SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
BRIEF REPORT OF RAPID REVIEW
COMPONENT: COVID-19

TITLE: SHOULD THE BNT162b2 COVID-19 VACCINE BE USED FOR CHILDREN AGED 5 -11 YEARS OLD IN SOUTH AFRICA

DATE: 18 JULY 2022

KEY FINDINGS

- A rapid review was conducted to evaluate the efficacy, safety and effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech BNT162b2, tozinameran, two-dose, 10µg) vaccine to prevent morbidity and mortality associated with COVID-19 in children aged 5–11 years old.
- We searched the eCOVID-19 RecMap, World Health Organization (WHO), Joint Committee on Vaccination and Immunisation (JVIC) and Centre for Disease Control and Prevention (CDC databases for COVID-19 paediatric guidelines and recommendations on 23 June 2022. Additionally, we searched the Cochrane Library COVID-19 study register, COVID-nma.com living review database and the McMaster University Living Evidence Synthesis websites for trials and observational studies on 23 and 27 June 2022 respectively. We identified one eligible trial and 11 observational studies.
- Randomised clinical trial: we identified one trial (n = 2,285) conducted in United States, Spain, Finland and Poland. Two-dose BNT162b2 vaccine compared to placebo may result in a reduced risk of COVID-19 infection ≥7 days after the second dose, Risk Ratio (RR) 0.09 (95% CI 0.03 to 0.32), n = 2,261, moderate certainty evidence, 19 fewer cases per 1,000 vaccines delivered (ranging from 15 to 21 fewer cases). Serious adverse events were reported in 2/1,518 (0.1%) of BNT162b2 recipients and 1/750 (0.1%) of placebo recipients, from the first dose to one month after the second dose, low certainty evidence.
- Observational studies: two-dose BNT162b2 vaccine compared to placebo may result in:
  - reduction in COVID-19 infection (day 14 - 90), Odds Ratio (OR) 0.46 (95% CI 0.23 to 0.93), n = 3,096,179, low certainty evidence, 137 fewer cases per 1,000 children who are vaccinated (from 15 to 214 fewer cases);
  - small reduction in the number of hospitalisations (day 21 - 90), OR 0.36 (95% CI 0.19 to 0.69), n = 3,022,159, moderate certainty evidence, 3 fewer hospitalisations per 10,000 children who are vaccinated (from 2 fewer to 4 fewer hospitalisations); and
  - little or no difference in mortality (day 84), OR 0.33 (95% CI 0.02 to 6.93), n = 2,831,532, low certainty evidence.

  However, it must be noted that death was rare, with two deaths reported overall in the RCT.
- Currently the paediatric-specific product is not registered in South Africa, and the cost is unknown.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation 1 of 2: CHILDREN AT HIGH RISK* 5 TO 11 YEARS OLD	We recommend against the option and for the alternative	We suggest not to use the option	We suggest using either the option or the alternative	We suggest using the option **in children at high risk***	We recommend the option
				X	

Type of recommendation 2 of 2: GENERAL CHILDREN POPULATION 5 TO 11 YEARS OLD	We recommend against the option and for the alternative	We suggest not to use the option **in the general population of children 5 to 11 years old**	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
		X			

Recommendation:
The NEML MAC on COVID-19 Therapeutics and VMAC suggested that COVID-19 vaccination using Pfizer-BioNTech BNT162b2 may be offered to children aged 5 – 11 years old considered at higher risk for severe illness and death* (conditional recommendation, low certainty evidence).

*High risk children include, but are not limited, to those with the following conditions: chronic respiratory disease; chronic heart conditions; chronic conditions of the kidney, liver or digestive system; chronic neurological disease; endocrine disorders, immunosuppression, asplenia or dysfunction on the spleen, serious genetic abnormalities.

Rationale:
There is a small absolute benefit in the prevention of incident COVID-19 cases and hospitalisation if a two-dose BNT162b2 vaccine is offered to children aged 5-11 years compared to placebo (low – moderate certainty evidence). However, general vaccination of this age-group may not be justified. Benefits are relatively small, there are challenges with implementation due to lack of availability of a paediatric formulation at this time, the programmatic cost is likely to be high, and there may be low uptake and acceptability.

