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 5 to 17 years old who received the standard full doses of any COVID-19 vaccine, what is the clinical and immunologic efficacy, effectiveness, and safety of a booster dose?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of monovalent BNT1262b2 mRNA (Pfizer-BioNTech) vaccine as booster in healthy children 12 to 17 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection* *After optimal coverage in the high-risk priority groups have been achieved.	Very low	Weak
There is no recommendation being made this time on booster administration in healthy children 5 to 11 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection due to lack of evidence.	None	None

Consensus Issues

The decision of the Panel to withhold a recommendation for the 5 to 11 age group was due to lack of evidence, with indirect evidence being used to evaluate this specific group. While the indirect evidence showed beneficial results, these were observational studies having low validity and subject to confounding bias.

KEY FINDINGS

- The evidence, as of November 3, 2022, includes four (4) observational studies on monovalent BNT162b2 mRNA vaccine as homologous first booster among healthy individuals 6 to 17 years of age compared to those who received standard doses of the primary series of COVID-19 vaccines.
- There were no studies found on children for bivalent mRNA vaccines, mRNA-1273 (Spike Vax), CoronaVac (Sinovac), BBIBP-CorV (Sinopharm), ChAdOx1 (AstraZeneca) and other vaccines as a booster.

<u>12 to 17 years old</u>

- A homologous booster dose of BNT162b2 mRNA vaccine given five months after the primary series demonstrated reduction in COVID-19 infection caused predominantly by Omicron and Delta variants, but no reduction in hospitalization. Myocarditis was not increased after a booster dose. There was no reported mortality. A moderate to large-fold increase in immunologic markers after a booster dose was noted. (Very low certainty due to inconsistency, imprecision, and serious risk of bias)

5 to 11 years old

- In the absence of studies in the 5 to 11 years old children, indirect evidence from the four studies in children aged 12 to 17 years on BNT162b2 mRNA vaccine as a booster dose was used. As shown above, benefit in preventing COVID-19 infection but not in hospitalization was demonstrated. There was a low incidence of serious adverse events. (Very low certainty)

INTRODUCTION

Data presented by local health authorities showed that over 48,000 children ages 19 and below have acquired COVID-19 as of February 2021 where 40.2% are from ages 15 to 20, 17.4% are ages 5 to 9, and 18.5% are ages 4 and below. (As of December 31, 2022) Globally, children account for up to 15% of confirmed cases [1]. Although mostly mild, COVID-19 in children can be severe with hundreds of recorded cases of multi-system inflammatory syndrome (MIS-C) [2-5].

The mRNA COVID-19 vaccines are recommended for children and adolescents 5 to 17 years old. The need for an additional dose of a COVID-19 vaccine in children after completion of the standard approved dosing regimen has been raised with the increasing evidence of waning vaccine effectiveness against COVID-19 over time and immune evasion against emerging variants of SARS-CoV-2 [6-10]. Reduced effectiveness of two doses of mRNA vaccines as primary vaccination had been reported since the emergence of SARS-CoV-2 omicron variants in December 2021 [11,12].

In the background of vaccine supply shortage and varying recommendations in giving booster doses to adolescents, there is a need to evaluate studies on risks and benefits of vaccine boosters and base the recommendations on sound evidence.

REVIEW METHODS

A systematic and comprehensive search in Medline thru PubMed, Cochrane COVID-19 Study Register, ClinicalTrials.gov, Chinese Clinical Trial Registry, EU Clinical Trials Register, medRxiv.org, bioRxiv.org, COVID-NMA, and L.OVE Platform for COVID-19 Evidence using “COVID-19 vaccine”, “booster or third dose or additional” as free text and MeSH terms was done until November 3, 2022. No restrictions as to language or publication status were set. Studies were eligible for inclusion if they (1) were randomized controlled trials, case-control, cohort studies, or descriptive studies (2) evaluated the efficacy, effectiveness or safety of any COVID-19 vaccine booster in healthy individuals 5 to 17 years of age who received the standard primary series of any COVID-19 vaccine and (3) compared the clinical and immunologic efficacy and effectiveness of a booster dose of any COVID-19 vaccine with a control group (no booster or placebo or second dose). A manual search of the reference lists of relevant studies was also done.

Clinical efficacy and effectiveness outcomes were RT-PCR-confirmed COVID-19 infection, hospitalization and COVID-related or all-cause mortality. Immunologic responses were reported as geometric mean, actual antibody titers, T-cell counts, or fold-changes (whether rise, no change, or decline), and compared pre- and post-booster, or placebo. Safety outcomes included incidence of local and systemic adverse reactions, adverse events, serious adverse events, and deaths among those given boosters compared with no booster.

Risk of bias assessment

Two authors independently evaluated the risk of bias of included studies. The risk of bias tools for observational studies (Newcastle Ottawa scales for Cohort and Case-control studies and JBI tool for descriptive studies) were used, as applicable.

Statistical Analysis

For the studies among children aged 12 to 17 years, RevMan 5.4 statistical software was used to pool the outcomes, with the odds ratio (OR) and its 95% confidence interval as the effect measures. Overall

effectiveness was determined and stratified by variants, if applicable. Immunologic responses in antibody titers or T-cell counts after the booster dose were noted. The fold-changes in these titers (whether rise, no change or decline) were qualified based on the WHO criteria of no to minimal for < 2 fold, moderate for 2-5-fold, and large for > 5-fold changes.

Safety outcomes were summarized using descriptive statistics, if applicable.

