ORIGINAL ARTICLE

Efficacy, Effectiveness, and Safety of COVID-19 Vaccine Compared to Placebo in Preventing COVID-19 Infection among 12-17 Years Old: A Systematic Review

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ABSTRACT

Objectives. The World Health Organization recently revised their recommendations and considered healthy children and adolescents as low priority group for COVID-19 vaccine. This review comprehensively assessed existing clinical evidence on COVID-19 vaccine in 12-17 years old.

Methods. Included in this review were any type of study that investigated the efficacy, immunogenicity, safety, and effectiveness of COVID-19 vaccine on protection against SARS-COV-2 infection in 12-17 years old. Various electronic databases were searched up to March 15, 2023. Studies were screened, data extracted, risk of bias appraised, and certainty of evidence was judged using GRADE. 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. There were six randomized controlled trials and 16 effectiveness studies (8 cohorts and 8 case control). Low certainty evidence showed that BNT162b2 (Pfizer) was effective, immunogenic, and safe in healthy adolescents. There were 15 effectiveness studies on BNT162b2 (Pfizer) in healthy adolescent and one on immunocompromised patients. 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 noted that BNT 162b2 was also immunogenic in 12-21 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. Low to very low certainty evidence were noted on the safety and immunogenicity of two vector base vaccines (ChAdOx1-19 and Ad5 vector COVID vaccine) and two inactivated vaccines (CoronaVac and BBIBP CorV).

Conclusion. There is presently low certainty evidence on the use of RNA vaccines in 12-17 years old. The recommendation on its use is weak. There is presently insufficient evidence for the use of inactivated and vector-based COVID-19 vaccines. Different countries should consider whether to vaccinate healthy adolescent without comprising the other recommended immunization and health priorities that are crucial for this age group. Other factors including cost-effectiveness of vaccination and disease burden should be accounted.

Keywords: RNA vaccine, vector-based vaccine, inactivated vaccine

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INTRODUCTION

COVID-19 has affected more than 690 million people worldwide with 696 million death affecting all age groups.[1] The CDC reported that rate ratio of COVID 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.[2] However, children and adolescents have the potential to become reservoir 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. The WHO however on March 28 2023[3] have asked countries to reassess the need to continue to vaccinate low priority group which includes healthy children and adolescents.

Considering these and the resources needed for COVID vaccination of children, there is a need to comprehensively assess existing clinical evidence on the use of COVID-19 vaccine in 12-17 years old as a basis for recommending it.

METHODS

Included in this review was any type of study that investigated the efficacy, immunogenicity, safety, and effectiveness of COVID-19 vaccine on protection against SARS-COV-2 infection in patients 12-17 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 LOVE. 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 15, 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 – efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccine. Studies were screened, data extracted and risk of bias appraised by two independent reviewers using quality assessment tool of Cochrane for RCT, Newcastle Ottawa for case control and cohort studies and Amstar for meta-analysis. (Appendix 1) Any disagreement between the two was discussed with a third reviewer. 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 2. There were four meta-analysis/systematic review, (three efficacy and safety of the COVID-19 vaccines[4-6] and one effectiveness study on BNT162b2[7]). All were assessed in AMSTAR to have a critically low rate of confidence in the results. Since they were moderate to high risk of bias, we used the available studies we have searched and assessed them.

There were initially seven RCT 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)[8] and mRNA-1273 (Moderna)[9]]; two phase 2 trials on vector based [for ChAdOx1 (Covishield, Astra Zeneca)[10] and recombinant Ad5-vector[11]]; and two Phase 1 studies in inactivated vaccine CoronaVac[12] and BBIBP-CorV[13]. There was also one completed trial on DNA ZyCoV but since the 12-17 years old was only 3% of the trial population in the study, the results of this study were not included in the present review.[14]

There were also 16 effectiveness studies of BNT162b2 (Pfizer) with two studies that reported on BNT162b2, mRNA and Ad26 vaccines.[15-16] Of these, 15 were on healthy adolescents and one was on 12-21 years old with rheumatic diseases on immunomodulatory treatment.[17] The variants in the studies were on Alpha and Delta in two[15,18]; Delta in four[19-22]; Delta and Omicron in three[23-25]; two in Omicron[26,27]; and in five studies it was not reported[16,17,28-30]. The variants were based on the predominat strain at the time of the research in six studies and in another five it was detected by viral sequencing.