Although there is no direct evidence of enhanced benefit for children at high-risk of severe COVID-19, the benefit reported in studies in children aged 5 – 11-year-olds is likely to apply to this group. In addition, this group may have greater benefit due to their higher risk of severe disease. They are likely to be easy to reach for vaccination via their health care providers, as they will already be in care due to their pre-existing conditions. The vaccine for this age group is not yet registered by SAHPRA. However, for the children considered at higher risk, making use of a reduced dose of the available adult vaccine is suggested.

This review will be updated as further evidence is produced or the context changes. In particular, it will be revisited once the registration of the paediatric dosage form is confirmed, and a price is obtained.

Level of Evidence: low certainty evidence

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC ON COVID-19 Therapeutics: Andy Gray, Andy Parrish, Karen Cohen.

VMAC: Barry Schoub, Ames Dhai, Clive Gray, Glaudina Loots, Gregory Hussey, Helen Rees, Richard Lessells, Wolfgang Presier, Rudzani Muloiwa, Tamara Kredo, Cheryl Cohen, Wendy Burgers. *Observers*: Nicholas Crisp, Malusi Mpumlwana, Mvuyisi Mzukwa, Koleka Mlisana. *Secretariat*: Khadija Jamaloodien, Lesley Bamford, Marione Schonfeldt, Ruth Lancaster, Nasreen Seedat.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated when evidence that is more relevant becomes available.

PROSPERO registration: CRD42021286710

BACKGROUND

On 10 September 2021, the South African Health Products Regulatory Authority approved the use of the BNT162b2 vaccine for children aged 12 years and older (1). In the week of 10-16 October 2021, 14.7% of new COVID-19 cases reported were in the 12–17-year age group, and from mid-October 2021, children aged 10-19 years made up 9.2% of the total number of COVID-19 cases reported since the beginning of the pandemic in South Africa. The goal of vaccination of children and adolescents is to shorten the duration of symptoms, limit transmission to others, and allow an earlier return to school and normal activities (2). It is considered particularly important for those with underlying conditions such as diabetes, cancer, human immunodeficiency virus (HIV) and obesity (2). Data from the National Institute for Communicable Diseases (NICD) has shown that adolescents with these underlying conditions are at greater risk of death from COVID-19 compared to adolescents without underlying conditions (2).

Unpublished data from the NICD in children ≤18 years admitted with COVID-19 showed increased risk in mortality in individuals with hypertension (adjusted Odds Ratio [aOR] 2.24; 95%CI 1.09-4.62), diabetes (aOR 2.40; 95%CI 1.30-4.42), malignancy (aOR 4.78; 95%CI 1.93-11.84), previous tuberculosis (TB) (aOR 2.28; aOR 1.10-4.73), and HIV (aOR 2.90; 95% CI 1.89-4.46). In a model with combined number of comorbidities instead of individual comorbidities, compared to children with no comorbidities, the risk of mortality was increased in children with one comorbidity (aOR 3.00; 95%CI 2.34-3.84), two comorbidities (aOR 3.69; 95%CI 2.34-5.82), and three or more comorbidities (aOR 4.42; 95%CI 2.11-9.25), model adjusted for sex, race, health sector and province. A systematic review looking at poor prognostic factors for COVID-19 in children and adolescent highlighted congenital heart disease, chronic pulmonary disease, neurological diseases, and obesity as being associated with unfavourable outcome (3).

In South Africa, adolescents are only offered the BNT162b2 vaccine (Pfizer–BioNTech) vaccine, whereas adults can get the BNT162b2 or the Janssen vaccine. From 09 December 2021, all children 12 years and older are eligible to receive two doses of BNT162b2 vaccine 42 days apart (4). The BNT162b2 vaccine (Pfizer–BioNTech) is a lipid nanoparticle formulation containing nucleoside-modified mRNA encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral spike glycoprotein (5). In large, multinational randomised controlled trials, BNT162b2 had an acceptable safety profile characterized by transient mild-to-moderate injection-site pain, fatigue, and headache, was more immunogenic among 12-to-15-year-olds than among young adults and was reported as 95 to 100% efficacious in preventing COVID-19 illness from 7 days to about 2 months after the second dose (6-7). In comparison to adults, children and adolescents with COVID-19 are more likely to have only mild or asymptomatic infections, less likely to suffer persistent symptoms and less likely to be hospitalised or die from COVID-19. However, they can transmit COVID-19 to others, especially in settings where there is poor implementation of public health and social measures (2).

