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 adolescents 12 to 17 years old, what is the efficacy, effectiveness and safety of COVID-19 vaccine in preventing COVID-19 infection?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of the BNT162b2 (Pfizer-BioNTech) vaccine, [given as 0.3mL (30ug) intramuscular injections, in 2 doses, 21 days apart] for healthy children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection.	Low	Weak
We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5mL (100ug) intramuscular injections, in 2 doses, 28 days apart] for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection.	Low	Weak
There is insufficient evidence to recommend the use of the following for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection: a. ChAdOx1 (AstraZeneca b. CoronaVac (Sinovac) c. BBIBP-CorV (Sinopharm-Beijing) d. Recombinant Adenovirus	 Very low Low Low Low	None
There is insufficient evidence to recommend BNT162b2 in immunocompromised children 12 to 17 years to prevent symptomatic SARS-CoV-2 infection.	Very low	None

Consensus Issues

The Panel opted to specify age groups per vaccine recommendation to reflect the varying age ranges reflected in the available evidence presented for each vaccine. In this update, the Panel opted to change the certainty of evidence for the Pfizer vaccine to reflect the new evidence gathered in the literature search. Additionally, the Panel decided to update the CoronaVac vaccine recommendation wording to insufficient evidence considering the issues of vaccine hesitancy and potential implication of suggesting against vaccination.

KEY FINDINGS

- All retrieved studies were published, which included 4 meta-analyses/systemic reviews, 7 RCTs, and 15 effectiveness studies
- Low certainty evidence showed that BNT162b2 (Pfizer-BioNTech) was effective, immunogenic and safe in healthy adolescents. There was no new trial on this vaccine in 12 to 17 years. However, there were 12 new effectiveness studies on BNT162b2 (Pfizer-BioNTech) in healthy adolescents. It was protective against infection with any of the variants, with higher protection against Delta than Omicron. BNT162b2 is protective against hospitalization and emergency and urgent care (high

certainty); and critical care and MIS-C (low). Very low certainty evidence from one study noted that BNT 162b2 was also immunogenic in 12 to 21 years old with rheumatic diseases while on immunomodulatory treatment but with possible increased exacerbation of illness.

- Low certainty evidence demonstrated that mRNA-1273 (Moderna) was effective, immunogenic and safe. There was no new trial in mRNA-1273 vaccine. There were two phase 2 trials on vector-based vaccines (ChAdOx1-19 and Ad5 vector COVID-19 vaccine). There were also two phase 1/2 RCTs on safety and immunogenicity of inactivated vaccines (CoronaVac and BBIBP CorV). The RCT on CoronaVac was reported in the previous review.

WHAT'S NEW IN THIS VERSION?

This updated review includes three additional RCTs on the use of COVID-19 vaccine in 12 to 17 years, of which two were vector-based and one inactivated vaccine. They were Phase 1 to 2 clinical trials and reported mostly the immunogenicity and safety of the vaccines. These bring to six the total number of efficacy trials, three of which were included in the original evidence.

There were also 13 effectiveness studies on the use of COVID-19 vaccines among 12 to 17 years, 12 on the healthy population and one on immunocompromised patients which were used as new evidence. Based on the new studies, certainty of evidence on the use of BNT162b2 in the healthy population was downgraded to low with weak recommendation. Evidence for COVID-19 vaccination of immunocompromised children 12 to 17 years old is presented but the evidence is still to recommend BNT162b2 in to prevent symptomatic SARS-CoV-2 infection.

PREVIOUS RECOMMENDATION
As of 21 October 2021

We recommend the use of the BNT162b2 (Pfizer-BioNTech) vaccine, [given as 0.3mL (30ug) intramuscular injections, in 2 doses, 21 days apart] for children 12 to 15 years old to prevent symptomatic SARS-CoV-2 infection. *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5mL (100ug) intramuscular injections, in 2 doses, 28 days apart] for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of CoronaVac (Sinovac), [given as 0.5mL (600SU) intramuscular injection, in 2 doses, 28 days apart] for children 3 to 17 years old to prevent symptomatic SARS-CoV-2 infection. *(No evidence; Weak recommendation)*

Consensus Issues
The issue of myocarditis associated with the mRNA vaccines in children was a major consideration in the recommendation, particularly with the mRNA-1273 (Moderna) vaccine. Despite the low incidence of post-vaccination myocarditis, some Panel members considered it significant enough, especially when normal children are concerned, to weigh heavily on the benefit risk ratio. The suspension of the use of mRNA-1273 among children in some countries due to the myocarditis issue was also raised, resulting in the cautious recommendation given for this vaccine. The Panel emphasized that warnings should be given to the parents and caregivers of the vaccine recipients to consult immediately in case of symptoms occurring after vaccination, which may suggest the development of myocarditis.

INTRODUCTION

COVID-19 has affected more than 650 million people worldwide with 6.6 million deaths affecting all age groups. The CDC reported that the rate ratio of COVID-19 cases in children 5 to 17 years and in those >18 years is the same but the number of hospitalization and death in children is less and symptoms are often milder. However, children and adolescents have the potential to become reservoirs of the virus and infect the other members of the household. There is also the risk of developing severe infection in children and development of Multisystem Inflammatory Syndrome which may indicate the need for vaccination. Vaccination may also improve the psychological growth of children allowing interaction with other children and participation in other outdoor activities.

Considering these and the resources needed for COVID-19 vaccination of children, there is a need to comprehensively assess existing clinical evidence to evaluate the risk and benefits as a basis for the recommendations.

REVIEW METHODS

Included in this review were any type of study that investigated the efficacy, immunogenicity, safety and effectiveness of COVID-19 on protection against SARS-COV-2 infection in patients 12 to 17 years old. Various electronic databases including MEDLINE, Cochrane CENTRAL, ClinicalTrials.gov, MedRXIV, BioRXIV were comprehensively searched as well as the following registries: Chinese Clinical Trial Registry, EU Clinical Trial Registry and L.OVE. Published/ongoing studies on the COVID-19 Open Living Evidence Synthesis: https://covid-nma.com and LOVE Platform for COVID-19 Evidence were also included. The last search date was March 6, 2023 using a combination of subject headings and keywords for the following PICO: P – 12 to 17 years old, adolescent, child; I – Covid 19 vaccine; C – no vaccine; and O – prevention of SARS-CoV-2 transmission. (Appendix 2) Studies were screened, data extracted, risk of bias appraised by the reviewers using the quality assessment tool of Cochrane for RCT, Newcastle Ottawa for case control

and cohort studies and Amstar for meta-analysis. Certainty of evidence was judged using the GRADE approach. Review Manager 5.4 was used to estimate pooled effects. Difference between the two groups was described as mean difference for continuous variables and as relative risk or odds ratio for categorical variables.

RESULTS

Characteristics of included studies

All retrieved studies were published. The characteristics of the included studies are summarized in Appendix 4. There were four meta-analyses/systematic reviews, 3 on efficacy and safety of the COVID-19 vaccines [1-3] and one effectiveness study on BNT162b2 [4]. All were assessed in AMSTAR to have a critically low rate of confidence in the results. Since these meta-analyses/systematic reviews were of moderate to high risk of bias, available individual studies we have searched were used as evidence.

There were initially seven RCTs on the use of COVID-19 vaccines in children and adolescents in the healthy population. There were two Phase 2 interim reports on efficacy, safety and/or immunogenicity of mRNA for BNT162b2 (Pfizer-BioNTech) [5] and mRNA-1273 (Moderna) [6]; two phase 2 trials on vector based for ChAdOx1 (COVISHIELD, AstraZeneca) [7] and recombinant Ad5-vector [8]; and two Phase 1 studies in inactivated vaccine (CoronaVac) [9] and BBIBP-CorV [10]. There was also one completed trial on DNA ZyCoV-D but since the 12 to 17 years was only 3% of the trial population in the study, the results of this study were not included in the present review.

There were also 15 effectiveness studies of BNT162b2 (Pfizer-BioNTech) with two studies that reported on BNT162b2, mRNA and Ad26 vaccines [12,13]. Of these, 14 were on healthy adolescents and one was on 12 to 21 years old with rheumatic diseases on immunomodulatory treatment [14]. The variants in the studies were on Alpha and Delta in two [12,15]), Delta in four [16-19] , Delta and Omicron in three [20-22]; one in Omicron [23]; and in five studies [13,14,24-26] it was not reported. The variants were based on the predominant strain at the time of the research in five studies [12,16,20,22] and in another five it was detected by viral sequencing [15,17,19,21,23].

Healthy 12 to 17 year old population

mRNA vaccine

The results of the efficacy, immunogenicity and safety of BNT162b2 and mRNA-1273 trials have been previously reported. There are presently no new trials on mRNA vaccines in adolescents.

BNT162b2

The BNT162b2 trial randomized 2260 patients aged 12 to 15 years old (vaccine n=1131; control n=1129). Among 1983 participants who could be evaluated, there was no evidence of COVID-19 infection seven days or more after dose 2 of the vaccine in the vaccine recipients (0/1005) as compared to 16 of 978 in the placebo showing protective effect (RR 0.03, 95% CI 0.00-0.49). In 360 participants, the geometric mean fold rise was higher in the 12 to 15 years age group as compared to the 16 to 25 years, which met the criterion for non inferiority (Mean Difference 116.9, 95% CI 97.6-136.19). Moderate certainty of evidence showed that any serious adverse effect was higher in the vaccine group, but this was not significant compared to the placebo group (RR 3.99, 95% CI 0.45-35.67).

Efficacy Outcomes

Fifteen observational studies (8 cohort and 7 case control) reported the effectiveness of vaccines. Thirteeen of the studies used BNT162b2 while the two were on BNT162b2, mRNA-1273 and Ad5 vector based. Only the data of the BNT162b2 was reported in this review as the data on the two latter vaccines were on 16 to

19 years old. For the data on vaccine effectiveness, the one 14 days after two doses of vaccines have been given were used.

BNT162b was protective against COVID-19 infection with any of the variants, with higher protection for Delta (OR 0.05, 95% CI 0.05-0.05; I^2=98%, 8 studies) than for Omicron variant (OR 0.37, 95% CI 0.36-0.390; I^2=99%, 3 studies). In studies that the variants were not known, the COVID-19 vaccine was also shown to be protective (OR 0.01, 95% CI 0.01-0.02; I^2=99%, 3 studies, n=4051). The certainty of evidence was assessed as moderate for the Delta and very low for Omicron and unknown variants due to the heterogeneity of the studies.