Healthy 12-17-Year-Old Population

RNA vaccine

The results of the efficacy, immunogenicity, and safety of BNT162b2 and mRNA 1273 trials have been previously reported.[31] There are presently no new trials on RNA vaccines in adolescents. The GRADE summary of these vaccines is presented in Table 1.

BNT162b2

The BNT162b2 trial randomized 2260 12 to 15 years old [vaccine: 1131; placebo (saline):: 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 recipients (0/1005) as compared to 16 of 978 in the placebo showing protection [RR: 0.03; (95% CI: 0.00, 0.49)]. In 360 participants, the geometric mean fold rise was higher in the 12-15 years old as compared to the 16-25 years old [Mean Difference: 116.9 (97.6, 136.19)], which met the noninferiority criterion (lower boundary of the two sided

95% confidence interval greater than 0.67) and indicated a greater response in 12 to 15 years old. Moderate certainty evidence showed that any serious adverse effect was higher in the vaccine group but this was not significant compared to the placebo [RR: 3.99 (95% CI: 0.45, 35.67)].

Effectiveness

Sixteen observational studies (8 cohort and 8 case control) reported the effectiveness of vaccines. Fourteen of the studies used BNT162b2. Two other studies[15,16] were on effectiveness of BNT 162b2, 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 and 18 years and above.

For the data on vaccine effectiveness, we used the data on 14 days after two doses of the vaccines have been given.

COVID infection

The BNT162b (Pfizer) vaccine was protective against COVID infection with any of the variants with higher protection for Delta [OR: 0.05 (0.05, 0.05), I2=98%, 8 studies] than for Omicron variant [OR 0.37 (0.36, 0.390, I^2=99%,

Table 1. GRADE Summary Table of Critical Outcomes of COVID-19 Vaccines in 12-17 year-old Healthy Children

Vaccine / Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
mRNA vaccine – BNT162b2 - Pfizer BioNTech					
Efficacy: symptomatic COVID-19 infection	1 RCT (n=1983)	RR 0.03	RR 0.00 to 0.49	Benefit	High
Immunogenicity: Neutralizing anti-bodies – Titers were compared to subject 16-25 years old and not to placebo	1RCT (n=360)	MD 116.9 GMFR higher	MD 97.61 to 136.19 higher	Benefit	Moderate
Serious Adverse Event from dose 1 through 1 month after dose 2	1RCT (n=2260)	RR 3.99	RR 0.45, 35.67	Inconclusive	Moderate
Any related adverse event leading to discontinuation from dose 1 through 1 month after dose 2	1RCT (n=2260)	RR 3.053	RR 0.123 to 73.699	Inconclusive	Moderate
Hospitalization	2 observational (n=185026)	OR 0.09	OR 0.05 to 0.15	Benefit	High
Emergency and Urgent Care	1 observational (5753 cases vs 20791 controls)	OR 0.17	OR 0.16 to 0.19	Benefit	High
ICU	3 observational (318 cases 355 controls	OR 0.13	OR 0.4 to 0.41	Benefit	Low
MIS-C	1 observational (70 cases 213 controls)	OR 0.09	OR 0.04 to 0.29	Benefit	Low
mRNA 1273 Vaccine – Moderna					
Efficacy: COVID-19 infection	1 RCT (n=3236)	RR 0.5000	RR 0.0030 to 1.0234	Benefit	Moderate
Immunogenicity: Pseudovirus neutralizing antibodies Age 12-17 vs Age 18-24	1 RCT (n=636)	MD 100.4 higher	MD 85.93 lower to 286.73 higher	Inconclusive	Low
Any solicited adverse reaction after 1st dose	1 RCT (n=3720)	RR 1.47	RR 1.41 to 1.54	Harm	High
Any solicited adverse reaction after 2nd dose	1 RCT (n=3698)	RR 1.306	RR 0.845 to 2.008	Inconclusive	Moderate
Unsolicited adverse event up to 28 days after injection (headache)	1 RCT (n=3726)	RR 1.070	RR 0.686 to 1.660	Inconclusive	Moderate
Unsolicited adverse reaction up to 28 days after injection (lymphadenopathy)	1 RCT (n=3726)	RR 10.770	RR 4.407 to 26.341	Harm	Moderate
Recombinant vector-based vaccine – Covishield, AZT1222 – AstraZeneca					
Efficacy of vector-based vaccine: COVID-19 infection	1 RCT (n=150)	RR 1.000	RR 0.3011 to 3.3209	Inconclusive	Very Low
Immunogenicity: pseudovirus neutralizing antibodies	1 RCT (n=46)	MD 242 Inhibitory concentration higher	MD 101.95 to 382.05 higher	Benefit	Low
Immunogenicity: Anti spike IgG Age 12-17 vs age 18-25	1 RCT (n=56)	MD 73144 AU/mL higher	MD 57014.73 to 89273.27 higher	Benefit	Low
Adverse events after 1st dose	1 RCT (n=76)	RR 1.4677	RR 0.3725 to 5.7825	Inconclusive	Low
Adverse events after 2nd dose	1 RCT (n=76)	RR 0.6770	RR 0.2101 to 2.1846	Inconclusive	Low
Adverse effect probably related to vaccine	1 RCT (n=76)	RR 0.2381	RR 0.0049 to 11.5220	Inconclusive	Low