Following vaccine trials in adults and adolescents that showed acceptable safety and efficacy, a randomised trial of a lower-dosage formulation of the BNT162b2 (Pfizer–BioNTech) vaccine was conducted in children aged 5 to 11 years of age (8). Based on findings from safety and immunogenicity assessments among 48 children in the phase 1 study, a dose level of 10 µg was selected as the dose for the vaccine efficacy trial. In the subsequent phase 2–3 trial, a total of 2,268 children were randomly assigned to receive the BNT162b2 vaccine (1,517 children) or placebo (751 children). The primary endpoint was immunological (geometric mean ratio of neutralizing titres in 5-11-year-olds vs. 16-25-year-olds in the pivotal trial), but vaccine efficacy of 90.7% (95% confidence interval [CI], 67.7 to 98.3) against symptomatic COVID-19 from 7 to 126 days after the second dose was reported. There were three cases of newly diagnosed COVID-19 cases among BNT162b2 vaccine recipients *vs*. 16 among placebo recipients. The BNT162b2 vaccine had a favourable safety profile with no reported vaccine-related serious adverse events after a median follow-up of 2.3 months (8).

The randomised trial described above was conducted during a period when variants of concern other than Omicron, such as the Delta variant, were dominant in the United States. Several observational studies that assessed the effectiveness of the BNT162b2 vaccine against Omicron among adults, adolescents, and children reported that the protection conferred by the vaccine was considerably lower against both infection and hospitalisation than the protection the vaccine conferred against previous variants (9-12). This review aimed to assess the effectiveness of two-doses, 10µg, intramuscular (IM) BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in children aged 5-11 years old with or without co-morbidities on symptomatic laboratory confirmed COVID-19, hospitalisation due to COVID-19, COVID-19 related death, serious adverse events, and other adverse events.

<u>At risk paediatric patients aged 5-11 years:</u>
Risk groups for SARS-CoV-2-associated hospitalisation and death are defined in children 5-11 years old[1]. Also see Table 1 below.

Table 1: CONDITIONS OF AT-RISK PAEDIATRIC PATIENTS 5-11 YEARS

Disease state	Comment
Chronic respiratory disease	Including those with poorly controlled asthma[2] that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, cystic fibrosis, ciliary dyskinesias and bronchopulmonary dysplasia
Chronic heart conditions	Haemodynamically significant congenital and acquired heart disease, or less severe heart disease with other comorbidity. This includes: - Single ventricle patients or those palliated with a Fontan (Total Cavopulmonary Connection) circulation - Those with chronic cyanosis (oxygen saturations <85% persistently) - Patients with cardiomyopathy requiring medication - Patients with congenital heart disease on medication to improve heart function - Patients with pulmonary hypertension (high blood pressure in the lungs) requiring medication
Chronic conditions of the kidney, liver or digestive system	Including those associated with congenital malformations of the organs, metabolic disorders and neoplasms, and conditions such as severe gastro-oesophageal reflux that may predispose to respiratory infection as well as renal and liver failure.

1 https://assets.publishing.services.gov.uk/government/uploads/system/uploads/attachment_data/file/1007737/Greenbook_chapter_14a_30July2021.pdf

2 https//www.cdc.gove/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#children