RESULTS

Characteristics of included studies

As of November 03, 2022, four studies on monovalent BNT162b2 (Pfizer-BioNTech) vaccine as a first booster for children were found. There were no studies for mRNA BNT162b2, mRNA-1273 (Spike Vax), BBIBP-CorV (Sinopharm) Corona Vac (Sinovac), ChAdOx1 (AstraZeneca) and other vaccines. There were no studies found on bivalent vaccines as the first booster in this age group.

BNT1262b2 (Pfizer-BioNTech) vaccine
Four published studies were included in this review, with two case-control studies and one before-and after interventional study all as a homologous booster, and one report [14-17]. (Flowchart for identifying and selecting the studies is presented in Appendix 3 Figure 1)

In the two case-control studies on effectiveness, adolescents 12 to 17 years of age (n=4109) were enrolled [14,17]. For both studies, the RT-PCR test was done $\geq$ 5 months after two doses of monovalent BNT162b2 vaccine for the non-booster group. For the booster group, RT-PCR test was done $\geq$ 7 days after a booster dose in one study [17] and a median (IQR) time of 19 (9 to 32) days after BNT162b2 booster in another study [14]. The test results were the basis for assigning cases (n=1013) and control (n=3096).

Exposure was a booster dose of BNT162b2 mRNA vaccine, administered at least 5 months after the second dose. Outcomes were COVID-19 infection in both studies and hospitalization for one [17]. Occurrence of COVID-19 infection, caused predominantly by Omicron and Delta variants, was observed up to 60 days after the second dose.

Uncontrolled before-after study on immunogenicity included 120 adolescents with post-booster specimens for analysis. Paired pre-and-post-booster blood specimens were provided by 31 adolescents for determination of geometric mean (GM) of anti-spike-receptor-binding-domain IgG (anti-S-RBD IgG), % Inhibition of surrogate virus neutralization test (sVNT) and pseudo virus neutralization test (sNVT) against omicron and delta variants. Samples were collected prior to and two to four weeks after booster. Fold changes from pre- to post-booster were reported [16].

The safety study report on January 5, 2022 used the US Vaccine Adverse Events Reporting System (VAERS), which is a passive reporting system that accepts and analyzes reports of adverse events following vaccination. A subgroup of individuals 12 to 17 years of age who either received two doses of BNT162b2 as primary series or homologous booster of BNT162b2 reported non-serious and serious adverse events, including myocarditis and pericarditis, which were reported up to 45 days post vaccination [15]. (Appendix 2)

Methodological Quality Assessment of Included Studies

The two case-control studies did not control the confounding variables except for age. In the uncontrolled before-after study, the surveillance report was based on passive reporting. The overall risk of bias of the studies and report was rated serious. There was also imprecision and inconsistency in some outcomes, and indirectness for the age group 5 to 11 years of age. (Appendix 5)

Study Outcomes

12 to 17 years old
BNT162b2 Homologous Booster

Effectiveness

COVID-19 Infection

A booster dose of monovalent BNT162b2 demonstrated significantly lower odds of COVID-19 from 14 to 59 days after booster vaccination compared with those who did not receive a booster dose (pooled OR 0.37, 95% CI 0.24-0.56) (very low certainty) [14,17]. (Appendix 5)

Subgroup Analysis: COVID-19 Omicron-predominant Variant

Pooling of two studies showed that a booster dose of BNT162b2 significantly lowered the odds of COVID-19 Omicron-predominant variant compared with no booster (pooled OR 0.17, 95% CI 0.10-0.32, n=1526) (very low certainty) [14,17]. (Appendix 5)

Hospitalization

There was no significant difference in hospitalization for COVID-19 caused by either Omicron or Delta variant between those given BNT162b2 mRNA booster and not (OR 1.62, 95% CI 0.16-17.72, n=86) (very low certainty) [17]. (Appendix 6, 7)

Immunogenicity

In the before-and after interventional study, overall, the booster dose with BNT162b2 resulted in a moderate 3.8-fold increase in anti-S-RBD IgG geometric mean titers [from 837BAU/mL (95% CI 728-953) to 3,041BAU/mL (95% CI 2893-3229)]. Subgroup analysis of paired sera (n=31) confirmed the results from the unpaired, overall comparison where similar fold rises were observed (very low certainty) [16].

Omicron Variant sub-analysis:

After the first booster dose, there was a large 8-fold increase in surrogate virus neutralization test (sVNT) against Omicron variant [from median (IQR) of 11.9% inhibition (95% CI 0-23.9) to 94.4% inhibition (95% CI 90.6-97.4)] compared to pre-booster values (very low certainty) [16].

Delta Variant sub-analysis

There was no significant change in sVNT against the Delta variant [from median (IQR) of 82.9% inhibition (95% CI 64.1-95.6) to 100% inhibition (95% CI 99.9-100.0)] compared with pre-booster values (very low certainty) [16]. (Appendix 6, 7)

Safety

The VAERS report presented safety concerns with follow-up surveillance ranging from immediately to 60 days post-BNT162b2 vaccination. Serious adverse events were 0.005% after a booster dose among 16 to 24 years of age. SAE incidence rate post-second dose in 12 to 15 years of age was 0.005% (846 of 18,707,169) and 0.002% (1 of 47,040) post-first booster in 16 to 17 years of age.