Table 1. GRADE Summary Table of Critical Outcomes of COVID-19 Vaccines in 12-17 year-old Healthy Children *(continued)*

Vaccine / Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Recombinant Adenovirus Vectored COVID-19 Vaccine					
Immunogenicity: Pseudovirus neutralizing antibody	1 RCT (n=150)	MD 161.2 higher	MD 134.3 higher to 188.1 higher	Benefit	Low
Any solicited local adverse reaction 14 days after any dose (age 6 to 17)	1 RCT (n=150)	RR 6.000	RR 1.942 to 18.534	Harm	Low
Any solicited systemic adverse reaction 14 days after any dose (age 6 to 17)	1 RCT (n=150)	RR 3.700	RR 1.550 to 8.832	Harm	Low
Inactivated Virus – CoronaVac					
Immunogenicity: neutralizing antibody	1 RCT (n=102)	MD 144 higher	MD 108.34 to 179.66	Benefit	Low
Overall adverse reaction within 0-28 days after 1st and 2nd dose	1 RCT (n=122)	RR 1.4318	RR 0.8007 to 2.5604	Inconclusive	Moderate
Unsolicited adverse reaction within 0-28 days after 1st and 2nd dose	1 RCT (n=122)	RR 0.7000	RR 0.1643 to 2.9831	Inconclusive	Low
Solicited adverse reaction within 0-28 days after 1st and 2nd dose	1 RCT (n=122)	RR 1.7500	RR 0.9186 to 3.3339	Inconclusive	Low
Inactivated Virus – BBIBP-CorV					
Immunogenicity: pseudovirus neutralizing antibodies	1 RCT (n=112)	MD 190.15 higher	MD 172.77 to 207.52 higher	Benefit	Low
Systemic adverse reactions (after 1st dose)	1 RCT (n=336)	RR 1.194	RR 0.662 to 2.156	Inconclusive	Low
Systemic adverse reactions (after 2nd dose)	1 RCT (n=333)	RR 3.267	RR 0.780 to 13.679	Inconclusive	Low
Systemic adverse reactions (after 3rd dose)	1 RCT (n=333)	RR 1.960	RR 0.239 to 16.044	Inconclusive	Low

Figure 1. Forest plot of Effectiveness of COVID-19 vaccine against hospitalization.

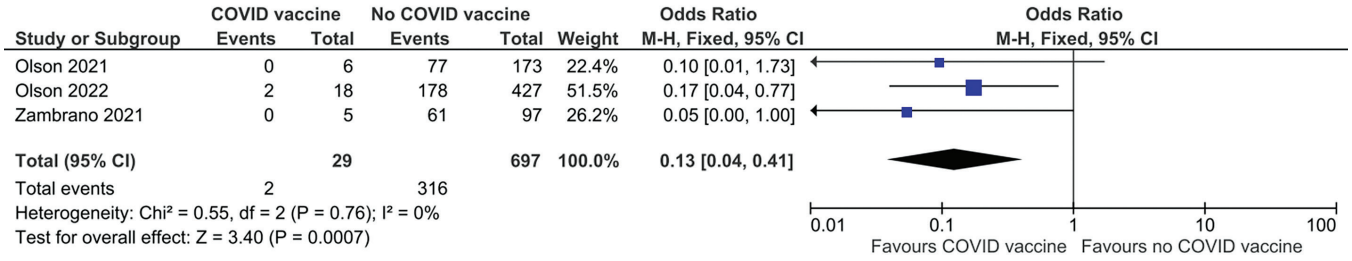

Figure 2. Forest plot of Effectiveness of COVID-19 vaccine against ICU admission.