Chronic neurological disease	This includes those with - Neuro-disability and/or neuromuscular disease that may occur as a result of conditions such as cerebral palsy, autism, epilepsy and muscular dystrophy - Hereditary and degenerative disease of the nervous system or muscles, other conditions associated with hypoventilation - Severe or profound multiple learning disabilities (PMLD), Down's syndrome, those on the learning disability register - Neoplasm of the brain
Endocrine disorders	Including diabetes mellitus, Addison's and hypopituitary syndrome
Immunosuppression	Immunosuppression due to disease or treatment, including: - Those undergoing chemotherapy or radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients - Genetic disorders affecting the immune system (e.g., deficiencies of IRAK-4 or NEML, complement disorder, SCID) - Those with haematological malignancy, including leukaemia and lymphoma - Those receiving immunosuppressive or immunomodulating biological therapy including transplant patients - Those treated with or likely to be treated with high or moderate dose corticosteroids - Those receiving any dose of non-biological oral immune modulating drugs e.g., methotrexate, azathioprine, 6-mercaptopurine or mycophenolate - those with auto-immune diseases who may require long term immunosuppressive treatments. Children who are about to receive planned immunosuppressive therapy should be considered for vaccination prior to commencing therapy.
Asplenia or dysfunction on the spleen	Including hereditary spherocytosis, homozygous sickle cell disease and thalassemia major
Serious genetic abnormalities that affect a number of systems	Including mitochondrial disease and chromosomal abnormalities

RESEARCH QUESTION: What is the effectiveness of the BNT162b2 vaccine to prevent morbidity and mortality associated with COVID-19 in children aged 5–11 years old?

METHODS

We searched the eCOVID-19 RecMap, World Health Organization (WHO), Joint Committee on Vaccination and Immunisation (JCVI) and Centre for Disease Control and Prevention (CDC databases for COVID-19 paediatric guidelines and recommendations on 23 June 2022. Additionally, we searched the Cochrane Library COVID-19 study register, COVID-nma.com living review database (www.covid-nma.com) website and the McMaster University Living Evidence Synthesis (https://www.mcmasterforum.org/) for trials and observational studies on 23 and 27 June 2022 respectively. These databases systematically search PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov. Search terms used are found in Appendix 1. Screening of records, and selection of articles was done independently by one reviewer (SE) then cross-checked by (NG). Data extraction was done by two reviewers (SE) and (NG) and cross-checked by a third reviewer (NB). The main characteristics of the included study and study outcomes are shown in Table 4. Table 5 presents results of the search for planned/ongoing trials on the COVID-nma website.

We used Review Manager (Revman) 5 software to perform the analyses. AGREE II scores for guidelines

were obtained from the eCOVID-19 RecMap team (https://covid19.recmap.org/about) (13) (Table 2). The risk of bias (ROB) for one included trial (8) was obtained from the COVID-nma website, we obtained the ROBINS-I assessment for the observational studies from the McMaster University Living Evidence Synthesis (14) or where needed the ROBINS-I tool was used and appraisal performed in duplicate (Table 3). We reported risk ratios and odds ratios for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (15). Table 6 and Table 7 is a GRADE evidence profile for the comparison of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, compared to no vaccine. Table 8 and Table 9 is a GRADE summary of findings table for this comparison.

ELIGIBILITY CRITERIA FOR REVIEW

Population: Children 5-11 years of age (Sub-group population: Children 5-11 years of age with comorbidities)

Intervention: BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, 2-doses, 10µg, intramuscular (IM).

Comparators: Placebo or no vaccine

Outcomes:

- Symptomatic laboratory confirmed COVID-19,
- Hospitalisation due to COVID-19,
- COVID-19 related death,
- Serious adverse events, Other adverse events

Study designs: Randomised control trials and observational studies

Note: A two-step process was undertaken 1) RCTs; followed by 2) observational studies separately with their own efficacy and safety measures reported separately.

RESULTS

SEARCH RESULTS

We searched for guidelines from the US CDC, the WHO SAGE, and the UK JCVI. We found two guidelines from CDC and WHO SAGE, and one updated statement on vaccination of children aged 5 to 11 years from JCVI. One trial and one observational study were identified through the NEML MAC committee. A COVID-19 Living Evidence Synthesis and the COVID-nma.com living review databases were searched and found ten eligible observational studies. Five studies were excluded for incorrect population, intervention, and ongoing trials. Table 5 represents ongoing trials that will be monitored for publication.