Among the 47,040 adolescents given a booster, one case of myocarditis (0.002%) was reported but otherwise there was no mortality (very low certainty) [15]. (Appendix 6, 7)

5 to 11 years old

In the absence of studies on the 5 to 11 years old age group, the above findings for 12 to 17 years of age are indirect evidence on the efficacy, immunogenicity, and safety of BNT162b2 mRNA as booster dose in 5 to 11 years of age. (Appendix 6, 7)

RECOMMENDATIONS FROM OTHER GROUPS

HTAC-DOH (updated July 11, 2022) recommends monovalent BNT162b2 mRNA vaccine as a booster dose in individuals 12 to 17 years of age at least five months after second dose of the primary vaccination series. For 5 to 11 years old, recommendation is only for primary series with mRNA vaccines, but none for booster dose [18].

The following recommendations are for bivalent BNT162b2 mRNA vaccine as a booster dose in individuals 5 to 17 years of age.

Table 1. Summary of Recommendations from Other Groups

Group / Agency	Age group	Recommendation
US CDC As of updated Dec 9, 2022 AAP As of updated October 12, 2022	5 to 11 years old	Recommends a booster dose with **a bivalent mRNA vaccine (Pfizer-BioNTech or Moderna)** at least two months after the completion of the primary vaccination series or after monovalent mRNA booster
US CDC As of updated Dec 9, 2022 AAP As of updated October 12, 2022	12 to 17 years old	Recommends a booster dose with **a bivalent mRNA vaccine (Pfizer-BioNTech or Moderna)** at least two months after the completion of the primary vaccination series or after monovalent mRNA booster [19,20].
WHO As of updated Nov 11, 2021 European CDC As of updated Feb 8, 2022		Recommends to consider vaccinating children and adolescents only when high vaccine coverage (primary series and boosters) has been achieved in the high priority-use groups [21,22].

ONGOING STUDIES AND RESEARCH GAPS

12 to 17 years old

Search of ClinicalTrials.gov registry on October 11, 2022 yielded four ongoing randomized controlled trials on the efficacy, immunogenicity and safety of BNT162b2 and recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rs) with matrix-m1™ adjuvant COVID-19 vaccine booster in healthy individuals registered at ClinicalTrials.gov and EU Clinical Trials Register. (Appendix 8)

5 to 11 years old

As of December 18, 2022, one clinical trial on efficacy and safety of a booster in children (monovalent mRNA-1273) is still in recruitment phase, one (monovalent mRNA1262b2) is active, not recruiting while one trial (inactivated SARS-CoV-2 vaccine) and an observational study (Comirnaty vaccine) have yet to start recruitment. (Appendix 8)

Additional and better certainty of evidence is needed in the following areas to inform practice on the implementation of a booster vaccination program in children aged 5 to 17 years against COVID-19:

1. Duration of protection of the primary and booster vaccines in children (based on breakthrough infection rates over time or long-term vaccine efficacy/effectiveness data)
2. Clinical efficacy / effectiveness of booster vaccination for the different COVID-19 vaccines
3. Clinical efficacy/effectiveness of booster vaccination against infection with variants of concern
4. Efficacy and long-term safety for both mRNA vaccines and non-mRNA vaccines
5. Optimum timing (interval from primary series) of booster administration
6. Benefit/harm ratio of homologous versus heterologous booster vaccination
7. Cost-effectiveness of booster vaccination of children versus primary vaccination program

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=5/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)	Varies	Uncertain			• There were 15,705,714 cases of COVID-19 in less than < 18 years of age in the US representing 17.5% of the total cases, with mortality rate of <0.1% (CDC COVID-Data Tracker, November 01, 2022). • COVID-19 can cause severe illness in children, both with and without underlying medical conditions. Though it is very rare, some children who have had COVID-19 may later develop Multi System Inflammatory Syndrome in Children (MIS-C). (CDC)
Benefits	Large	Moderate (2)	Small (3)	Trivial	Varies	Uncertain	• There was small to moderate reduction in the odds of COVID-19 with monovalent BNT162b2 mRNA vaccine. There was insufficient evidence on prevention of hospitalization and mortality.
Harm	Large	Moderate (1)	Small (3)	Trivial (1)	Varies	Uncertain	• Majority of reported adverse events were non-serious in one descriptive study. Incidence of myocarditis was much lower post-booster than post-primary series in one descriptive study.
Certainty of Evidence	High	Moderate	Low	Very low (5)			• Very low certainty of evidence from observational studies. It was downgraded due to serious risk of bias, indirectness, imprecision, and inconsistency, with small sample size.

Balance of effects	Favors vaccination		Probably favors vaccination (4)	Does not favor vaccination	Probably favors no vaccination	Favors no intervention	Varies (1)	
Values	Important uncertainty or variability		Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			• COVID-19 vaccine hesitancy among Filipinos was reported at 37.5% (n= 2,698) in a nationwide open-access online survey two months before the rollout of the national vaccination program. Large majorities of the respondents would only receive the COVID-19 vaccines after many others had received it (n= 5,237, 72.8%).
Resources Required	Don't know	Varies	Large cost (4)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• In March 18, 2021, the government estimated that it would spend an average cost of around PHP 1,300.00 per person for the country's vaccination program, to include the 2-dose vaccine cost and ancillaries.
Certainty of evidence of required resources	No included studies (3)		Very low (1)	Low (1)	Moderate	High		
Cost effectiveness	No included studies (1)	Varies	Favors the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison	Probably favors the intervention (3)	Favors the intervention	
Equity	Uncertain (1)	Varies (2)	Reduced	Probably reduced	Probably no impact	Probably increased (2)	Increased	