3 studies]. In studies that the variants were not known, the COVID vaccine was also shown to be protective (OR: 0.01 [0.01, 0.02], I^2=99%, 3 studies. n=4051]. Certainty of evidence was assessed as low to very low due to heterogeneity of studies.

High certainty evidence showed that COVID vaccination in 12-17 years old was protective from hospitalization [OR: 0.09 [0.05, 0.15], I^2=27%, 2 studies] (Figure 1) and from Emergency and Urgent Care [OR: 0.17 (0.16-0.19), 1 study]. In these studies, the predominant variant was Delta. Low certainty evidence also showed that BNT 162 b2 was also protective against ICU care [OR: 0.13 (0.04, 0.41), I^2=0%, 3 studies] (Figure 2); critically Ill [OR: 0.17 (0.04, 0.73) I^2=0%, 3 studies]; and MIS-C [OR: 0.09 (0.04, 0.24) 1 study]. The

evidence on protection against hospitalization, and emergency and urgent care was upgraded due to very large effect.

mRNA-1273

The mRNA-1273 trial[9] randomized 3732 12 to 17 years old, 2489 received the vaccine. There was one COVID infection and seven in the placebo (saline) [RR: 0.05, (95% CI: 0.003, 1.0234)] 14 days after dose 2. Six hundred thirty-six (636) participants had immunologic studies. The number of patients with serologic response was similar in the 12 to 17 and 18 to 25 years old. However, the Geometric Mean Pseudovirus Neutralizing Antibody Ratio was higher in the 12 to 17 years old than in young adults [MD: 100.4; -85.93, 286.73)], which met the noninferiority criterion of more than 90% power of immune response for adolescents over young adults 18 to 25 years old. Moderate to high certainty evidence showed increased risk of adverse effects 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 vaccine group. There was 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 dose.

Vector-based Vaccine

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

ChAdOx1-19 (Astra Zeneca)

Efficacy

A single-blind randomized phase 2 trial[10] in 6-17 years old was conducted in which among the 12-17 years old, 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. Efficacy was based on the number of self-reported confirmed cases (PCR or lateral flow assay). Results showed no difference in the risk in infection in those who were given the ChADOx1-19 and Meningococcal vaccine (RR: 1.00; 0.3, 3.32). The quality of the evidence was downgraded to very low as there was serious risk of bias, imprecision, and suspected publication bias.

Immunogenicity

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 was higher in the vaccine group for anti spike IgG by PPD (MD: 73144; 95% CI: 57014.73, 89273.27) and pseudo neutralizing antibodies (MD: 242.00, 95% CI 101.95, 382.05). There was no report of noninferiority criterion. Certainty of evidence was downgraded as low due to indirectness and suspected publication bias.

Safety

The proportion of participants with adverse effects after dose 1 (RR: 1.467; 0.3725, 5.7825) and dose 2 (RR: 0.6770; 0.2101, 2.1846) were similar in both groups. There were four serious adverse effects in the vaccine group (RR: 3.197; 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 vaccine[11] versus placebo (vaccine excipients) was conducted in 430 participants at least 6 years old, 150 (34.9%) of which were 6-17 years old. There was no separate data for 12-17 years old.

Only the immunogenicity and safety of the vaccine was assessed. The prime-booster vaccination 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 geometric mean titres of the RBD binding ELISA antibodies day 28 after prime vaccination met the noninferiority margin of 0.5 GMT ratio [6-17 years: 1091.6 (873, 1363) vs 18 to 55 years: 608 (374, 988)]. After boost vaccination, the RBD binding ELISA titres in 6-17 and 18 to 55 years were similar to the prime vaccination but there was a significant increase in GMT of those >55 years (338; 263, 434) on day 84.

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

Inactivated vaccine

There are presently two Phase1/2 randomized controlled trials on inactivated vaccines: CoronaVac[12] and BBIBP[13].

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 28 days after the second dose was higher in 3.0 μg dose than the 1.5 μg dose (RR: 0.09, 0.0054, 1.708). The Geometric Mean neutralizing antibody titre was higher in the vaccine than in control (aluminum hydroxide) group (MD: 144; 95% CI: 108.34, 179.66). Noninferiority criterion was not stated. The overall adverse effect within 28 days after first and second vaccine dose in the control group was not significantly different from vaccine group (RR: 1.432; 0.8007, 2.5604). The most common local adverse effect was pain (RR: 9.2; 2.25, 37.5) and most common systemic adverse effect was fever

(RR: 1.16; 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 imprecision in the adverse effects data and suspected publication bias.