COVID-19 vaccination in 12 to 17 years old was protective from hospitalization (OR 0.09, 95% CI 0.05-0.15; I^2=27%, 2 studies) and from Emergency and Urgent Care (OR 0.17, 95% CI 0.16-0.19, 1 study) with high certainty of evidence. In these studies, the predominant variant was Delta. BNT162b2 was also protective against ICU care (OR 0.13, 95% CI 0.04-0.41; I^2=0%, 3 studies); critically Ill (OR 0.17, 95% CI 0.04-0.73; I^2=0%, 3 studies); and MIS-C (OR 0.09, 95% CI 0.04-0.24; 1 study) with low certainty of evidence. The evidence on protection against hospitalization and emergency and urgent care was upgraded due to very large effect.

mRNA-1273

Efficacy and Immunogenicity Outcomes

The mRNA-1273 trial randomized 12 to 17 years old (n=3732), 2489 of which received the vaccine. Protective effect was demonstrated with only one COVID-19 infection 14 days after dose 2 and seven in the placebo (RR 0.05, 95% CI 0.003-1.0234). Only 636 participants had immunologic studies. The number of patients with serologic response was similar in the 12 to 17 and 18 to 25 years. However, the Geometric Mean Pseudovirus Neutralizing Antibody Ratio was higher in the 12 to 17 years than in young adults but was not significantly different (MD 100.4, -85.93 to 286.73).

Safety Outcomes

Moderate to high certainty evidence showed increased risk of adverse reactions after dose 1 (RR 1.47, 95% CI 1.41-1.54) but not for dose 2 (RR 1.306, 95% CI 0.845-2.008) in the vaccine group. There were also no difference in risk of unsolicited headaches (RR 1.070, 95% CI 0.686-1.660) but higher risk for lymphadenopathy (RR 10.770, 95% CI 4.407-26.341) up to 28 days after any of the doses.

Vector-based vaccine

There were two vector based trials, one on ChAdOx1-19 conducted in the UK and another on Recombinant Adenovirus Type-5-vector in China. Only the ChAdOx1-19 trial reported the efficacy.

ChAdOx1-19 (AstraZeneca)

Efficacy Outcomes

A single-blind randomized phase 2 trial was conducted among 6 to 17 years old in which among the 12 to 17 years old age group, 120 were given the vaccine with intervals that varied from 28 to 112 days. There was a total of 30 controls who were given Meningococcal vaccine, 16 in the 28 days and 14 in the 112 days interval. Results showed no difference in the risk of infection in those who were given the ChADOx1-19 and Meningococcal vaccine (RR 1.00, 95% CI 0.3-3.32). The quality of the evidence was downgraded to very low as there was serious risk of bias, imprecision and possible publication bias.

Immunogenicity Outcomes

Baseline and post-vaccination humoral responses against anti-spike IgG, pseudovirus neutralizing antibody and the antireceptor domain were measured on Day 0, 28, 84 and 112 days after the second dose. The geometric mean concentration (GMC) of the antibodies for the vaccine were higher in the vaccine group. Anti-spike IgG by PPD (MD 73144, 95% CI 57014.73-89273.27) and pseudo neutralizing antidodies (MD

242.00, 95% CI 101.95-382.05) were also reported. Certainty of evidence was downgraded as low due to indirectness and suspected publication bias.

Safety Outcomes

The proportion of participants with adverse events after dose 1 (RR 1.467, 95% CI 0.3725-5.7825) and dose 2 (RR 0.6770, 95% CI 0.2101-2.1846) were similar in both groups. There were four serious adverse effects in the vaccine group (RR 3.197, 95% CI 0.1905-43.82) but none were deemed vaccine related.

Recombinant Adenovirus Type 5-Vectored COVID-19 vaccine

A Phase 2 randomized placebo controlled trial of Ad5 vectored COVID-19 vaccine versus placebo was conducted in 430 participants at least 6 years old, 150 (34.9%) of which were 6 to 17 years. There was no separate data for 12 to 17 years old.

Only the immunogenicity and safety of the vaccine was assessed. The prime boost regime of Ad5 vectored COVID-19 vaccine elicited a seroconversion neutralizing antibodies to pseudovirus in 98% of participants (MD 161.2, 95% CI 134.3-188.1). The humoral immune response elicited by Ad5 vectored COVID 19 vaccine decreased with age.

Within 14 days of the vaccine, there was significantly more adverse reactions in the vaccine, both local (RR 6.00, 95% CI 1.942-18.534) and systemic (RR 3.700, 95% CI 1.550-8.832). Most common vaccine-related local adverse effect was pain in the injection site while the most common systemic adverse effect was fever.

Inactivated vaccine

There are presently two Phase 1/2 randomized contorolled trials on inactivated vaccines: Coronavac and BBIBP.

Coronavac

The safety and immunogenicity of CoronaVac has been previously reported in the initial review. There is no new study on CoronaVac. The proportion of participants with seroconversion rate to neutralizing antibodies to COVID-19 28 days after the second dose was higher in 3.0μg dose than the 1.5μg dose (RR 0.09, 95% CI 0.0054-1.708). The Geometric Mean neutralizing antibody Titre was higher in the vaccine than in control group (MD 144, 95% CI 108.34-179.66). The overall adverse reaction within 28 days after first and second vaccine dose in the placebo group was not significantly different from vaccine group (RR 1.432, 95% CI 0.8007-2.5604). The most common local adverse effect was pain (RR 9.2, 95% CI 2.25-37.5) and most common systemic adverse effect was fever (RR 1.16, 95% CI 0.41-3.2). The vaccine was not recommended in the initial review in the absence of information on the clinical efficacy. Overall certainty of evidence was low due to imprecion in the adverse effects data and possible publication bias.

BBIBP

The RCT on Phase 2 of BBIBP (Beijing Institute of Biological Products, Beijing China) has 240 participants in the 13 to 17 years old age group. One hundred eighty participants were randomly assigned to 2, 4 or 8μg vaccines and 60 as controls (saline and aluminum hydroxide).

Immunogenicity Outcomes

Immunogenicity was assessed by measurement of infectious SARS-CoV-2 neutralizing antibody on Days 0, 28, 56 and 84. All 83 (100%) participants in the 2μg, 82 of 83 (99%) in the 4μg and all 82 in the 8μg seroconverted on day 28 and seroconversion reached 100% in all three doses at day 56. The mean pseudovirus neutralizing antibody on day 84 was higher in the vaccine group (MD 190.15, 95% CI 172.77-207.52).

Safety Outcomes

There was no significant difference in the occurrence of systemic adverse reactions in the vaccine group from the placebo group after the first (RR 1.194, 95% CI 0.662-2156), second (RR 3.267, 95% CI 0.78-13.679) and third (RR 1.960, 95% CI 0.239-16.044) dose. Fever was the most common systemic adverse reaction within 14 days after primary (RR 7.00, 95% CI 1.737-28.212) and booster dose (RR 6.500, 95% CI 0.875-48.292).

Certainty of evidence

Table 1. Certainty of evidence for each vaccine

Vaccine	Certainty of Evidence	Reason
mRNA vaccines		
BNT162b2 (Pfizer-BioNTech)	Low	Low certainty of evidence in observational studies that reported its effectiveness in protection against ICU and MIS-C
mRNA (Moderna)	Low	Low certainty of evidence due to indirectness (immunogenicity as a surrogate marker) and imprecision (wide confidence interval in the efficacy, immunogenicity and safety results)
Vector based		
COVISHIELD (AstraZeneca)	Very low	Very low certainty of evidence in efficacy result due to serious risk of bias (diagnosis of SARS COV2 was based on self reported parameter, either by PCR or lateral flow assay, regardless of symptoms), imprecision and possible publication bias (only one Phase 1 / 2 trial with small sample size)
Recombinant Adenovirus vectored COVID-19	Low	Low certainty of evidence as there is indirectness (data is for 6-17 years old, no separate data for 12-17 years). There is also possible publication bias (only one Phase 1 / 2 trial with small sample size)
Inactivated vaccines		
CORONAVAC	Low	Low certainty of evidence as there is imprecision in the safety data. There is also possible publication bias (only one Phase 1 / 2 trial with small sample size)
BBIBP	Low	Low certainty of evidence as there is imprecision in the safety data. There is also possible publication bias (only one Phase 1 / 2 trial with small sample size)

Immunocompromised Patients

BNT162b2 vaccine on patients with Autoimmune Inflammatory Rheumatic Diseases (AIIRD)

A prospective multicenter cohort study evaluated the short term effcacy, safety and immunogenicity of BNT162b2 among 91 adolescent and young adults 12 to 21 years with various autoimmune inflammatory rheumatic disease, 80% of which were on immunomodulatory medications. Forty healthy adolescents who were also vaccinated with BNT162b2 served as controls.

Efficacy Outcomes

There was no COVID-19 infection detected among the AIIRD patients and controls during the 3 months post-vaccine follow up (RR 0.4607, 95% CI 0.0090-22.078).

Immunogenicity Outcomes

Thirty seven patients and 22 controls were evaluated for immunogenicity. The seropositivity for the anti-S1/S2 antibodies was similar in AIIRD and controls (RR 0.97, 95% CI 0.78-1.21). However the anti-S1/S2 antibody levels were significantly lower in patients with AIIRD compared with controls (MD -145.80, 95% CI -195.85 to -95.75; P<0.001).

Safety Outcomes

Prevalence of mild adverse effects of the vaccine was similar in AIIRD and controls with local pain as the most common side effect both after the first (RR 0.99, 95% CI 0.82-1.20) and second dose (RR 0.97, 95% CI 0.78-1.21).

Hospitalization within 2 to 4 weeks after dose 1 (RR 2.198, 95% CI 0.108-44.747) and dose 2 (RR 1.382, 95% CI 0.058-33.207) was not different between AIIRD and healthy controls. Risk of exacerbation of Rheumatic dose within 2 to 4 weeks after dose 1 (RR 5.000, 95% CI 0.274-85.375) and after dose 2 (RR 1.382, 95% CI 0.058-33.207).