Appendix 2: Search Strategy

Table 2. Database search strategy

Database	Search Terms	Date/Time	Yield	Eligible
PubMed	((children) AND (COVID-19 vaccine OR Pfizer vaccine OR Pfizer-BioNTech)) AND (randomized)	Oct. 19, 2022 05:43:25	515	2 effectiveness 1 immunogenicity 1 safety
Cochrane Central Register of Controlled Trials	Pfizer COVID-19 vaccine in Title Abstract Keyword AND children OR adolescents in Title Abstract Keyword - (Word variations have been searched0	Oct 18 8:42 pm	16	0
Cochrane COVID-19 Study Register	COVID-19 vaccine AND children OR adolescents AND booster	Oct. 20, 2022 11:25:48	26	0
LOVE platform for COVID-19 Evidence	(title:(child OR adolescent) OR abstract:(child OR adolescent)) AND (title:(covid-19 vaccine OR Pfizer vaccine OR Pfizer-BioNTech) OR abstract:(covid-19 vaccine OR Pfizer vaccine OR Pfizer-BioNTech)) AND (title:(Randomized) OR abstract:(Randomized))	Oct. 20, 2022 11:25:48	79	0
ClinicalTrials.gov	booster dose, third dose | Interventional Studies | COVID-19 | Child	Nov 3, 2022 18:28:00	10	4- ongoing
Chinese Clinical Trial Registry	COVID-19	Oct 18 11:00 pm	504	3-ongoing
EU Clinical Trials Register	COVID-19 vaccine AND child OR adolescent "COVID 19 vaccine" AND booster OR third dose	Oct 20, 2022 13:59:00	157	1- ongoing
bioRxiv.org medRxiv.org	"COVID-19 vaccine AND booster AND child OR adolescents AND randomized"	Oct 20, 2022, 15:48:00	201	0
COVID-NMA	RCTs on vaccines	Oct 20, 2022, 14:47:00	154	0
Cross-referencing			10	0
Total			1, 672	Included- 4 Ongoing- 8

Appendix 3: PRISMA flow diagram

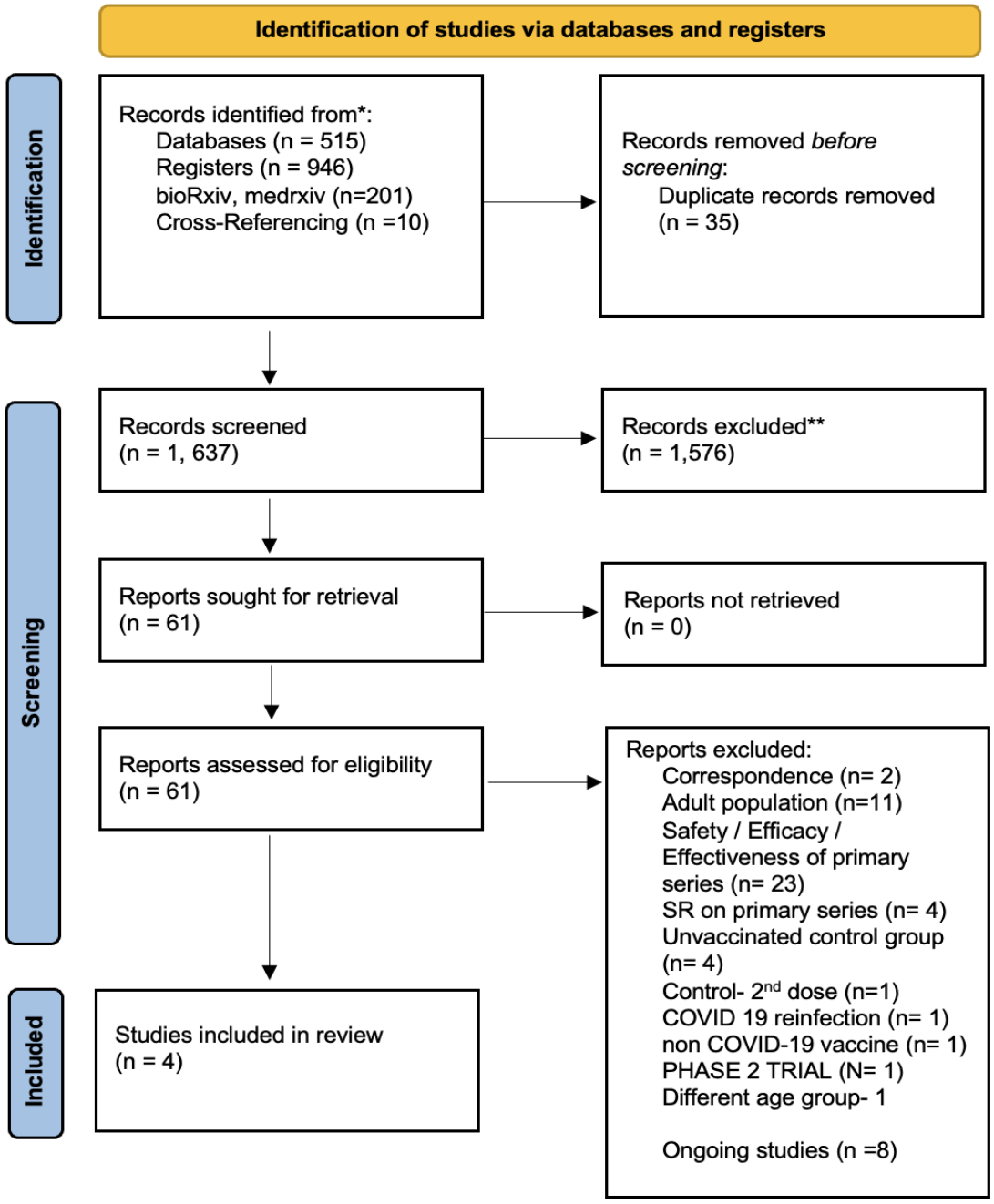

Figure 1. PRISMA flow diagram.