BBIBP-CorV

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

Immunogenicity

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 2 μg, 82 of 83 (99%) in the 4 μg, and all 82 in the 8 μg 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; 172.77, 207.52).

Safety

There was no significant difference in the occurrence of systemic adverse effect in the vaccine group from the placebo group after the first [RR: 1.194 (0.662, 2156)], second [RR: 3.267; (0.78, 13.679)], and third [RR: 1.960 (0.239, 16.044)] dose. Fever was the most common systemic adverse effect within 14 days after prime (RR: 7.00; 1.737, 28.212) and boost (RR: 6.500; 0.875, 48.292) vaccination.

Immunocompromised Patients

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

A prospective multicenter cohort study evaluated the short term efficacy, safety, and immunogenicity of BNT162b2 among 91 adolescent and young adults 12-21 years old 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. The GRADE summary is presented in Table 2.

Efficacy

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

Immunogenicity

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; 0.78, 1.21). However, the anti-S1/S2 antibody levels were significantly lower in patients with AIIRD compared with controls (MD: -145.80; -195.85, -95.75, P<0.001).

Safety

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 dose (RR: 0.99; 0.82, 1.20) and second dose (RR: 0.97; 0.78, 1.21).

Hospitalization within 2 to 4 weeks after dose 1 (RR: 2.198; 0.108, 44.747) and dose 2 (1.382; 0.058, 33.207) was not different in the AIIRD and healthy controls. Risk of exacerbation of rheumatic disease was similar within 2 to 4 weeks after dose 1 (RR: 5.000; 0.274, 85.375) and after dose 2 (RR: 1.382; 0.058, 33.207).

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

Table 2. GRADE Summary Table of BNT162b2 Primary Series in Immunocompromised Children 12-21 years old

Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
BNT162b2 - Pfizer BioNTech					
Efficacy within 3 months after vaccination	1 Observational (n=131)	RR 0.445	0.009, 22.078	Inconclusive	Very Low
Immunogenicity Anti- S1/S2 antibody levels 2-9 weeks after dose 2	1 Observational (n=59)	MD 145.8	195.85 lower to 95.05 lower	Harm	Very Low
Hospitalization within 2 to 4 weeks after dose 1	1 Observational (n=129)	RR 2.198	0.108, 44.747	Inconclusive	Very Low
Hospitalization within 2 to 4 weeks after dose 2	1 Observational (n=128)	RR 1.382	0.058, 31.207	Inconclusive	Very Low
Exacerbation of Rheumatic Disease within 2 to 4 weeks after dose 1	1 Observational (n=129)	RR 5.000	0.274 85.375	Inconclusive	Very Low
Exacerbation of Rheumatic Disease within 2 to 4 weeks after dose 2	1 Observational (n=128)	RR 1.382	0.058, 33.207	Inconclusive	Very Low

DISCUSSION

The administration of the primary series of the RNA COVID-19-vaccines in the 12-17 years old has been recommended since 2021 by different international[32-34] and local[35,36] agencies including the Department of Health and Philippine Pediatric Society. At that time, the available evidence was on the randomized controlled trial on BNT 162b2 (Pfizer)[8] and the mRNA-1273 (Moderna)[9]. Thus, in the first review of this investigation,[31] the BNT162b2 was strongly recommended in 12 to 15 years old to prevent symptomatic COVID-19 infection and the mRNA-1273 had weak recommendation due to low certainty of evidence in the immunogenicity. Subsequently, the mRNA-1273 was also endorsed for use in adolescents after it was shown that the benefit far outweighs the risk, with risk of myocarditis and pericarditis of 56 cases per million doses.[37] Since then, there has been additional five clinical trials and 16 effectiveness studies that are available for review.