Certainty of Evidence

The lone study on immunocompromised adolescents was rated as very low overall certainty of evidence. The prospective cohort study downgraded for indirectness because the immunocompromised subjects were compared to healthy controls whose baseline risk are likely to be different.

RECOMMENDATIONS FROM OTHER GROUPS

The following are recommendations / guidelines from regulatory agencies on the use of COVID-19 vaccines in children:

Table 2. Summary of Recommendations from other Organizations on the use of COVID-19 vaccines in children

Group / Agency	Recommendation
World Health Organization (WHO) As of August 11, 2022 [27]	• Consider COVID-19 vaccination in children when high vaccine coverage with 2 doses and booster doses has been achieved in the high priority groups • Children should continue to receive the recommended childhood vaccines for other infectious disease
Advisory Committee on Immunization Practices (ACIP) US CDC As of Nov 1, 2022 [28]	• Recommends COVID-19 vaccine for everyone age >6 months and older and booster for everyone 5 years and older if eligible. • Complete primary series with the same manufacturer's product. If the previously administered products are unknown, not available, contraindicated or a mixed manufacturer-product series (Pfizer-BioNTech and Moderna vaccines), follow a 3-dose schedule. A third dose of either a monovalent Moderna vaccine or a bivalent Pfizer-BioNTech vaccine should be administered at least 8 weeks after the second dose to complete the primary series. These children cannot receive any booster dose.
Health Technology Assessment of the Department of Health Philippines [29]	• Use of RNA vaccines among adolescents ages 12 to 17 years. Standard vaccination vaccine should be followed in administering to vaccine to adolescents
Philippine Pediatric Society-Pediatric Infectious Disease Society of the Philippines As of September 16, 2021 [30]	• Once the whole country has a sufficient percentage vaccinated in the priority adult groups, children 12 years and above can be considered for vaccination • Vaccine roll out in high transmission area and should prioritize adolescents that are qualified in the A3 (children with co-morbidities) and A1 (children of healthcare frontliners) category
European Center for Disease Prevention and Control As of February 8, 2022	• All 30 EU/EEA countries recommend primary vaccination against COVID-19 for 12 to 17 years old. • Recommendation regarding the booster dose for adolescent varies depending on the country

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The estimated average cost for the vaccination program is PHP 1,300.00 per person (2-dose vaccine cost and ancillaries) [32]. As of December 2022, vaccine wastage of initially procured vaccines have already amounted to 2.7 million (2.02%) of the 134 million of the total number of procured vaccines. No cost-effectiveness study was found.

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

A qualitative survey among 1,692 Filipinos between 18 to 24 years old showed that people who perceive themselves as in a "very good" or "excellent" state of health are 57.03% unlikely to complete their COVID-19 vaccinations [33].

In a survey [34] of unvaccinated individuals (April to May 2021) aged 18 to 25 years old (n=565, 70.3%), majority were willing to accept COVID-19 vaccine. For those who refused, safety was their main concern.

In another survey on COVID-19 vaccine brand hesitancy [35] was conducted July to August 2021 (n=1,599) among respondents $\geq$ 18 years from different vaccination priority groups in various parts of the country with various educational backgrounds, employment status, and vaccination attitude. Vaccine hesitancy was attributed to beliefs about vaccine safety and effectiveness, negative vaccine-related experiences, the need for other measures to protect them from COVID-19 infection, vaccines not yet being fully approved by FDA and misinformation about COVID-19 vaccines.

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Appendix 1: Preliminary Evidence to Decision

Table 3. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)	Varies	Uncertain			
Benefits	Large (2)	Moderate (5)	Small	Trivial	Varies	Uncertain	**Pfizer BNT162b2** • There was no evidence of COVID-19 infection seven days or more after dose 2 of the vaccine in the vaccine recipients (0/1005) as compared to 16 of 978 in the placebo (RR 0.03, 95% CI 0.00-0.49) • The BNT162b was protective against COVID-19 infection with any of the variants with higher protection for Delta (OR 0.05, 95% CI 0.05-0.05, I2=98%, 8 studies) than for Omicron.variant (OR 0.37, 95% CI 0.36-0.390, I2=99%, 3 studies) **AstraZeneca ChAdOx1-19** • A single-blind randomized phase 2 trial in 6 to 17 years old showed no difference in the risk in infection in those who were given the ChADOx1-19 and Meningococcal vaccine (RR 1.00, 95% CI 0.3-3.32). **Ad5 Vaccine** • The prime boost regime of Ad5 vectored COVID-19 vaccine elicited a seroconversion neutralizing antibodies to pseudovirus in 98% of participants (MD 161.2, 95% CI 134.3-188.1)

							Inactivated Vaccine (Coronavac and BBIBP) • The safety and immunogenicity of CoronaVac has been previously reported in the initial review. There is no new study on CoronaVac For BBIBP, the mean pseudovirus neutralizing antibody on day 84 was higher in the vaccine group (MD 190.15, 95% CI 172.77-207.52)
Harm	Large	Moderate (2)	Small (4)	Trivial	Varies	Uncertain	**Pfizer BNT162b2** • Moderate certainty evidence showed that any serious adverse effect was higher in the vaccine group. (RR 3.99, 95% CI 0.45-35.67) **AstraZeneca ChAdOx1-19** • Moderate certainty evidence showed increased risk of adverse reactions after dose 1 (RR 1.47, 95% CI 1.41-1.54) and dose 2 (RR 1.306, 95% CI 0.845-2.008) in vaccine group. There were also more unsolicited headaches (RR 1.070, 95% CI 0.686-1.660) and lymphadenopathy (RR 10.770, 95% CI 4.407-26.341) up to 28 days after any of the dose **Ad5 Vaccine** • Within 14 days of the vaccine, there was significantly more adverse reactions in the vaccine, both local (RR 6.00, 95% CI 1.942-18.534) and systemic (RR 3.700, 95% CI 1.550-8.832). Most common vaccine related local adverse effect was pain in injection site, while most common systemic adverse effects were fever, followed by headache and fatigue.

							Inactivated Vaccine (Coronavac and BBIBP) • For Coronavac, he overall adverse reaction within 28 days after first and second vaccine dose was higher in the vaccine group (RR: 1.432, 95% CI 0.8007-2.5604). The most common local adverse effect was pain (RR 9.2, 95% CI 2.25-37.5) and most common systemic adverse effect was fever (RR 1.16, 95% CI 0.41-3.2). • For BBIBP, systemic adverse reaction was more common in the vaccine group after the first (RR 1.194, 95% CI 0.662-2.156), second (RR 3.267, 95% CI 0.78-13.679) and third (RR 1.960, 95% CI 0.239-16.044) dose.
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low (1)			
Balance of effects	Favors vaccination (2)	Probably favors vaccination (4)	Does not favor vaccination	Probably favors no vaccination	Favors no intervention	Varies	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			• A qualitative survey among 1,692 Filipinos between 18 to 24 years old showed that people who perceive themselves as in a “very good” or “excellent” state of health are 57.03% unlikely to complete their COVID-vaccinations [33]. • Survey (Pagador) of unvaccinated individuals (April to May 2021), 18 to 25 yo (n= 565, 70.3%): majority willing to accept COVID-19 vaccine. For those who refused, safety was their main concern. • Survey on COVID vaccine brand hesitancy (Amit) conducted July to August 2021 (n= 1,599): Respondents were ≥ 18 years from

								different vaccination priority groups in various parts of the country with various educational backgrounds, employment status, and vaccination attitude. Vaccine hesitancy was attributed to beliefs about vaccine safety and effectiveness, negative vaccine-related experiences, the need for other measures to protect them from COVID-19 infection, vaccines not yet being fully approved by FDA) and misinformation about COVID-19 vaccines.
Resources Required	Don't know	Varies	Large cost (5)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• Estimate vaccination program: average cost of PHP 1,300.00 per person (2-dose vaccine cost and ancillaries. • As of Dec 2022, vaccine wastage of initially procured vaccines have already amounted to 2.7 million (2.02%) of the 134 million of the total number of procured vaccines
Certainty of evidence of required resources	No included studies (3)		Very low (1)	Low (1)	Moderate (1)	High		
Cost effectiveness	No included studies (5)	Varies	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention (1)	Favors the intervention	• No cost-effectiveness study was found
Equity	Uncertain (2)	Varies	Reduced	Probably reduced (1)	Probably no impact	Probably increased (2)	Increased (1)	
Acceptability	Don't know (1)		Varies (1)	No	Probably no	Probably yes (4)	Yes	
Feasibility	Don't know (1)		Varies (1)	No	Probably no	Probably yes (2)	Yes (2)	

Appendix 2: Search Strategy and Results

Table 4. Database search strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline https://pubmed.ncbi.nlm.nih.gov/	"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 September 9, 2022	Nov 30, 2022 21:04:00GMT +8	269	Xia et al (2022): https://pubmed.ncbi.nlm.nih.gov/34536349/ **3-17 years old** Frenck Jr. (2021): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8174030/ **12-15 years old** Creech et al. (2022): https://pubmed.ncbi.nlm.nih.gov/35544369/ **6-11 years old** Du et al. (2022): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9046659/ **3-17 years old** Zhu et al. (2022): https://pubmed.ncbi.nlm.nih.gov/34551104/ **6-17 years old** Li et al. (2022): https://pubmed.ncbi.nlm.nih.gov/35691324/ **6-17 years old** Akash Khobragade (2022): https://pubmed.ncbi.nlm.nih.gov/35367003/ **12-17 years old**
CENTRAL https://www.cochranelibrary.com/advanced-search	[COVID-19] explode all trees and with qualifier(s): [prevention & control – PC] AND MeSH descriptor: [Pediatric] this term only	Nov 30, 2022	0	0

