials	not serious	not serious	not serious	serious[b]	none	18/84 (21.4%)	16/84 (19.0%)	**RR 1.13** (0.62 to 2.05)	**25 more per 1,000** (from 72 fewer to 200 more)	⨁⨁⨁◯ Moderate	CRITICAL
Safety - Total Adverse Reactions within 30 days after whole course of vaccination - dose: 5 mcg												
1 (n=168)	randomised trials	not serious	not serious	not serious	serious[b]	none	14/84 (16.7%)	16/84 (19.0%)	**RR 0.88** (0.46 to 1.68)	**23 fewer per 1,000** (from 103 fewer to 130 more)	⨁⨁⨁◯ Moderate	CRITICAL
Safety - Total Adverse Reactions within 30 days after whole course of vaccination - dose: 10 mcg												
1 (n=168)	randomised trials	not serious	not serious	not serious	serious[b]	none	13/84 (15.5%)	16/84 (19.0%)	**RR 0.81** (0.42 to 1.58)	**36 fewer per 1,000** (from 110 fewer to 110 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. GMT is an indirect evidence of vaccine efficacy
b. wide confidence intervals, crosses 1.0 threshold

Appendix 7: Ongoing Studies

Table 10. Characteristics of ongoing studies

Trial Code or Num	Title	Population	Intervention	Comparator	Outcome	Status
NCT05468736	Study to Evaluate Safety and Immunogenicity of COVID-19 Vaccine in Children 6 Months to < 12 Years (COVID-19)	Pediatric participants (3 age cohorts; 6 to < 12 years, 2 to < 6 years, and 6 to < 24 months of age)	2 primary doses and a booster dose of NVX CoV2373	Placebo	Adverse Event, Clinical Efficacy, Antibody Response	Recruiting Estimated Study Completion Date: Sept 8, 2025
NCT04800133	Covid-19 Vaccination in Adolescents and Children (COVAC)	Children and Adults (Age 0 to 100 years old)	BNT162b2 & CoronaVac	None	Adverse Reactions, Antibody Response	Active, NOT recruiting Estimated Study Completion Date: May 31, 2025
NCT04816643	A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children and Young Adults	Pediatric participants (6 months to 18 years)	BNT162b2 vaccine	Placebo	Adverse Reactions, Immunobridging, Difference in seroresponse, vaccine efficacy	Active, NOT recruiting Estimated Study Completion Date: May 34, 2024
NCT05295290	Study of Myo/Pericarditis Associated With COMIRNATY (Vaccine to Prevent COVID-19) in Persons <21 Years of Age	Persons less than 21 years old	COMINARTY	Data on similarly aged persons with myocarditis/ pericarditis associated with COVID-19, including MIS-C, without exposure to COMIRNATY.	cardiac and non-cardiac long-term outcomes after receiving COMINARTY	Not yet recruiting Estimated Study Completion Date: Oct 15, 2028
NCT05436834	A Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 COVID-19 Vaccine in Healthy Children Between 6 Months to Less Than 6 Years of Age	Pediatric participants (6 months to < 6 years old)	mRNA-1273.214 (bivalent) as primary series and as booster dose for mRNA-1273	None	Adverse Reactions, Geometric Mean measurements of neutralizing antibodies, Seroresponse rate	Recruiting Estimated Study Completion Date: Oct 31, 2023
NCT04918797	COVAXIN in a Pediatric Cohort (COVAXIN-Peds)	Pediatric participants (2 to 18 years old)	COVAXIN	None	Reactogenicity, Immunogenicity	Completed Actual Study Completion Date: Jan 25, 2022
NCT05003466	Study of Inactivated SARS-CoV-2 Vaccine (Vero Cells) in Healthy Population Aged 3 to 17 Years (COVID-19)	Pediatric participants (3 to 17 years old)	SARS-CoV-2 Vaccine (Vero Cells), Inactivated	Placebo	Seroconversion rate, GMT of antibody, Adverse Event	Not yet recruiting Estimated Study Completion Date: April 2023
NCT05543616	A Study to Learn About COVID-19 Bivalent BNT162b2 Omicron Containing Vaccine in Healthy Children	Pediatric participants (6 months to 11 years)	BNT162b2 (bivalent)	None	Adverse Reactions, Geometric Mean of antibodies, Seroresponse rate	Recruiting Estimated Study Completion Date: Feb 19, 2025
NCT05584202	Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273.214 SARS-CoV-2 (COVID-19) Vaccine in Infants (BabyCOVE)	Pediatric participants (2 months to 6 months old)	mRNA-1273.214	Placebo	Adverse Reactions, Geometric Mean of antibodies, Seroresponse rate	Recruiting Estimated Study Completion Date: Mar 8, 2024

ChiCTR2100048439	A randomized, blinded, placebo-controlled phase I clinical trial to evaluate the safety and tolerability of recombinant novel coronavirus (COVID-19) vaccine (CHO cells) in healthy people aged 3 to 17 years	Pediatric participants (3 to 17 years old)	recombinant novel coronavirus (COVID-19) vaccine (CHO cells)	Placebo	SARS-Cov-2 neutralizing antibody	Recruiting
2021-001357-31	Immune Responses Induced by Vaccination Against COVID-19 in Dutch healthy subjects	Children & Adults (0 to 60 years old)	Any Corona vaccination	None	COVID-19 vaccine (e.g. Spike protein)-specific serum IgG antibody level; reactogenicity	Ongoing
2021-002966-41	Anti-Covid-19 vaccine protection in immunocompromised children (1-15 years) with acute leukemia and their siblings (≥ 12 years). Phase I-II trial evaluating safety and post-vaccination humoral and cellular immunogenicity / PACIFIC STUDY	immunocompromised children (1-15 years) with acute leukemia and their siblings (≥ 12 years)	BNT162b2	None	Safety and immunogenicity	Ongoing
2021-002613-34	Prospective monitoring of antibody response following COVID-19 vaccination in patients with Down Syndrome	Persons with Down syndrome (children and adults)	Comirnaty COVID-19 mRNA Vaccine (nucleoside modified); COVID-19 Vaccine Moderna; AstraZeneca AB;	None	antibody response as compared to healthy control	Ongoing
2021-003277-55	COVID-19 Antibody Responses in Cystic Fibrosis: CAR-CF	Persons with Cystic Fibrosis (Chlidren & Adults)	Comirnaty COVID-19 mRNA Vaccine; Vaxzevria suspension for injection COVID-19 Vaccine (ChAdOx1-S [recombinant]); COVID-19 Vaccine Moderna dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified); COVID-19 Vaccine Janssen suspension for injection COVID-19 vaccine (Ad26.COV2-S [recombinant])	None	Seroresponse rate, Incidence of symptomatic COVID-19, Levels and duration of anti-SARS-CoV-2 antibodies in pwCF following natural infection and vaccination SARS-CoV-2	Ongoing
2020-005442-42	A phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo controlled, observer-blinded safety, tolerability, and immunogenicity study of a sars-cov-2 RNA vaccine candidate against covid-19 in healthy children <12 years of age\	Pediatric participants (6 months to <12 years)	BNT162b2	Placebo	Safety & Tolerability (Adverse Reactions), Immunogenicity (Geometric Mean of antibodies)	Ongoing
2021-001290-23/ NCT04895982	A phase 2b, open-label study to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants ≥2 years of age	immunocompromised patients more than 2 years old	BNT162b2	None	Adverse Reactions, Geometric Mean Titers of antibodies	Recruiting Estimated Study Completion Date: Jan 15, 2024