Our present findings from observational studies showed that the BNT162b2 was protective for COVID-19 infection, showing it has greater protection for Delta than the Omicron variant. A recent study done in Hong Kong also confirmed that the vaccine was effective against the latest Omicron BA2.[27] The Omicron variant has at least 50 mutations, 36 of which has been in the virus spike protein and therefore may explain its ability to evade immunity. We also showed that BNT162b2 was protective for hospitalization, and emergency and urgent care admissions, with data obtained from studies that reported Delta and/or Omicron as predominant variants. The evidence was based mostly on case control studies but was upgraded due to the very large effect. The findings are similar with the report of the US Coronavirus Disease 2019-Associated Surveillance Network (COVID-NET) which showed that the monthly hospitalization rate of unvaccinated adolescents in the US is six times greater than those who are vaccinated.[38] Evidence however has low certainty in the prevention of Multisystem Inflammatory Syndrome and the need for ICU care, and more studies are needed. Likewise, immunocompromised 12-17 years old are considered high priority for vaccination but present findings are still inconclusive with regards its efficacy and safety in this group of patients.

The issue of myocarditis with use of RNA vaccines, is a major concern. A review of the safety data of Vaccine Adverse Event Reporting System demonstrated that it is a rare event after vaccination. From December 2020 to August 2021, the reported cases of myocarditis among males with BNT162b2 were 70, 106 and 52 cases per million in 12-15, 16-17 and 18-24 years old, respectively while in mRNA-1273, it was 56 cases per million in 18-24 years old. These cases are presently being verified by the Centers for Disease Control and Prevention. Among 36,209 individuals 12-17 years old, there were 5 (0.014%) cases of myocarditis, all males after the second BNT162b2 dose.[38] There was also an increased risk of diarrhea in females after second dose [RD: 0.10%; 0.0-0.21; p=0.03]), and increased risk of myalgia [RD: 0.08%; -0.01 to 0.19, p=0.04] and chills [RD: 0.08%; 0.01 to 0.16, p=0.019] in males as compared with developing these symptoms before being given the first dose.

Apart from the RNA vaccines, the safety and immunogenicity of vector-based, inactivated and DNA vaccines have also been published. Only the vector-based (AZD1222) vaccine has an interim efficacy report[10] but with only 150 participants 12-17 years old. The results are presently inconclusive due to imprecision. With CoronaVac,[12] publication bias is suspected as the clinical trial published has no efficacy results but the vaccine continued to be given in 3 to 18 years old in Hong Kong, China since January 2022.[27] Only the inactivated vaccine BBIBP-CorV used three doses in their primary series during their phase 1/2 trial. Results of the study showed that at day 56 (28 days after second dose), SARS-CoV-2 neutralizing antibody titres of 3-5, 6-12 and 13-17 years were similar to the antibody levels elicited in adults. Thus, in their phase 3 trials in 3-17 years old, only a two shot regimen of BBIBP-CorV is used. There is also an interim report on ZyCoV-D, DNA- based vaccine manufactured in India with a reported 67% vaccine efficacy with no difference in number of adverse events between treatment and placebo group.[14] However, the majority were mostly 18 to 60 years old and 12 to 17 years old comprised only 3.5% of participants.

CONCLUSION

There is presently low certainty evidence on the use of RNA vaccines in 12-17 years old. The recommendation on its use is weak. There is presently insufficient evidence for inactivated and vector-based COVID-19 vaccines. Different countries should consider whether to vaccinate healthy adolescent without comprising the other recommended immunization and health priorities that are crucial for this age group. Other factors including cost-effectiveness of vaccination and disease burden should be accounted. We await the results of four ongoing studies on COVID-19 vaccine in children and adolescent (Appendix 3).

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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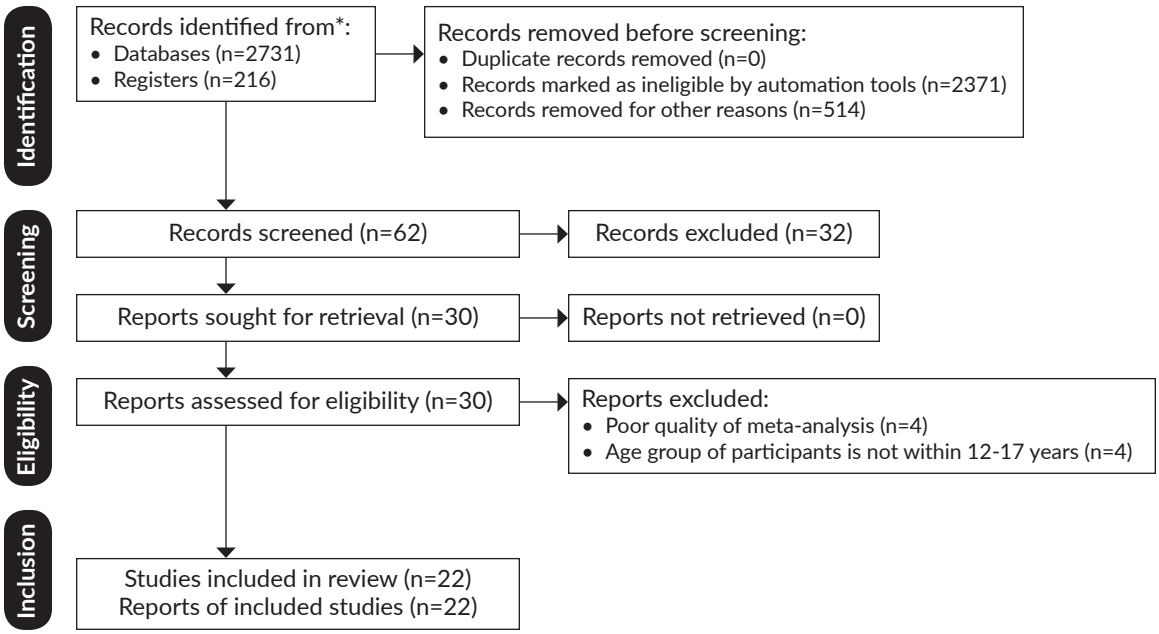
APPENDICES