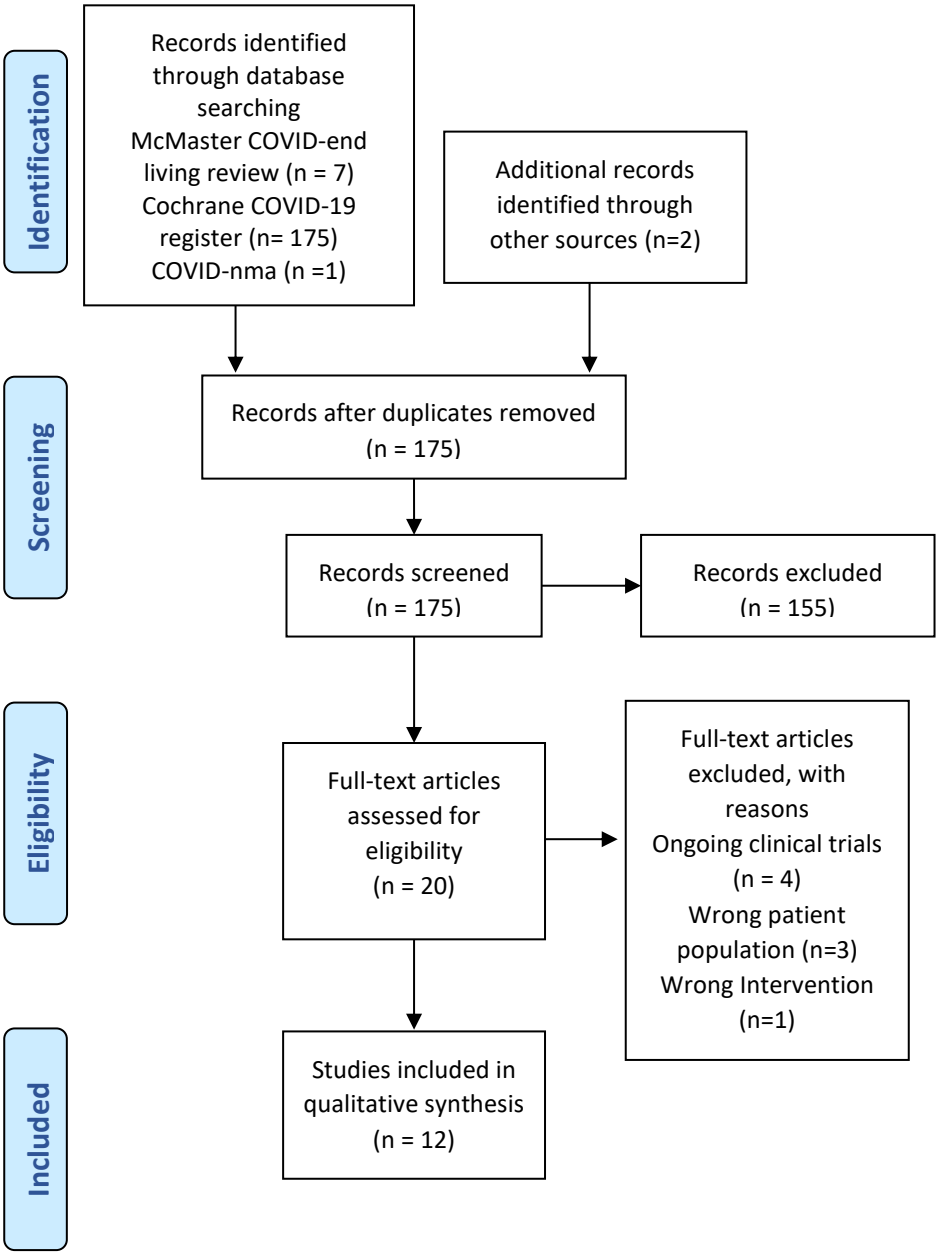

Figure 1: PRISMA FLOW DIAGRAM FOR REVIEW

DESCRIPTION OF THE GUIDELINES AND STUDIES

GUIDELINES

See Table 2. The UK JCVI issued a statement in December of 2021 on the vaccination of children aged 5 to 11 years old, which advised on children in a clinical risk group or who are household contacts of someone who is immunosuppressed. This statement was updated in February 2022.