	Filter: January 1 to September 9, 2022	21:08:00GMT +8		
ClinicalTrials.gov https://clinicaltrials.gov/	Condition or disease: “Covid19” Intervention/treatment: “Vaccine” Others: Pediatric, child, toddler, infant “COVID-19 Vaccines,” “SARS-CoV-2,” “COVID-19,” “Adolescent,” “Child,” “Infant” and “Randomized controlled trial”	Nov 30, 2022, 21:28:21 GMT +8	24	Novavax: https://clinicaltrials.gov/ct2/show/NCT04611802?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=2&rank=3 **12-<18 years** (Active, not yet recruiting) COVAXIN: https://clinicaltrials.gov/ct2/show/NCT04918797?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=2&rank=5 **2-18 years** (Completed) Novavax: https://clinicaltrials.gov/ct2/show/NCT05468736?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=2&rank=6 **6 months-<12 years** (Recruiting) COVAC: https://clinicaltrials.gov/ct2/show/NCT04800133?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=2&rank=7 **Children under 18 years old** (Active, not recruiting) Phase 1 Study of Intranasal PIV5 COVID-19 Vaccine Expressing SARS-CoV-2 Spike Protein in Healthy Adults and Adolescents (CVXGA1-001): https://clinicaltrials.gov/ct2/show/NCT04954287?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=11 **12-17 years** (Recruiting) 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: https://clinicaltrials.gov/ct2/show/NCT04816643?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=14

				6 months-12 years (Active, not recruting) TURKOVAC Vaccine: https://clinicaltrials.gov/ct2/show/NCT05230940?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=15 **16-18 years old** (Recruiting) Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals: https://clinicaltrials.gov/ct2/show/NCT04368728?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=16 **12-18 years old** (Active, not recruiting) A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of BNT162b2 RNA-Based COVID-19 Vaccines Against COVID-19 in Healthy Participants: https://clinicaltrials.gov/ct2/show/NCT04713553?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=18 **12-18 years old** (Completed) Humoral and Cellular İmmune Response to SARS-CoV-2 mRNA BNT162b2 Vaccine in Children With Chronic Kidney Diseases: https://clinicaltrials.gov/ct2/show/NCT05465863?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=3&rank=19 **12-18 years old** (Completed) COMINARTY: https://clinicaltrials.gov/ct2/show/NCT05295290?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=4&rank=22 **Children Less Than 21** (Not yet recruiting) TEENCOVE: https://clinicaltrials.gov/ct2/show/NCT04649151?term=vacc

				ine%2C+pediatric&type=Intr&cond=covid-19&draw=4&rank=23 **12-18 years old** (Recruiting) 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: https://clinicaltrials.gov/ct2/show/NCT05436834?term=vaccine%2C+pediatric&type=Intr&cond=covid-19&draw=4&rank=24 **6 months-less than 6 years of age** (Recruiting) Study of Inactivated SARS-CoV-2 Vaccine (Vero Cells) in Healthy Population Aged 3 to 17 Years(COVID-19): https://clinicaltrials.gov/ct2/show/NCT05003466?term=booster+dose%2C+third+dose&type=Intr&cond=COVID-19&age=0&draw=2&rank=4 **3-17 years old** (Not yet recruiting) A Controlled Phase 2/3 Study of Adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Vaccine (SCB-2019) for the Prevention of COVID-19 (SCB-2019): https://clinicaltrials.gov/ct2/show/NCT04672395?term=booster+dose%2C+third+dose&type=Intr&cond=COVID-19&age=0&draw=2&rank=6 **12-18 years old** (Active, not yet recruiting) A Study to Evaluate Different Dose Levels of Ad26.COV2.S in Healthy Adolescents From 12 to 17 Years Inclusive (HORIZON 2): https://clinicaltrials.gov/ct2/show/NCT05007080?term=generation&cond=COVID-19&intr=vaccine&draw=5&rank=36 **12-17 years** (Recruiting)
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	Target Disease: “covid-19” Intervention: “vaccine” (multiple words not allowed)	Nov 30, 2022, 21:32:21 GMT +8	60	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: http://www.chictr.org.cn/showprojen.aspx?proj=129744 **3-17 years old** (Not yet recruiting)

EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	"COVID-19 vaccine AND Infant OR Toddler OR Child OR Pediatric"	Nov 30, 2022, 11:32:00 GMT +8	156	2021-003388-90: Prospective monitoring of immune response following COVID-19 vaccination in children with cancer **Children, adolescents under 18** (Ongoing) 2021-001357-31: Immune Responses Induced by Vaccination Against COVID-19 in Dutch healthy subjects **Infants, toddlers, children < 18 years old** (Ongoing) 2020-005444-35: A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEAL... **In utero, under 18** (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 ... **1-15 years old, < 18** (Ongoing) 2021-002613-34: Prospective monitoring of antibody response following COVID-19 vaccination in patients with Down Syndrome **Children under 18** (Ongoing) 2020-004272-17: A Double-blind, Randomized, Controlled, Phase 2/3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of CpG 1018/Alum-Adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Subunit Vaccine (S... **Adolescents under 18** (Ongoing) 2021-003277-55: COVID-19 Antibody Responses in Cystic Fibrosis: CAR-CF **1-18 years old** (Ongoing) 2021-005043-71: A Phase 2, Comparative Randomised Trial to Evaluate the impact of reduced COVID-19 mRNA

				vaccination regimens on immunological responses and reactogenicity in paediatric subjects with and without pr... **Adolescents under 18** (Ongoing) 2021-005903-11: A Phase 3, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of The Vaccine Candidate BNT162b2 Against COVID-19 i.. **Adolescents under 18** (Ongoing) 2020-005442-42: A PHASE 1, OPEN-LABEL DOSE-FINDING STUDY TO EVALUATE SAFETY, TOLERABILITY, AND IMMUNOGENICITY AND PHASE 2/3 PLACEBOCONTROLLED, OBSERVER-BLINDED SAFETY, TOLERABILITY, AND IMMUNOGENICITY STUDY OF A S... **Infants, toddlers, adolescents, and children < 18 years old** (Ongoing) 2021-001290-23: A PHASE 2b, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF VACCINE CANDIDATE BNT162b2 IN IMMUNOCOMPROMISED PARTICIPANTS ≥2 YEARS OF AGE **2-18 years old** (Ongoing)
medRxiv.org bioRxiv.org	"COVID 19 vaccine pediatric" Filter: January 1, 2022 to September 9, 2021	Sep 09, 2022, 21:48:21 GMT +8	557	Chemaitelly: https://www.medrxiv.org/content/10.1101/2022.07.26.22278045v1 **5-17 years old** Dorabawila: https://www.medrxiv.org/content/10.1101/2022.02.25.22271454v1 **5-17 years old** Sadeghi: https://www.medrxiv.org/content/10.1101/2022.01.11.22269113v1

				2-21 years old González: https://www.medrxiv.org/content/10.1101/2022.04.18.22273978v1 **3-17 years old** Powell: https://www.medrxiv.org/content/10.1101/2021.12.10.21267408v3 **12-17 years old** Veneti: https://www.medrxiv.org/content/10.1101/2022.03.24.22272854v1 **12-17 years old** Ionescu (BOOSTER DOSES): https://www.medrxiv.org/content/10.1101/2022.06.27.22276790v3 **12-17 years old** Gómez (HETEROLOGOUS VACCINES): https://www.medrxiv.org/content/10.1101/2022.03.03.22271313v2 **3-18 years old** Duque: https://www.medrxiv.org/content/10.1101/2022.09.09.22279426v1 **3-18 years old**
https://covid-nma.com/	Vaccines > Living Evidence Synthesis (Vaccines RCT)	Sep 10, 2022, 11:47:59 GMT +8	154	Khobragade A, Lancet, 2022: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00151-9/fulltext **12-18 years old** Creech CB, N Engl J Med, 2022: https://www.nejm.org/doi/full/10.1056/NEJMoa2203315

				6-11 years old Thuluva , medRxiv, 2022 a: https://www.medrxiv.org/content/10.1101/2022.04.20.22274076v1.full **5-18 years old** Liu LTC, medRxiv, 2022: https://www.medrxiv.org/content/10.1101/2022.03.14.22272325v1 **12-17 years old** Moreira E D, N Engl J Med, 2022: https://www.nejm.org/doi/full/10.1056/NEJMoa2200674 **16-18 years old** Li G, SSRN, 2021: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3989844 **12-17 years old** Vadrevu KM, medRxiv, 2022 (Booster): https://www.medrxiv.org/content/10.1101/2022.01.05.22268777v1.full **12-18 years old** Xia S , Lancet, 2021: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00462-X/fulltext **3-17 years old** Thomas S, N Engl J Med, 2021: https://www.nejm.org/doi/full/10.1056/NEJMoa2110345?query=featured_home **12-18 years old** Frenck R, N Engl J Med, 2021: https://www.nejm.org/doi/full/10.1056/NEJMoa2107456 **12-15 years old**

				Han B, SSRN, 2021: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3820545 **3-17 years old** Ella R, Lancet Infect Dis, 2021 b: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00070-0/fulltext#seccestitle10 **12-18 years old**
LOVE Platform for COVID-19 Evidence (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=ile)	"COVID 19 Vaccination" Filter keyword: pediatric OR infant OR toddler OR child OR adolescent (No date filter)	Nov 30, 2022, 12:06:01 GMT +8	21	0