Appendix 4: Study Appraisal

Table 3A. Risk of Bias Assessment of studies on 12-17 years old
(Newcastle Ottawa Scale for Case-Control Studies)

Scale	Tartof et al.	Klein et al.
Selection		
1.Adequate Case Definition	with independent validation (*)	with independent validation (*)
2.Representativeness of the cases	consecutive or obviously representative series of cases (*)	consecutive or obviously representative series of cases (*)
3.Selection of controls	Registry records	Registry records
4.Definition of controls	No history of disease (endpoint) (*)	No history of disease (endpoint) (*)
Comparability		
1.Comparability of cases and controls	Study controls for age (*)	Study controls for age (*)
Exposure		
1.Ascertainment of exposure	Secure registry record (*)	Secure registry record (*)
2.Same method of ascertainment for cases and control	Yes (*)	Yes (*)
3.non-response rate	NA	NA
Score and Interpretation	Serious risk of bias (6/9)	Serious risk of bias (6/9)

Table 3B. Quality assessment Tool for Pre and Post- Intervention Design for Study on 12-17 year old,
(Assessment is based on paired sera, sensitivity analysis)

	Assavavongwaikit et al.
Sampling a. Was probability sampling used? (1) b. Was sample size justified to obtain adequate power? (1) subtotal n/2	0
Design a. one pretest or baseline and several post-test measures (2) OR b. simple before and after study (1) subtotal n/2	1
Control of confounders Does the study employ a comparison strategy? An attempt to create or assess equivalence of groups at baseline by: a. matching group participants (2) b. statistical control (1) c. none (0) subtotal n/2	0
Data collection and outcome measurement a. Was the DV directly measured by an assessor? (1) b. were dependent variables either directly measured (2) or self-reported (1) c. were dependent variables measured reliably (1)? d. were dependent variables measured validly? (1) subtotal n/5	5

Statistical analysis and conclusions a. Was (were) the statistical test(s) used appropriate for the main outcome and at least 80% of the others? (1) b. Were p values and confidence intervals reported properly? (1) c. If multiple outcomes were studied, were correlations analyzed? (1) d. Were missing data managed appropriately? (1) subtotal n/4	4
Drop outs Is attrition rate <30% (1) Subtotal n/1	1
Total n/16 Interpretation (n/16) Low < 0.60 Medium 0.61- 0.79 High 0.80- 1	11/16 = 0.69 **moderate quality** (0.60-0.80)

Table 3C. Risk of Bias Assessment for Study on 12-17 years old
(Joanna Briggs Institute appraisal tool for descriptive studies)

	Su **moderate quality**
1. Were there clear criteria for inclusion in the case series?	Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes
3. Were valid methods used for identification of the condition for all participants included in the case series?	Passive Reporting/ Surveillance / Verification done
4. Did the case series have consecutive inclusion of participants?	Yes
5. Did the case series have complete inclusion of participants?	Passive Reporting/ Surveillance/ Verification done
6. Was there clear reporting of the demographics of the participants in the study?	Yes
7. Was there clear reporting of clinical information of the participants?	Yes
8. Were the outcomes or follow up results of cases clearly reported?	Yes
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes
10. Was statistical analysis appropriate?	Yes

Appendix 5: Forest Plots

Forest Plot of studies on 12-17 years old

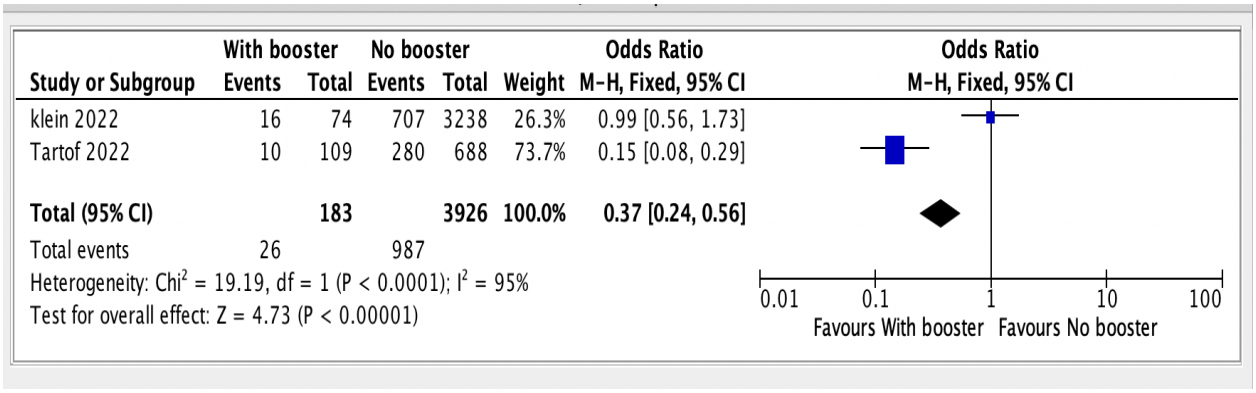

Figure 2. Forest Plot on monovalent BNT162b2 Homologous booster and COVID-19 Infection (Omicron or Delta Variant) as outcome