The WHO SAGE Interim recommendations for use of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine, under emergency use listing was first issued in January 2021, further updated in June 2021, November 2021, and January 2022. The guidance covers vaccination recommendations for BNT162b2 in a variety of populations including children and adolescents (16).

The US CDC Advisory Committee on Immunization Practices interim recommendation for the use of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in children aged 5 – 11 years was published in November 2021. The advisory was based on the phase 2/3 trial data only. The CDC issued an update in June 2022, recommending expanded access to children aged six months and older, and suggesting that children five years and older should receive a COVID-19 booster vaccination if eligible.

THE SUMMARY OF RECOMMENDATIONS FOR CHILDREN AGED 5 TO 11 YEARS AND THE AGREE II APPRAISAL CAN BE SEEN IN Table 2. REFER TO APPENDIX 2 FOR THE AGREE II ITEM SCORES FROM THE ECOVID-19 RECMAP

Table 2: SUMMARY OF GUIDELINE RECOMMENDATIONS

Citation	Recommendation	AGREE II score
Joint Committee on Vaccination and Immunization [Internet]. JCVI statement on vaccination of children aged 5 to 11 years old. [Published 16 Feb 2022; cited 28 June 2022]. Available from: https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-aged-5-to-11/jcvi-statement-on-vaccination-of-children-aged-5-to-11-years-old Updated statement	**1. JCVI advises a non-urgent offer of two 10 mcg doses of the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) to children aged 5 to 11 years of age who are not in a clinical risk group.** The 2 doses should be offered with an interval of at least 12 weeks between doses. **2.** The intention of this offer is to increase the immunity of vaccinated individuals against severe COVID-19 in advance of a potential future wave of COVID-19. **3.** "This advice on the offer of vaccination to 5- to 11-year-olds who are not in a clinical risk group is considered by JCVI as a one-off pandemic response programme [footnote 1]. As the COVID-19 pandemic moves further towards endemicity in the UK, JCVI will review whether, in the longer term, an offer of vaccination to this, and other paediatric age groups, continues to be advised" ***Remarks*** **1.** "This should not displace delivery of paediatric non-COVID-19 or COVID-19 immunisation programmes" **2.** "Delivery of paediatric non-COVID-19 immunisation programmes across all ages should receive due attention, particularly where vaccine coverage has fallen behind due to the COVID-19 pandemic and where there is evidence of health inequalities" **3.** "Use of the Pfizer-BioNTech 10 mcg paediatric formulation vaccine should be encouraged for all pupils in the relevant academic year for children aged 11 to 12 to reduce complexity in programme delivery and expected reactogenic events for individuals"	Low AGREE II score due to limited information provided in methods Scope and purpose: **86%** Stakeholder involvement: **29%** Rigor of development: **38%** Clarity of presentation: **76%** Applicability: **57%** Editorial independence: **50%**

Citation	Recommendation	AGREE II score
World Health Organization [Internet]. Interim recommendations for the use of Pfizer-BioNTech COVID-19 vaccine BNT162b2, under emergency use listing: interim guidance [updated 21 January 2021; cited 23 June 2022]. Available from: https://apps.who.int/iris/handle/10665/351139	1. **WHO recommends that countries consider using BNT162b2 in children aged 5- 17 years only when high vaccine coverage (primary series and boosters) has been achieved in the higher priority-use groups.** Countries should consider the individual and population benefits of immunising children and adolescents in their specific epidemiological and social context when developing their COVID-19 immunisation policies and programmes 2. The **recommended schedule is two doses […] 10µg, 0.2ml each** for children aged 5 to 11 years given intramuscularly in the deltoid muscle. WHO recommends that the second dose be provided 4 to 8 weeks after the first, preferably 8 weeks as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/pericarditis **Specific populations** 1. **Children aged 5 to 17 years with comorbidities that put them at higher risk of severe COVID-19 should be offered vaccination** 2. **Moderately and severely immunocompromised persons (ICPs), including persons living with HIV with CD4 cell count of <200 cells/µl:** WHO recommends an extended primary series including an additional (third) dose […] (10µg) for ICPs aged 5 to 11 years. Available evidence suggests that an additional (third) dose should be given 1-3 months after the second dose in the standard primary series in order to increase protection as quickly as possible in ICPs. If more than 3 months have elapsed since the second dose in the primary series, the additional (third) dose should be given at the earliest opportunity. (Conditional recommendation, low certainty of evidence)	Scope and purpose: **91.7%** Stakeholder involvement: **52.8%** Rigor of development: **58.3%** Clarity of presentation: **58.3%** Applicability: **27.1%** Editorial independence: **95.8%**
Woodworth K, *et al*. The advisory committee on immunization practices' recommendation for the use of Pfizer-BioNTech COVID-19 vaccine in children aged 5 – 11 years – United States, November 2021. MMWR Morb Mortal Wkly Rep. 2021;70(45):1579-83. DOI: http://dx.doi.org/10.15585/mmwr.mm7045e1	The Pfizer-BioNTech COVID-19 vaccine is **recommended for persons 5-11 years of age in the U.S. population under the FDA's Emergency Use Authorization**. (Strong recommendation, very low certainty of evidence)	Scope and purpose: **97.2%** Stakeholder involvement: **63.9%** Rigor of development: **77.1%** Clarity of presentation: **36.1%** Applicability: **39.6%** Editorial independence: **33.3%**