Appendix 3: PRISMA flow diagram

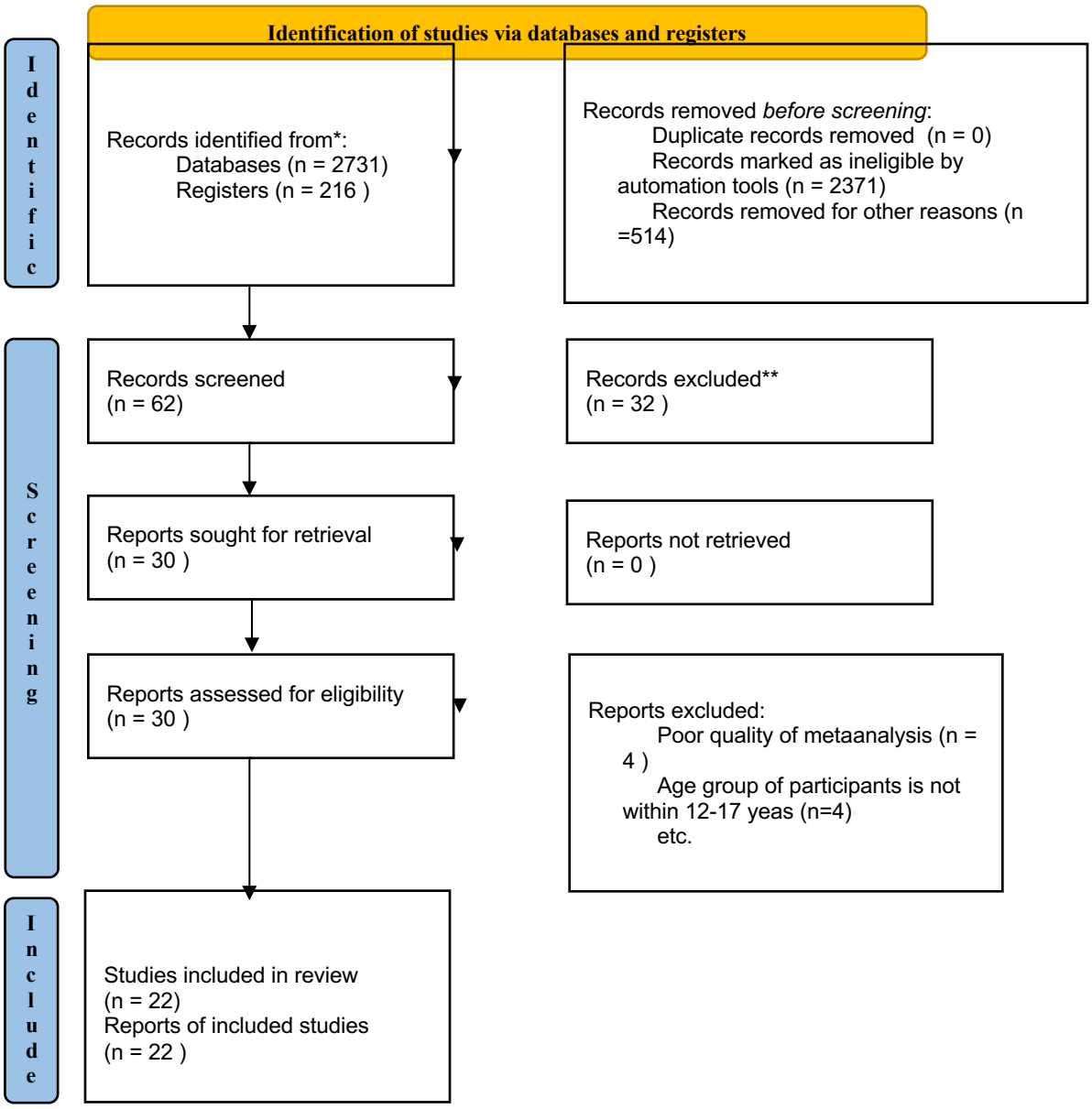

Figure 1. PRISMA flow diagram.

Appendix 4: Characteristics of Included Studies

Table 5. Characteristics of included studies

Study ID	Study Type	Country	Number of patients	Population	Intervention	Control	Outcome
DNA vaccine							
Khobragade (Lancet April 2022)	RCT Phase 3	India	935	12-17 years N=935	ZyCOV-D (DNA VIRUS) 3 doses(2 mg) intradermally 28 days apart N=448	Placebo N=487	Efficacy: - First occurrence of symptomatic RT PCR positive COVID-19 28 days after 3rd vaccine - First occurrence of asymptomatic, mild, moderate, severe COVID and death 28 days after 3rd vaccine Immunogenicity - IgG antibody against S1 antigen - Neutralizing antibody titre against SARS COVID 19 at Day 0, 56 and 84 - Assessment of IFN from peripheral blood mononuclear cells Safety: - Incidence of solicited and unsolicited after each dose - Incidence of adverse effects after each dose
Vector based vaccine							
Li (Lancet June 2022)	RCT Phase 2	UK	262	6-17 years N=262	ChAdOx1 (vector based vaccine) 2 doses intramuscularly on D0 and D28 or D84 N= 211 (D0 and D28: N= 105; D0 and D84: N= 106)	Capsular Group B Meningococcal vaccine D0 and D28 or D84 N= 30	Safety - Solicited and unsolicited local and systemic adverse effect 7 and 28 days after vaccination - Serious adverse event throughout the study Immunogenicity - Anti spike IgG - Anti-nucleocapsid IgG Efficacy - Number of self-reported PCR confirmed or lateral flow assay-confirmed COVID infection
Zhu (Clin Inf Dis July 2022)	RCT Phase 2b	China	150	6-17 healthy participants N=150	Ad5-vectored COVID-19 vaccine 0.5 ml of	Placebo with excipients as vaccine but no viral particles	Immunogenicity: - GMT of RBD specific ELISA antibodies and pseudovirus 28 days after vaccination

					5 x 10^5 viral particles per dose 56 days apart N=100	N= 50	= Specific T cell responses at 28 days after prime vaccination Safety: - Incidence of adverse reaction within 14 days after each vaccination - Adverse event within 28 days after each vaccination - Serious adverse events reported up to 6 months after vaccination
mRNA BNT162b2 and mRNA 1273							
Ali (NEJM Dec 2021)	RCT phase 2/3	USA	3732	12-17 healthy participants N= 3732	mRNA-1272 100 µg for 2 doses 28 days apart N= 2489	Placebo N = 1243	Efficacy: - COVID 19 infection (asymptomatic or confirmed) 14 days after dose 2 - Geometric Mean Titre ratio of pseudovirus neutralizing antibody titres compared to adults 18-25 years 28 days after Dose 2
Frenk (NEJM May 2021)	RCT Phase 3 (interim report)	USA	2260	12 to 15 healthy N= 2260	BNT 162b2 mRNA 30 µg x 2 doses 21 days apart N = 1131	Placebo N = 1128	Efficacy - Effectiveness against confirmed COVID 19 7 days after Dose 2 Immunogenicity - SARS COV 2 serum neutralizing assay - Receptor binding domain or S1 binding IgG - GNT rise from baseline to 1 month after Dose 2 Safety - Local and systemic events 7 days after each dose - Serious adverse events 1 month and 6 months after Dose 2
Heshin-Bekenstein (Rheumatology 2022)	Prospect ive cohort	Israel and Slovenia	131	12 to 21 years with autoimmune rheumatic disease on immunosupp ressive N= 131	BNT 162b2 mRNA x 2 doses 21 days apart N= 91	Healthy controls with no previous COVID infection and no history of immunosuppres sion N= 40	Safety - Assessed by a questionnaire through telephone calls regarding local and systemic side effects - Disease activity assessed by in person clinical examination and visual analogue scale 0-10 Immunogenicity - Serum IgG antibody levels against SARS COV-2 S1/S2 glycoprotein (neutralizing antibody) 2-9 weeks after second dose

							Efficacy - Presence of COVID infection 3 months after vaccination
Florentino (Lancet Nov 22)	Case control	Brazil and Scotland	630944	12-17 years vaccinated with BNT162b2 N= 630, 944	**Cases:** With symptoms and SARS COV 2 positive N=236,563 (A) Brazil N= 17,6002 [Delta variant: 25, 711; Omicron: 150,291] (B) Scotland N= 60,561 [Delta: 34,384; Omicron: 26,177]	**Controls:** With symptoms and SARS COV 2 negative N= 394, 381 A) Brazil N= 327,774 [Delta variant: 122, 999; Omicron: 204,775] (B) Scotland N= 66,607 [Delta: 47,013; Omicron: 19,594]	Vaccine effectiveness (BNT162b2 Pfizer) - Symptomatic COVID 19 in Brazil and Scotland - Length of time from first or second dose vaccine to development of symptoms in COVID 19 positive and negative adolescents - Severe COVID 19 infection in terms of hospital admission or death
Freedman (Emerging Inf Dis Nov 2021)	Retrospective Cohort	Israel	8268	12 to 15 years Note: denominator of vaccinated and unvaccinated in person days	BNT162b2 vaccine two doses 21 days apart Vaccinated who had SARS CoV-2 2 to 4 weeks after second dose N= 124	Unvaccinated who had SARS CoV-2 during the same period as those who were vaccinated: N= 8144	Effectiveness - Vaccine effectiveness: 1- incidence rate ratio [ratio of rate fo PCR confirmed infection in vaccinated and unvaccinated group
Olson (MMWR Oct 2021)	Case control	USA	464	12-18 years Hospitalized patients N=464	**BNT162b2** **Cases:** COVID 19 illness and RT PCR positive N=179	**Controls:** with COVID 19 illness but RT PCR negative OR no COVID 19 illness and with or without COVID test N=285	Vaccine Effectiveness (fully vaccinated with 2 doses of BNT162b2 with 2nd dose >14 days after illness) - against hospitalization - ICU admissions - Critically ill patients on life support
Inactivated vaccines							
Xia (Lancet Inf Dis Feb2022)	RCT Phase 1	Henan China	240	13-17 years	BBIBP-CorV (Beijing Institute	Phase 2: 13-17 years N-60	Immunogenicity:

	and phase 2			N=240 60 each for vaccine dose of 2/4/8 µg and control	of Biological Products, Henan China) x 3 doses 28 day apart Phase 2: 13-17 years: N= 180; 60 each for vaccine dose of 2/4/8 µg]		- Neutralizing antibody titres on Days 0, 28, 56 and 84 days for each dose and each subgroup Safety - Occurrence of adverse reactions 7 days after vaccination - Occurrence of adverse reactions within 30 days after whole vaccination process - Abnormal change in the laboratory test results four days after each vaccination
Han (Lancet Inf Dis Dec 2021)	Phase 1/2	Hebei Province China	660	1 to 17 years N = 480 (12-17 years: n=180)	Coronavac inactivated vaccine, 1.5 µcg or 3.0 µcg 28 days apart N = 383 12-17 years: 144 1.5 µcg: 72 3.0 µcg: 72	Alum Phase 2 N=96 12-17 years: n= 36	Immunogenicity - Neutralizing antibodies at D28 after second dose - Geometric Mean Titre of COVID 19 neutralizing antibodies - Seropositive rates and Geometric increase of COVID 19 neutralizing antibodies Safety - Vaccine related adverse reaction within D28 after dose 1 and dose 2 - Serious adverse events and abnormal changes in laboratory measurements at D3 of each dose