Appendix 1. PRISMA diagram of included studies in the efficacy, effectiveness, and safety of COVID-19 vaccine in 12-17 years old.

Appendix 2. Characteristics of included studies

Study ID	Study Type	Country	Population	Intervention	Control	Outcome	
Vector-based vaccine							
Li[10]	RCT Phase 2	UK	6-17 years old N=262	ChAdOx1 (AZD1222) 2 doses intra-muscularly 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[11]	RCT Phase 2b	China	6-17 years old healthy participants N=150	Ad5-vectored COVID-19 vaccine 0.5 ml of 5 x 10^5 viral particles per dose 56 days apart N=100	Placebo with excipients as vaccine but no viral particles N= 50	Immunogenicity: • GMT of RBD specific ELISA antibodies and pseudovirus 28 days after vaccination • 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[9]	RCT phase 2/3	USA	12-17 years old 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 old 28 days after Dose 2	
Frenk[8]	RCT Phase 3 (interim report)	USA	12 - 15 years old healthy participants 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	
Immunocompromised							
Heshin-Bekenstein[17]	Prospective cohort	Israel and Slovenia	12 - 21 years old 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 immuno-suppression 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

Appendix 2. Characteristics of included studies *(continued)*

Study ID	Study Type	Country	Population	Intervention	Control	Outcome	
Normal Adolescent							
Britton[15]	Retrospective Test negative Case control	USA	12-19 years old 180,112 Cases: 39422 Controls: 140690	Vaccinated: 69301 (BNT162b: 60678; mRNA-1273: 6749; Ad26: 1874)	Unvaccinated	Symptomatic SARS-CoV-2 infection by NAAT result	Pre Delta Delta (prevalent strain)
Florentino[23]	Case control	Brazil and Scotland	12-17 years old 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]	12-17 years old 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)
Fowlkes[24]	Prospective cohort	USA (Arizona, Florida, Texas, Utah)	12-5 years old N=312	Vaccinated with BNT162b2 (n=227)	Unvaccinated (n=85)	Vaccine effectiveness against Delta and Omicron infections	Delta Omicron (whole genome sequencing)
Glatman-Freedman[26]	Retrospective Cohort	Israel	12-15 years old 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[30]	Retrospective cohort	Korea	16 - 18 years old N=1,299,965	BNT162b2 vaccine Vaccinated with: With one dose: 444,322 With two doses: 439079	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[18]	Cohort	Denmark	12 to 17 years old	BNT162b2 vaccine N=278,649 Dose 1: 229799 Dose 2: 175176	No vaccine N=2,786.490	Vaccine effectiveness after 20 days of Dose 1 and 60 days after Dose 2	B.1.177 lineage Alpha Delta (genome sequencing)
Klein[25]	Case control test negative	USA (10 US states)	12-15 years old 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: 14 days of dose 2 7 days of dose 3	Omicron Delta (predominant variant)