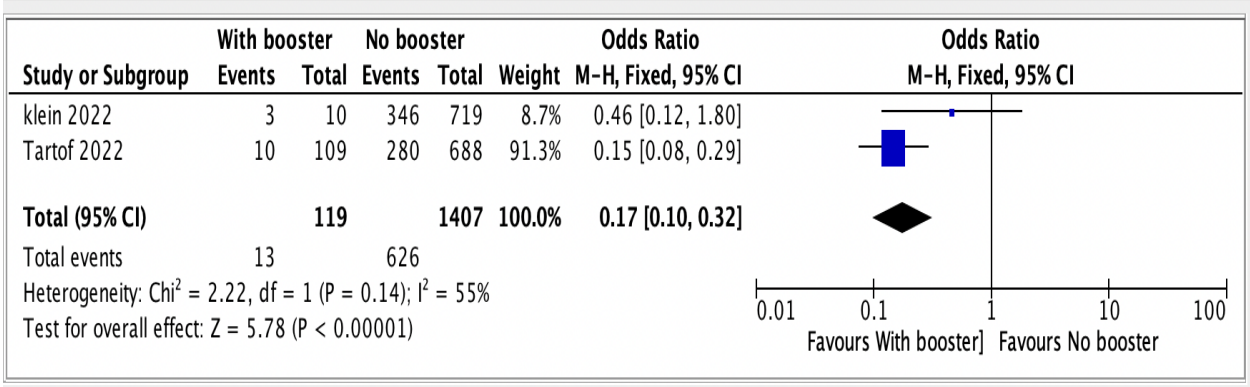

Figure 3. Forest Plot on monovalent BNT162b2 Homologous booster COVID-19 Infection (Omicron-Dominant Variant) as Outcome

Appendix 6: Grade Evidence Profile

For 12- 17 years of age

Table 4. Effectiveness and Safety of homologous first booster of monovalent BNT162b2 mRNA in healthy adolescents 12 to 17 years of age.

Author(s): Eva I. Bautista, Carolina Lina L. Tapia, Ma. Lucila Perez

Question: BNT162b2 mRNA COVID-19 booster compared to No booster for preventing COVID-19

Certainty assessment							No. of Patients		Effect		Certainty	Importance
No. of Studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNT162b2 mRNA COVID-19 booster	No booster	Relative (95% CI)	Absolute (95% CI)		
COVID-19- Associated Hospitalization (BNT162b2 Homologous 1st booster)												
1[1]	observational studies	serious[a]	not serious	not serious	serious [b]	none	15 cases	71 controls	**OR 1.62** (0.16 to 16.72)	-	⨁◯◯◯ Very low	CRITICAL
							-	4.2%		**24 more per 1,000** (from 35 fewer to 381 more)		
Serious adverse Events, BNT162b2 Homologous 1st booster												
1[2]	observational studies	serious [c,d]	not serious	not serious	not serious	none	Serious adverse events were reported in 846 (0.005%)adolescents 12-15 years of age after 2nd dose with chest pain (n=443, 0.002%), increased troponin (n=333, 0.002%), and myocarditis (n=221, 0.001%) as the most common. There was one reported serious adverse event (0.002%) among adolescents 16-17 years of age after a booster dose.				⨁◯◯◯ Very low	CRITICAL
Myocarditis, BNT162b2 Homologous 1st booster												
1[2]	observational studies	serious [c,d]	not serious	not serious	not serious	none	Among 47, 040 adolescents 16 to 17 years of age who received a booster dose, there was one (0.002%) reported myocarditis.				⨁◯◯◯ Very low	CRITICAL
Mortality, BNT162b2 Homologous 1st booster												
1[2]	observational studies	serious [c,d]	not serious	not serious	not serious	none	Among 47, 040 adolescents 16-17 years of age who received a booster dose, there was no reported mortality.				⨁◯◯◯ Very low	CRITICAL
COVID-19 (Omicron or Delta variant), BNT162b2 Homologous 1st booster												
2[1,3]	observational studies	serious[1,3,a]	serious[1,3,e]	not serious	not serious	none	1013 cases	3096 controls	**OR 0.37** (0.24 to 0.56)	-	⨁◯◯◯ Very low	CRITICAL
							-	5.1%		**31 fewer per 1,000** (from 38 fewer to 22 fewer)		
COVID-19, BNT162b2 Homologous 1st booster, Omicron-Predominant												
2[1,3]	observational studies	serious[1,3,a]	serious[1,3,f]	not serious	not serious	none	888 cases	1857 controls	**OR 0.17** (0.10 to 0.32)	-	⨁◯◯◯ Very low	CRITICAL
							-	11.9%		**97 fewer per 1,000** (from 106 fewer to 78 fewer)		

CI: confidence interval; **OR:** odds ratio

Explanations

a. Only age was adjusted in the analysis. Other confounding variables were not adjusted in the analysis.
b. Confidence interval includes the value of 1- no effect
c. Descriptive study. No comparison with those not given booster
d. Passive reporting
e. I2 is 95%.
f. I2 is 55%.

Table 5. Immunogenicity of homologous first booster of monovalent BNT162b2 mRNA in healthy adolescents 12 to 17 years of age.