Study ID	Country	Study Type	Population	Intervention	Comparator	Outcome	Variant
Immunocompromised							
Heshin-Bekenstein (Rheumatology 2022)	Israel and Slovenia	Prospective cohort	12 to 21 years with **autoimmune rheumatic disease on immunosuppressive** N= 131	BNT 162b2 mRNA x 2 doses 21 days apart N= 91	Healthy controls with no previous COVID infection and no history of immunosuppression N= 40	Safety - Assessed by a questionnaire through telephone calls regarding local and systemic side effects - Disease activity assessed by in person clinical examination and visual analogue scale 0-10 Immunogenicity - Serum IgG antibody levels against SARS COV-2 S1/S2 glycoprotein (neutralizing antibody) 2-9 weeks after second dose Efficacy - Presence of COVID infection 3 months after vaccination	Not reported
Normal Adolescent							
Britton (JAMA Feb 2022)	USA	Retrospective Test negative Case control	12 to 19 years 180,112 **Cases: 39422** **Controls: 140690**	**Vaccinated: 69301** (**BNT162b:** 60678; **mRNA-1273**: 6749; **Ad26**: 1874)	**Unvaccinated**	Symptomatic SARS CoV2 infection by NAAT result	Pre Delta Delta (prevalent strain)
Florentino (Lancet Nov 22)	Brazil and Scotland	Case control	12 to 17 years vaccinated with BNT162b2 N= 630, 944 **Cases:** With symptoms and SARS-COV-2 positive N=236,563	12-17 years vaccinated with BNT162b2 N= 630,944	Unvaccinated	Vaccine effectiveness (BNT162b2 Pfizer) - Symptomatic COVID 19 in Brazil and Scotland - Length of time from first or second dose vaccine to development of symptoms in COVID 19 positive and negative adolescents - Severe COVID 19 infection in terms of hospital admission or death	Delta Omicron (prevalent strains)

			(A) Brazil N= 17,6002 [Delta variant: 25, 711; Omicron: 150,291] (B) Scotland N= 60,561 [Delta: 34,384; Omicron: 26,177] **Controls:** With symptoms and SARS COV 2 negative N= 394, 381 A) Brazil N= 327,774 [Delta variant: 122, 999; Omicron: 204,775] (B) Scotland N= 66,607 [Delta: 47,013; Omicron: 19,594]				
Fowlkes (March 2022)	USA (Arizona, Florida, Texas, Utah)	Prospective cohort	12 to 15 years N=312	Vaccinated with BNT162b2 (n=227)	Unvaccinated (n=85)	Vaccine effectiveness against Delta and Omicron infections	Delta Omicron (whole genome sequencing)
Freedman (Emerging Inf Dis Nov 2021)	Israel	Retrospective Cohort	12 to 15 years Note: denominator of vaccinated and unvaccinated in person days	BNT162b2 vaccine two doses 21 days apart Vaccinated who had SARS CoV-2 2 to 4 weeks after second dose N=124	Unvaccinated who had SARS CoV-2 during the same period as those who were vaccinated: N= 8144	Effectiveness - Vaccine effectiveness: 1- incidence rate ratio [ratio of rate of PCR confirmed infection in vaccinated and unvaccinated group	Delta (viral sequencing)
June Choe Y (Dec 2021)	Korea	Retrospective cohort	16 to 18 years old N=1,299,965	BNT162b2 vaccine Vaccinated with: With one dose: 444,322 With two doses: 439079;qqqqq	No vaccine N=863,341	Vaccine effectiveness computed as reduction in cases in vaccinated children to unvaccinated children Prevalence of serious and non serious adverse events	Not reported
Kildegard BMJ	Denmark	Cohort	12 to 17 years	BNT162b2 vaccine N=278,649 Dose 1: 229799	No vaccine 2,786.490	Vaccine Effectiveness after 20 days of Dose 1 and 60 days after Dose 2	B.1.177 lineage Alpha Delta (genome

				Dose 2: 175176			sequencing)
Klein MMWR March 2022	USA (10 US states)	Case control test negative	**12 to 15 years** **Cases: Vaccinated after Dose 2** 12-15 years: 6064 16-17 years: 4413 **After Dose 3** 12-15 years: 10 16-17 years: 64 **Controls:** 12-15 years: 12,064 16-17 years: 7421	**BNT162b2 vaccine** After Dose 2 and Dose 3	Unvaccinated	Vaccine Effectiveness after: 1. 14 days of dose 2 2. 7 days of dose 3	Omicron Delta (predominant variant)
Lin NEJM Jan 2022	USA (North Carolina)	Surveillance	12 to 17 years: 806634	Vaccinated with: 1. BNT162b2: 396158 2. mRNA: 688 **3. Ad26: 187**	Unvaccinated 436601	Vaccine effectiveness in reducing: 1. COVID 19 infection 2. Hospitalization 3. Death	Not reported
Lutrick (MMWR Dec 2021)	USA (Arizona)	Prospective Cohort	12 to 17 years N=243 12-15 years: 181 16-17 years: 62	Vaccinated with **BNT162b2** 12-15 years: 143 16-17 years: 51	Unvaccinated 12-15 years: 38 16-17 years: 11	Vaccine effectiveness using Cox proportional hazard wherein comparison of the RT PCR confirmed vaccinated and unvaccinated participants	Delta (predominant strain)
Oliveira (JAMA Mar 2022)	USA (Yale New Haven CT)	Case Control	12 to 18 years (N=542) **Case:** Positive for SARS -CoV-2 infection by RT PCR assay n=186 Fully vaccinated: 10 **Control:** Negative for SARS -CoV-2 infection by RT PCR assay n= 356 Fully vaccinated: 124	**BNT162b2**	Unvaccinated	Vaccine effectiveness in preventing COVID 19 infection computed as (1-OR) x 100% VE by the number of doses received	Delta (genomic sequencing)
Olson (MMWR Oct 2021)	USA	Case control	12-18 years Hospitalized patients	**BNT162b2**	**Controls:** with COVID 19 illness but RT	Vaccine Effectiveness (fully vaccinated with 2 doses of	Not reported

			N=464	**Cases:** COVID 19 illness and RT PCR positive N=179	PCR negative OR no COVID 19 illness and with or without COVID test N=285	BNT162b2 with 2nd dose >14 days after illness) - against hospitalization - ICU admissions - Critically ill patients on life support	
Olson (NEJM Feb 2022)	USA	Case Control Test negative	12-18 years Cases:	**BNT162b2** full vaccination	Unvaccinated	Vaccine Effectiveness: Odds Ratio: Antecedent full vaccination compared with two hospital admissions with COVID 19 symptoms but negative for COVID 19	Not reported
Tartof (Lancet Oct 2021)	USA (California)	Retrospective Cohort	12-15 years in Kaiser Permanente Southern California health Care System) N=201,622	Full vaccination with **BNT162b2** within 7 days or more after dose 2 n= 78843	Unvaccinated n= **104918**	1. SARS COV-2 infection via PCR test regardless of present of symptoms 2. COVID-19 hospital admission	Delta (genomic sequencies)
Zambrano (MMWR	USA (24 participating sites)	Test negative case control	Hospitalized 12-18 years old Case: MIS-C (n=102) Controls (n=180): with one COVID like symptoms but negative for COVID PCR	Fully vaccinated with **BNT162b2** vaccine Case: 5/102 Control: 65/181	Unvaccinated Case: 97/102 Control: 116/181	Vaccine Effectiveness against MIS-C: OR of full COVID 19 vaccination against MIS-C cases and controls using VE: 100 x (1-OR)	Delta (predominant variant)

Appendix 5: Risk of Bias Assessment of the Studies

Appendix 5.1: Risk of Bias Assessment of Randomized Trials

Khobragade, et. al. (April 2022)

Parameter	Basis	Assessment
Random Sequence Generation	Interactive web response	Low
Allocation concealment	Interactive web response	Low
Blinding of participants and personnel	Yes (double blind)	Low
Incomplete outcome data (efficacy)	Interim analysis (28 days after third dose of vaccine)	Unclear
Incomplete outcome data (safety)	Interim analysis (28 days after third dose of vaccine)	Unclear
Selective reporting	All planned outcomes reported	Yes

Li, et. al. (June 2022)

Parameter	Basis	Assessment
Random Sequence Generation	Computer generated randomization list	Low
Allocation concealment	Participants randomly assigned to received vaccine or placebo but not stated if there was allocation concealment	Unclear
Blinding of participants and personnel	Blinding of vaccine administrator and the outcome assessor but not the patient	Moderate
Incomplete outcome data (efficacy/immunogenicity)	Interim data on immunogenicity (28 days after 2nd dose)	Unclear
Incomplete outcome data (safety)	Data on safety available from 7 to 28 days after vaccination	Low
Selective reporting	All planned outcomes reported	Low

Zhu, et. al. (July 2022)

Parameter	Basis	Assessment
Random Sequence Generation	Generated by an independent statistician	Low
Allocation concealment	Individuals involved in randomization and masking not involved in trials	Low
Blinding of participants and personnel	Investigators, participants and laboratory staff were masked to treatment assignment	Low
Incomplete outcome data (efficacy)	Immunogenicity studies reported at 28, 56 and 84 days of boost vaccination	Low
Incomplete outcome data (safety)	Incidence of adverse reactions within 14 days after each vaccination and 28 days after each vaccination was reported	Low
Selective reporting	All planned outcome reported	Low

Xia, et. al. (Feb 2022)

Parameter	Basis	Assessment
Random Sequence Generation	Randomization number sequentially generated by an independent statistician using Stata	Low
Allocation concealment	Randomization number sequentially generated by an independent statistician using Stata	Low
Blinding of participants and personnel	Allocation masked from participants, investigators and outcome assessors	Low
Incomplete outcome data (efficacy)	Immunogenicity studies reported on Days 0, 28, 56 and 84 days	Low
Incomplete outcome data (safety)	Adverse reactions within 7 days after each vaccination and within 30 days after whole vaccination was analyzed	Low
Selective reporting	All planned outcome reported	Low