Appendix 2. Characteristics of included studies *(continued)*

Study ID	Study Type	Country	Population	Intervention	Control	Outcome	
Lin[16]	Retrospective Cohort (Surveillance System)	USA (North Carolina)	12-17 years old: 806634	Vaccinated with: BNT162b2: 396158 mRNA: 688 Ad26: 187	Unvaccinated 436601	Vaccine effectiveness in reducing: COVID-19 infection Hospitalization Death	Not reported
Leung[27]	Retrospective Cohort	Hong Kong China	3-18 years old	Vaccinated with 2 doses BNT162b2 12-17 years: 18277	Unvaccinated 12-17 years: 6565	Incidence rate of infection Incidence rate ratio of vaccinated against unvaccinated group	Omicron BA2 (predominant strain)
Lutrick[19]	Prospective Cohort	USA (Arizona)	12-17 years old 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[20]	Case Control	USA (Yale New Haven CT)	12-18 years old 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[28]	Case control	USA	12-18 years old 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	Not reported
Olson[29]	Case Control Test negative	USA	12-18 years old Cases: n=445 Control: n=777	BNT162b2 Fully vaccinated: n=299 Partially vaccinated: n=55	Unvaccinated N=441	Vaccine effectiveness: • hospitalization • ICU admission • Need of invasive or non-invasive intervention • Death	Not reported
Tartof [21]	Retrospective Cohort	USA (California)	12-15 years old 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	SARS COV-2 infection via PCR test regardless of present of symptoms COVID-19 hospital admission	Delta (genomic sequencies)
Zambrano[22]	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 2. Characteristics of included studies *(continued)*

Study ID	Study Type	Country	Population	Intervention	Control	Outcome	
Inactivated vaccines							
Xia[13]	RCT Phase 1 and phase 2	Henan, China	240	13-17 years old N=240 60 each for vaccine dose of 2/4/8 µg and control	BBIBP-CorV (Beijing Institute of Biological Products, Henan China) x 3 doses 28 days apart Phase 2: 13-17 years: N=180; 60 each for vaccine dose of 2/4/8 µg	Phase 2: 13-17 years old N=60	Immunogenicity: • 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

Appendix 3. Ongoing studies on COVID-19 vaccine in children

Clinical Trial ID/Title	Proponent	Start/ Expected Completion Date/Status	Study Design	Population	Intervention	Comparator	Outcome
NCT05157191 Safety of Pediatric COVID-19 Vaccination	Kaiser Permanente Columbia Hospital Children's Hospital Medical Center Cincinnati	April 6 2022 July 1 2023 Ongoing recruitment	Prospective observational study	5 to 16 years old given	mRNA COVID-19 vaccines		Local and systemic adverse reaction during the 7 days following vaccination Follow up 180 days after dose 2 for SAE and adverse event of special interest
NCT05652543 A Phase II Study to Evaluate the Safety & Immunogenicity of SARS-CoV-2 Alpha/ Beta/Delta/Omicron Variants COVID-19 Vaccine (SCTV01E)	Jiangsu Center for Disease Control and Prevention	January 5, 2023 August 2023	Randomized, double-blind, placebo-controlled	750 participants; 250 per age group ≥18 years old; 12-17 years old; 3-11 years old	Biological: SCTV01E To be given to participants who have received the primary series of COVID-19 vaccine recommended in their country	Biological: Placebo (normal saline)	Incidence and severity of SAE Immunogenicity: a. IgG total antibody 28 days post vaccination b. Neutralizing antibody titre against SARS-CoV-2 Omicron variant
NCT05013983 Clinical Trial of Recombinant COVID-19 Vaccine (Sf9 Cells) in Children and Adolescents	West China Hospital	March 7, 2022 April 30, 2023 Not yet recruiting	Randomized, double-blind, placebo-controlled study,	6-17 years old	Recombinant COVID-19 vaccine (Sf9 cells)	Placebo with absent study vaccine antigen	Incidence and severity of SAE 0-7 days after each vaccination Immunogenicity: a. GMT of RBD specific IgG antibody against SARS CoV2 b. GMT of SARS-CoV-2 specific neutralizing antibody
NCT04992208 Safety of an Inactivated SARS-CoV-2 Vaccine for Prevention of COVID-19 in Children and Adolescents	Yungping Center for Disease Control and Prevention Dali Yunnan China	August 5, 2021 December 25 2022 Ongoing recruitment	Multicenter Prospective Observational Study	3-17 years old	inactivated SARS-CoV-2 vaccine (CoronaVac)		Incidence and severity of SAE 0-7 days after each vaccination Immunogenicity: a. GMT of RBD specific IgG antibody against SARS-CoV-2 b. GMT of SARS-CoV-2 specific neutralizing antibody