Author(s): Eva I. Bautista, Carolina Lina L. Tapia, Ma. Lucila Perez
Question:monovalent BNT162b2 mRNA COVID-19 booster compared to No booster for preventing COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNT162b2 mRNA COVID-19 booster	No booster	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity, (Sub-Analysis) Delta Variant, BNT162b2 Homologous 1st booster												
1[1]	observational studies	Serious [a]	not serious	Serious [b]	not serious	none	There was no significant change in sVNT against the Delta variant [from median (IQR) of 82.9 % inhibition (95% CI 64.1, 95.6) to 100 % inhibition (95% CI 99.9, 100.0)] compared with pre-booster values.		⊕◯◯◯ Very low			IMPORTANT
Immunogenicity, (Sub-Analysis) Omicron Variant, BNT162b2 Homologous 1st booster												
1[1]	observational studies	Serious [a]	not serious	Serious [b]	not serious	none	After the first booster dose, there was an 8-fold increase in surrogate virus neutralization test (sVNT) against Omicron variant [from median (IQR) of 11.9 % inhibition (95% CI 0, 23.9) to 94.4 % inhibition (95% CI 90.6, 97.4)] compared to pre-booster values.		⊕◯◯◯ Very low			IMPORTANT
Immunogenicity, BNT162b2 Homologous 1st booster												
1[1]	observational studies	Serious [a, c]	not serious	Serious [b]	not serious	none	Unpaired overall comparison (pre-booster n=31, post-booster n=120) Geometric mean (95% CI) of anti-spike-receptor-binding-domain (S-RBD) IgG pre and post-booster showed a 3.8 fold rise [from 837 BAU/ mL (728, 953) to 3041 BAU/ mL (2893, 3229)]. Paired comparison (pre and post-booster n=31) median (IQR) ratios of post-booster and pre-booster of anti-S-RBD IgG 3.8 BAU/ mL fold rise (2.9, 4.7).		⊕◯◯◯ Very low			IMPORTANT

CI: confidence interval; **OR:** odds ratio

Explanations
a. Descriptive study. No comparison with those not given booster
b. surrogate measure of effectiveness
c. There were only 31 paired specimens for analysis out of 120 participants.

Appendix 7: Summary of Findings Evidence Table

Table 6. Effectiveness and Safety of a homologous first booster of monovalent BNT162b2 mRNA vaccine among 12-17 years of age.

Summary of findings:

BNT162b2 mRNA COVID-19 booster compared to No booster for preventing COVID-19

Patient or population: preventing COVID-19
Setting:
Intervention: monovalent BNT162b2 mRNA COVID-19 booster
Comparison: No booster

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (Studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No booster	**Risk with BNT162b2 mRNA COVID-19 booster**				
COVID-19- Associated Hospitalization (BNT162b2 Homologous 1st booster)	**Low**		**OR 1.62** (0.16 to 16.72)	15 cases 71 controls (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	
	42 per 1,000	**66 per 1,000** (7 to 423)				
Serious adverse Events, BNT162b2 Homologous 1st booster	Serious adverse events were reported in 846 (0.005%)adolescents 12-15 years of age after 2nd dose with chest pain (n=443, 0.002%), increased troponin (n=333, 0.002%), and myocarditis (n=221, 0.001%) as the most common. There was one reported serious adverse event (0.002%) among adolescents 16-17 years of age after a booster dose.			(1 observational study)[2]	⊕◯◯◯ Very low [c,d]	
Myocarditis, BNT162b2 Homologous 1st booster	Among 47, 040 adolescents 16 to 17 years of age who received a booster dose, there was one (0.002%) reported myocarditis.			(1 observational study)[2]	⊕◯◯◯ Very low [c,d]	
Mortality, BNT162b2 Homologous 1st booster	Among 47, 040 adolescents 16-17 years of age who received a booster dose, there was no reported mortality.			(1 observational study)[2]	⊕◯◯◯ Very low [c,d]	
COVID-19 (Omicron or Delta variant), BNT162b2 Homologous 1st booster	**Low**		**OR 0.37** (0.24 to 0.56)	1013 cases 3096 controls (2 observational studies)[1,3]	⊕◯◯◯ Very low [1,3,a,e]	
	51 per 1,000	**19 per 1,000** (13 to 29)				
COVID-19, BNT162b2 Homologous 1st booster, Omicron-Predominant	**Low**		**OR 0.17** (0.10 to 0.32)	888 cases 1857 controls (2 observational studies)[1,3]	⊕◯◯◯ Very low[1,3,a,f]	
	120 per 1,000	**23 per 1,000** (13 to 42)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Only age was adjusted in the analysis. Other confounding variables were not adjusted in the analysis.
b. Confidence interval includes the value of 1- no effect
c. Descriptive study. No comparison with those not given booster
d. Passive reporting
e. I2 is 95%.
f. I2 is 55%.

Table 7. Immunogenicity of homologous first booster of monovalent BNT162b2 mRNA in healthy adolescents 12 to 17 years of age.

Summary of findings:

BNT162b2 mRNA COVID-19 booster compared to No booster for preventing COVID-19

Patient or population: preventing COVID-19
Setting:
Intervention: monovalent BNT162b2 mRNA COVID-19 booster
Comparison: No booster