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES								
The Newcastle-Ottawa Scale quality instrument is scored by awarding a point for each answer that is marked with a symbol. Possible total points are 4 points for Selection, 2 points for Comparability, and 3 points for Outcome								
	Heshein Bekenstein	**Fowlkes**	**Freedman**	**June Choe**	**Kildegaard**	**Lin**	**Lutrick**	**Tartof**
Selection								
1) Representativeness of the exposed cohort >> a) truly representative * >> b) somewhat representative * >> c) selected group >> d) no description of the derivation of the cohort	A	A	A	A	A	A	A	A
2) Selection of the non exposed cohort >> a) drawn from the same community as the exposed cohort * >> b) drawn from a different source >> c) no description of the derivation of the non exposed cohort	A	A	A	A	A	A	A	A
3) Ascertainment of exposure >> a) secure record (eg surgical records) * >> b) structured interview * >> c) written self report >> d) no description	Structured interview	A (vaccine card, EMR, state immunization registries)	Record in database	A	A	A	Self reported signs and symptoms	Record
4) Demonstration that outcome of interest was not present at start of study >> a) yes * >> b) no	Yes	Yes	Not stated	A	Yes		Yes	Not written
Comparability								
Comparability of cohorts on the basis of the design or analysis controlled for confounders								
a. The study controls for age, sex, confounders*	Controlled for immunocompromised or healthy	Controlled for vaccination status	Controlled by vaccinatin status	Controlled for vaccination	Matched according to birth year, sex and municipality on the date of vaccination	A	A	Controlled for age

b, Study controls for other factors: (List) *						A		
c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders								
Outcome								
1) Assessment of outcome >> a) independent blind assessment * >> b) record linkage * >> c) self report >> d) no description	Record linkages*	Record linkage thru active surveillance	Record Database	Record Linkage	Records	Database of North Carolina	Data linkage	Registry of KPSC
2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow up period for outcome of interest)* b) no	**Yes**	**Yes**	**Yes**	**Y**	**Yes**		**Yes**	**Yes**
3) Adequacy of follow up of cohorts >> a) complete follow up - all subjects accounted for * >> b) subjects lost to follow up unlikely to introduce bias - small number lost - > 75% were follow up or description provided of those lost to follow up ø >> c) follow up rate < 75% and no description of those lost >> d) no statement	Complete*	A	Complete	Complete	Yes - defined complete follow up	Complete		Complete
	GOOD		GOOD					
Good quality: 3 or 4 stars in selection domain; 1 or 2 stars in comparability domain; 2 or 3 stars in outcome/exposure domain								
Fair quality: 2 stars in selection domain; 1 or 2 stars in comparability domain; 2 or 3 stars in outcome/exposure domain								
Poor quality: 0 or 1 star in selection domain; 0 star in comparability domain; 1 or 2 stars in outcome/exposure domain								
	Heshein Bekenstein	**Fowlkes**	**Freedman**	**June Choe**	**Kildegaard**	**Lin**	**Lutrick**	**Tartof**
Selection	****	****	***	****	***	***	****	***
Comparability	*	*	*	*	*	**	*	*
Outcome	***	***	***	***	***	**	**	**
	GOOD	GOOD	GOOD	GOOD	GOOD	GOOD	GOOD	GOOD

Appendix 5.3: Newcastle Ottawa Quality Assessment Scale for Case Control Studies

	Britton	Klein	Oliviera	Olson 2022	Zambrano
Selection					
1. Is the case definition adequate?					
a. yes, with independent validation *			*	*	*
b. yes, record linkages or based on self reports	self report	Yes			
c. no description					
2. Representativeness of the cases					
a. consecutive or obviously representative series of cases*	*	*	*	*	*
b. potential for selection biases or not stated					
3. Selection of controls					
a. community controls *	*	*	*	*	*
b. hospital controls					
c. no description					
4. Definition of Controls					
a. no history of disease (endpoint) *	*	*	*(NEG PCR)	*	*
b. no description of source					
Comparability					
1. Comparibility of cases and controls on the basis of the design or analysis					
a. Study control for (Select the most important factor)*	*vaccination status	Vaccination	Controlled for COVID RT PCR	COVID test	Presence of MISC
b. Study controls for any additional factor *					
Exposure					
1. Ascertainment of exposure					
a. secure record (surgical records) *	* (vaccination status based on information divulged during the test	*	PCR test	PCR test	PCR test
b. structured interview where blind to case control status*					
c. interviewer not blinded to case and control status					
d. written self report or medical record only					
e. no description					
2. Same method of ascertainment for cases and controls					
a. yes *	*	*	Yes	Yes	Yes
b. no					
3. Non-Response rate					
a. same rate for both groups *		NA		NA	
b. non respondents described					

Summary					
	Britton	**Klein**	**Oliviera**	**Olson 2022**	**Zambrano**
Selection	***	****	****	***	***
Comparability	*	*	*	*	*
Exposure	**	**	**	**	**
	GOOD	GOOD	GOOD	GOOD	GOOD

Appendix 6: Grade Evidence Profile

BNT162b2 (Pfizer) vaccine compared to Placebo for preventing COVID infection in 12-17 years old (Phase 3 trial)
Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With BNT162b2 (Pfizer) vaccine		Risk with Placebo	Risk difference with BNT162b2 (Pfizer) vaccine
Efficacy of BNT162b2 to Prevent Symptomatic COVID 19 Infection											
1983 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	16/978 (1.6%)	1/1005 (0.1%)	RR 0.03 (0.00 to 0.49)	16 per 1,000	**16 fewer per 1,000** (from 8 fewer to --)
Immunogenicity of BNT162b2											
360 (1 RCT)	not serious	not serious	serious[a]	not serious	none	⨁⨁⨁◯ Moderate	170	190	-	The mean immunogenicity of BNT162b2 was 1.4 GMFR	MD 116.9 GMFR higher (97.61 higher to 136.19 higher)
Any serious adverse event (SAE) from dose 1 through 1 month after dose 2											
2260 (1 RCT)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate	1/1129 (0.1%)	4/1131 (0.4%)	RR 3.99 (0.45 to 35.67)	1 per 1,000	**3 more per 1,000** (from 0 fewer to 31 more)
Hospitalization											
185026 (2 observational studies)	not serious	not serious	not serious	not serious	very strong association	⨁⨁⨁⨁ High	329/105 851 (0.3%)	15/79175 (0.0%)	OR 0.09 (0.05 to 0.15)	Low: 0 per 1,000	Low: **0 fewer per 1,000** (from 0 fewer to 0 fewer)
Emergency and Urgent Care											
5753 cases 20791 controls (1 observational study)	not serious	not serious	not serious	not serious	very strong association	⨁⨁⨁⨁ High	5753 cases 20791 controls		OR 0.17 (0.16 to 0.19)	Low: 0 per 1,000	Low: **0 fewer per 1,000** (from 0 fewer to 0 fewer)
Intensive Care Unit											
318 cases 355 controls (3 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ Low	318 cases 355 controls		OR 0.13 (0.04 to 0.41)	Low: 0 per 1,000	Low: **0 fewer per 1,000** (from 0 fewer to 0 fewer)

BNT162b2 (Pfizer) vaccine compared to Placebo for preventing COVID infection in 12-17 years old (Phase 3 trial)
Bibliography:

Certainty assessment							Summary of findings			
Multisystem Inflammatory Syndrome in Children										
70 cases 213 controls (1 observational study)	not serious	not serious	not serious	not serious	none	⊕⊕◯◯ Low	70 cases 213 controls	OR 0.09 (0.04 to 0.29)	**Low**	
									0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

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

Explanations
a. Indirect marker of efficacy
b. Wide confidence interval

MRNA 1273 (Moderna) vaccine compared to Placebo for preventing COVID infection in 12-17 years old (Phase 2)
Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With mRNA 1273 (Moderna) vaccine	Relative effect (95% CI)	Risk with Placebo	Risk difference with mRNA 1273 (Moderna) vaccine
Efficacy of mRNA-1273 vaccine (Moderna) against symptomatic COVID 19 infection											
3236 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	4/1073 (0.4%)	0/2163 (0.0%)	RR 0.0500 (0.0030 to 1.0234)	4 per 1,000	**4 fewer per 1,000** (from 4 fewer to 0 fewer)
Immunogenicity to pseudovirus neutralizing antibodies (12 to 17 years as compared to 18 to 25 years)											
636 (1 RCT)	not serious	not serious	serious[b]	serious[a]	none	⊕⊕◯◯ Low	296	340	-	The mean immunogenicity to pseudovirus neutralizing antibodies (12 to 17 years as compared to 18 to 25 years) was 296 pseudovirus neutralizing antibody titre	MD 100.4 pseudovirus neutralizing antibody titre higher (85.93 lower to 286.73 higher)
Any Solicited Adverse Reaction after the First dose											
3720 (1 RCT)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	806/1238 (65.1%)	2381/2482 (95.9%)	RR 1.47 (1.41 to 1.54)	651 per 1,000	**306 more per 1,000** (from 267 more to 352 more)
Any Solicited Adverse Reaction after Second Dose											
3698 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	680/1220 (55.7%)	2405/2478 (97.1%)	RR 1.306 (0.845 to 2.008)	557 per 1,000	**171 more per 1,000** (from 86 fewer to 562 more)
Unsolicited Adverse Event up to 28 days after any injection (Headache)											
3726 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	28/1240 (2.3%)	60/2486 (2.4%)	RR 1.070 (0.686 to 1.660)	23 per 1,000	**2 more per 1,000** (from 7 fewer to 15 more)
Unsolicited Adverse Reaction up to 28 days after any injection (lymphadenopathy)											
3726 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	5/1240 (0.4%)	108/2486 (4.3%)	RR 10.770 (4.407 to 26.341)	4 per 1,000	**39 more per 1,000** (from 14 more to 102 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
Explanations
a. Wide CI
b. Immunogenicity is a surrogate outcome