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No booster	Risk with BNT162b2 mRNA COVID-19 booster				
Immunogenicity, (Sub-Analysis) Delta Variant, BNT162b2 Homologous 1st booster	There was no significant change in sVNT against the Delta variant [from median (IQR) of 82.9 % inhibition (95% CI 64.1, 95.6) to 100 % inhibition (95% CI 99.9, 100.0)] compared with pre-booster values.			(1 observational study)[1]	⊕◯◯◯ Very low[a,b]	
Immunogenicity, (Sub-Analysis) Omicron Variant, BNT162b2 Homologous 1st booster	After the first booster dose, there was an 8-fold increase in surrogate virus neutralization test (sVNT) against Omicron variant [from median (IQR) of 11.9 % inhibition (95% CI 0, 23.9) to 94.4 % inhibition (95% CI 90.6, 97.4)] compared to pre-booster values.			(1 observational study)[1]	⊕◯◯◯ Very low[a,b]	
Immunogenicity, BNT162b2 Homologous 1st booster	Unpaired overall comparison (pre-booster n=31, post-booster n=120) Geometric mean (95% CI) of anti-spike-receptor-binding-domain (S-RBD) IgG pre and post-booster showed a 3.8 fold rise [from 837 BAU/ mL (728, 953) to 3041 BAU/ mL (2893, 3229)]. Paired comparison (pre and post-booster n=31) median (IQR) ratios of post-booster and pre-booster of anti-S-RBD IgG 3.8 BAU/ mL fold rise (2.9, 4.7).			(1 observational study)[1]	⊕◯◯◯ Very low[a,b,c]	

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Descriptive study. No comparison with those not given booster
b. surrogate measure of effectiveness
c. There were only 31 paired specimens for analysis out of 120 participants.

Appendix 8: Ongoing Studies

Table 8. Ongoing studies in 5 -11 years old

Study Title	Patients (n)	Interventions	Outcomes	Method	Status
A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age NCT04796896	Children, 6 months to 11 years 13575 estimated enrollment	mRNA-1273 or mRNA-1273.214 3 dose levels	*Primary:* ● Adverse events ● Serum antibody levels that meet or exceed threshold of protection from COVID-19 ● SARS-CoV-2 Specific Serum Antibody GMT ● Seroresponse rate SARS-CoV-2 ● Specific Serum Antibody GMT, post-booster dose *Secondary:* ● GM Value of SARS-CoV-2 S-Protein-Specific Binding Antibody (bAb) ● GM Value of SARS-CoV-2- Specific Neutralizing Antibody (nAb) ● SARS-CoV-2 Infections regardless of symptomatology ● Clinical signs of SARS-CoV-2 infection ● SARS-CoV-2 Infection Measured by RT-PCR and/or bAb Levels Against SARS-CoV-2 ● Nucleocapsid protein in participants with negative SARS-CoV-2 at baseline, in the absence of Any COVID-19 symptoms ● Number of participants with a first Occurrence of COVID-19 ● Clinical signs indicative of COVID-19	Phase 2/3 open-label, dose-escalation, age de-escalation, randomized, observer-blind, placebo-controlled trial Parts 1 and 3: Open-label Part 2: Randomized and Observer-blind	Recruiting
Study of Inactivated SARS-CoV-2 Vaccine (Vero Cells) in Healthy Population Aged 3-17 years (COVID-19) NCT05003466	Healthy individuals, 3-17 years old 480 estimated enrollment	SARS-CoV-2 Vaccine (Vero cells), Inactivated 3 doses	*Primary:* Seroconversion rate of SARS-CoV-2 neutralizing antibody GMT of SARS-CoV-2 neutralizing antibody *Secondary:* ● Adverse Reactions ● Serious AEs ● Seroconversion rate of SARS-CoV-2 IgG binding antibody ● GMT of SARS-CoV-2 IgG binding antibody ● GMT of SARS-CoV-2 neutralizing antibody ● Seropositive rate of SARS-CoV-2 neutralizing antibody ● Seropositive rate of SARS-CoV-2 IgG binding antibody	Double blinded RCT, Phase 2	Not yet recruiting
Comirnaty Korea PMS	Children 5 years and older N= 3,000	BNT162b2 (Comirnaty)	*Primary:* ● Solicited adverse events ● Unsolicited AEs *Secondary:* ● Adverse events ● Serious AEs ● Expected AEs	Observational: Prospective Case series (single arm, open-label, non-interventional)	Active, not recruiting

			• Adverse drug reactions • Serious Adverse drug reactions • Expected adverse drug reactions • Unexpected adverse drug reactions		
A Study to Learn About COVID-19 Bivalent BNT162b2 Omicron Containing Vaccine in Healthy Children NCT05543616	Sub-study D (SSD): Healthy children 5-12 years old 2270 participants (SSA to SSD)	Bivalent BNT1262b2	*Primary:* • Local reactions and systemic events following Dose 1 • Adverse events • SAEs • GMT of neutralizing antibody titers • Seroresponse rate *Secondary:* • GMT of neutralizing antibodies as a 3rd or 4th dose and 1 after dose 1 • Seroresponse rate as a 3rd or 4th dose and after dose 1	Interventional, non-randomized	Recruiting

Table 9. Ongoing Studies on 12-17 years old

	Title	Status	Start Date	Completion Date
NCT04955626	A phase 3 master protocol to evaluate additional dose(s) of BNT162b2 in healthy individuals previously vaccinated with BNT162b2	Active, not recruiting	July 1, 2021	April 12, 2023
NCT04611802	A phase 3, randomized observer-blinded, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of a SARS-COV-2 recombinant spike protein nanoparticle vaccine with matrix-m1TM adjuvant in adult participants > 18 years with a pediatric expansion in adolescents (12 to <18 years)	Active, not recruiting 33,000	December 27, 2020	June 30, 2023
NCT04368728	A phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals	Active, not recruiting (last update posted-Sept 15, 2022)	April 29, 2020	February 15, 2023
EudraCT Number: 2021-005197-25	A phase 3 master protocol to evaluate additional dose(s) of bnt162b2 in healthy individuals previously vaccinated with bnt162b2	Ongoing	Feb 22, 2022	