Vector based vaccine (Covishield, Astra Zeneca) compared to Meningococcal B vaccine for preventing COVID infection in 12-17 years old (Phase 2)
Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Meningococcal B vaccine	With vector based vaccine (Covishield, Astra Zeneca)	Relative effect (95% CI)	Risk with Meningococcal B vaccine	Risk difference with vector based vaccine (Covishield, Astra Zeneca)
Efficacy of vector base vaccine (Covishield, Astra Zeneca)											
150 (1 RCT)	serious [a]	not serious	not serious	serious[b]	publication bias strongly suspected[c]	⊕◯◯◯ Very low	0/30 (0.0%)	12/120 (10.0%)	**RR 1.0000** (0.3011 to 3.3209)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Immunogenicity to Pseudovirus neutralizing antibody (assessed with: Inhibitory concentration)											
56 (1 RCT)	not serious	not serious	serious[d,e]	not serious	publication bias strongly suspected[c]	⊕⊕◯◯ Low	10	46	-	The mean immunogenicity to Pseudovirus neutralizing antibody was **57** Inhibitory concentration	MD **242 Inhibitory concentration higher** (101.95 higher to 382.05 higher)
Immunogenicity: Anti spike IgG of 12 to 17 years as compared to 18 to 25											
56 (1 RCT)	not serious	not serious	serious[d,e]	not serious	publication bias strongly suspected[c]	⊕⊕◯◯ Low	10	46	-	The mean immunogenicity: Anti spike IgG of 12 to 17 years as compared to 18 to 25 was **227** AU/ml	MD **73144 AU/ml higher** (57014.73 higher to 89273.27 higher)
Number of Adverse Event after dose 1											
76 (1 RCT)	not serious	not serious	Not serious	serious[b]	publication bias strongly suspected[c]	⊕⊕◯◯ Low	2/14 (14.3%)	13/62 (21.0%)	**RR 1.4677** (0.3725 to 5.7825)	143 per 1,000	**67 more per 1,000** (from 90 fewer to 683 more)
Number of Adverse event after dose 2											
76 (1 RCT)	not serious	not serious	Not serious	serious[b]	publication bias strongly suspected[c]	⊕⊕◯◯ Low	3/14 (21.4%)	9/62 (14.5%)	**RR 0.6770** (0.2101 to 2.1846)	214 per 1,000	**69 fewer per 1,000** (from 169 fewer to 254 more)
Adverse effect probably related to the vaccine											
76 (1 RCT)	not serious	not serious	serious[e]	serious[b]	publication bias strongly suspected[c]	⊕⊕◯◯ Low	0/14 (0.0%)	0/62 (0.0%)	**RR 0.2381** (0.0049 to 11.5220)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

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

Explanations

a. Diagnosis of SARS COV2 was based on self reported parameter, either by PCR or lateral flow assay, regardless of symptoms
b. Wide confidence interval on the results of the efficacy and safety of the vaccine . Very few sample size
c. One trial only with small sample size
d. Immunogenicity is a surrogate marker
e. Comparison group were 18-25 years old not placebo or 2nd dose

Recombinant Adenovirus vectored COVID 19 vaccine compared to Placebo for preventing COVID infection in 12-17 years old (Phase 2b)
Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Recombinant Adenovirus vectored COVID 19 vaccine	Relative effect (95% CI)	Risk with Placebo	Risk difference with Recombinant Adenovirus vectored COVID 19 vaccine
Immunogenicity to pseudovirus neutralizing antibody 28 days after the second dose for 6-17 years (assessed with: pseudovirus neutralzing test)											
150 (1 RCT)	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	⨁⨁◯◯ Low	50	100	-	The mean immunogenicity to pseudovirus neutralizing antibody 28 days after the second dose for 6-17 years was **6.8**	MD **161.2 higher** (134.3 higher to 188.1 higher)
Any solicited local adverse reaction 14 days after any of the two doses in 6 to 17 years old											
150 (1 RCT)	not serious	not serious	serious[c]	not serious	publication bias strongly suspected[b]	⨁⨁◯◯ Low	3/50 (6.0%)	36/100 (36.0%)	**RR 6.000** (1.942 to 18.534)	60 per 1,000	**300 more per 1,000** (from 57 more to 1,000 more)
Any solicited systemic adverse reaction 14 days after any of the two doses in 6 to 17 years											
150 (1 RCT)	not serious	not serious	serious[c]	not serious	publication bias strongly suspected[b]	⨁⨁◯◯ Low	5/50 (10.0%)	37/100 (37.0%)	**RR 3.700** (1.550 to 8.832)	100 per 1,000	**270 more per 1,000** (from 55 more to 783 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
Explanations
a. Immunogenicity is a surrogate marker; data for 6-17 years and not for 12-17 years
b. Only one trial with small sample size
c. Data for 6-17 years, not for 12-17 years

Inactivated vaccine (Coronavac) compared to Aluminum Hydroxide adjuvant (control) for preventing COVID infection in 12-17 years old (Phase 1/2)
Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Aluminum Hydroxide adjuvant (control)	With Inactivated vaccine (Coronavac)	Relative effect (95% CI)	Risk with Aluminum Hydroxide adjuvant (control)	Risk difference with Inactivated vaccine (Coronavac)
Immunogenicity to neutralizing antibody 3 microgram (assessed with: Geometric Mean Titre)											
102 (1 RCT)	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	⊕⊕◯◯ Low	35	67	-	The mean immunogenicity to neutralizing antibody 3 microgram was 2.0 Neutralizing antibody titres	MD 144 Neutralizing antibody titres higher (108.34 higher to 179.66 higher)
Overall Adverse Reaction within 0-28 days after first and second dose of vaccine 3 micrograms											
122 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⊕⊕⊕◯ Moderate	11/42 (26.2%)	30/80 (37.5%)	RR 1.4318 (0.8007 to 2.5604)	262 per 1,000	**113 more per 1,000** (from 52 fewer to 409 more)
Unsolicited Adverse Reaction within 0-28 days after first and second dose of 3 microgram vaccine											
122 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⊕⊕◯◯ Low	3/42 (7.1%)	4/80 (5.0%)	RR 0.7000 (0.1643 to 2.9831)	71 per 1,000	**21 fewer per 1,000** (from 60 fewer to 142 more)
Solicited adverse reaction within seven days after first and second dose of vaccine 3 micrograms											
122 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⊕⊕◯◯ Low	9/42 (21.4%)	30/80 (37.5%)	RR 1.7500 (0.9186 to 3.3339)	214 per 1,000	**161 more per 1,000** (from 17 fewer to 500 more)

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

Explanations
a. Immunogenicity is a surrogate marker
b. Only one trial
c. Wide Confidence interval

Inactivated BBIBP-CorV compared to Saline and Aluminum hydroxide adjuvant (control) for preventing COVID infection in 12-17 years old
Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Saline and Aluminum hydroxide adjuvant (control)	With inactivated BBIBP-CorV	Relative effect (95% CI)	Risk with Saline and Aluminum hydroxide adjuvant (control)	Risk difference with inactivated BBIBP-CorV
Immunogenicity to pseudovirus neutralizing antibody on day 84 (8 microgram vaccine)											
112 (1 RCT)	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	⨁⨁◯◯ Low	28	84	-	The mean immunogenicity to pseudovirus neutralizing antibody on day 84 (8 microgram vaccine) was 2	MD 190.15 higher (172.77 higher to 207.52 higher)
Systemic adverse reaction within 7 days after first dose of 8 microgram vaccine											
336 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⨁⨁◯◯ Low	12/84 (14.3%)	43/252 (17.1%)	RR 1.194 (0.662 to 2.156)	143 per 1,000	**28 more per 1,000** (from 48 fewer to 165 more)
Systemic adverse reaction within seven days after second dose of 8 microgram vaccine											
333 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⨁⨁◯◯ Low	-/82	-/251	RR 3.267 (0.780 to 13.679)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Systemic adverse reaction within seven days after third dose of 8 microgram vaccine											
333 (1 RCT)	not serious	not serious	not serious	serious[c]	publication bias strongly suspected[b]	⨁⨁◯◯ Low	1/82 (1.2%)	6/251 (2.4%)	RR 1.960 (0.239 to 16.044)	12 per 1,000	**12 more per 1,000** (from 9 fewer to 183 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
Explanations
a. Immunogenicity is a surrogate marker
b. Only one trial; small sample size
c. Wide confidence interval

COVID (BNT162b2) vaccine compared to No vaccine for COVID infection in immunocompromised 12-21 years old on immunomodulatory treatment
Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No vaccine	With COVID (BNT162b2) vaccine		Risk with No vaccine	Risk difference with COVID (BNT162b2) vaccine
Efficacy of BNT162b2 (Pfizer) within 3 months after vaccination (assessed with: SARS COV-2 PCR)											
131 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	0/40 (0.0%)	0/91 (0.0%)	RR 0.4607 (0.0090 to 22.0780)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Immunogenicity to Anti S1/S2 antibody levels 2 to 9 weeks after dose 2											
59 (1 observational study)	serious[a]	not serious	serious[c]	not serious	none	⨁◯◯◯ Very low	22	37	-	Mean immunogenicity to Anti S1/S2 antibody levels 2 to 9 weeks after dose 2 was 12 anti S1/S2 antibody level	MD 145.8 anti S1/S2 antibody level lower (195.85 lower to 95.05 lower)
Hospitalization within 2 to 4 weeks after dose 1											
129 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	0/39 (0.0%)	2/90 (2.2%)	RR 2.198 (0.108 to 44.747)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Hospitalization within 2 to 4 weeks after dose 2											
128 (observational studies)	serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	0/40 (0.0%)	1/88 (1.1%)	RR 1.382 (0.058 to 33.207)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Exacerbation of Rheumatic Disease within 2 to 4 weeks after dose 1											
129 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	0/39 (0.0%)	5/90 (5.6%)	RR 5.000 (0.274 to 85.375)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Exacerbation of rheumatic Disease within 2 to 4 weeks after dose 2											
128 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	0/40 (0.0%)	1/88 (1.1%)	RR 1.382 (0.058 to 33.207)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio
Explanations
a. Control group are healthy adolescents and young adults and not those who have the disease but were not given the vaccine.
b. Wide confidence interval
c. Immunogenicity is a surrogate marker

Appendix 7: Ongoing Studies

Trial Code	Title	Population	Intervention	Comparator	Outcome	Status
NCT05157191	Safety of Pediatric Covid 19 Vaccinations	Children 5-16 years old	mRNA vaccines	None	Local and systemic reactions, adverse events	Recruiting
NCT05652543	A Phase Ⅱ Study to Evaluate the Safety & Immunogenicity of SARS-CoV-2 Alpha/Beta/Delta/Omicron Variants COVID-19 Vaccine	Children 3-17 years old	COVID-19 Vaccine (SCTV01E) Phase II	Placebo (saline)	Adverse events, Immunogenicity against Alpha/Beta/ Delta/Omicron Variants	Recruiting
NCT05013983	Clinical Trial of Recombinant COVID-19 Vaccine (Sf9 Cells) in Children and Adolescents	Children 6-17 years old	COVID-19 Vaccine (Sf9) Phase II	Placebo	Adverse Events, Tolerability, Imuunogenicity	Recruiting
NCT04992208	Safety of an Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Children and Adolescents	Children 3-17 years old with pre-existing conditions	Inactivated COVID-19 Vaccine (Sinovac / Coronavac) Phase IV	None	Adverse Events	Recruiting