RANDOMIZED CONTROLLED TRIAL AND OBSERVATIONAL STUDIES

One published trial (8) conducted in the United States (US) and Europe investigated the immunogenicity, safety, and efficacy of two doses of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine compared to no vaccine/placebo in children aged 5-11 years (N=2,268). There were eleven observational studies (pre-prints and published; 2021-2022) conducted in the US (9, 11-12, 17-20), Israel (21-22), Italy (23), and Canada (24) that investigated the safety, and effectiveness of two doses of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine compared to no vaccine/placebo in children aged 5-11 years. The follow-up duration ranged from 14 to 90 days during the Delta – Omicron dominance period. The analytic sample sizes ranged from n = 1,364 – 2,965,918, and ages ranged from 6 months to 18 years. Overall, the study arms compared vaccinated (partial/fully) *vs*. unvaccinated participants, with one study describing adverse events reported through the Adverse Events Reporting System managed by the CDC (passive surveillance) (19). Outcomes assessed in the included studies include i) symptomatic laboratory confirmed COVID-19 (8, 9, 11, 17, 21-23); ii) hospitalisation (9, 12, 18, 20, 23-24); iii) COVID-19 related death (23); iv) serious adverse events (8, 19) and v) other adverse events (8, 19). Although eligible, the Simmons 2022 *et al.* study (24) was excluded from the main analysis due to lack of outcome data among the 5–11-year-old age group. Table 4 presents a comprehensive description of included studies.

APPRAISAL OF GUIDELINES, TRIALS AND OBSERVATIONAL STUDIES

- Guidelines (AGREE II)

  The AGREE II scores for both guidelines are summarised in Table 2. More detail on the individual item scores within each domain of the AGREE II can be viewed in Appendix 2.

- Randomised controlled trials (Cochrane ROB 2.0) [n = 1]

  The Walter *et al.* (8) trial had an overall risk of bias of 'some concerns' due to deviations from the planned intervention. The authors' use of the per-protocol analysis of efficacy and immunogenicity outcomes was considered to be inappropriate since the intention was to assess the effect of the assignment to the intervention. The reasons for exclusion of outcomes were: 14 [0.9%] *vs*. 10 [1.3%] did not receive 2 doses; 64 [4.2%] *vs*. 11 [1.5%] had important protocol deviations as determined by the investigator or did not complete 1 month follow-up after the second dose. These deviations were a concern for confirmed symptomatic COVID-19 and confirmed severe COVID-19. All other domains had a low risk of bias.

- Observational studies (ROBINS-I) [n = 11]

  Of the eleven observational studies, eight studies (9, 12, 17-18, 19-20, 22, 24) presented with serious risk of bias, with only three having moderate risk (11, 21, 23). None had low risk of bias. Studies with serious risk of bias were downgraded for lack of adjustment for comorbidities, exclusion of previously infected participants, lack of an objective method for ascertainment of vaccination status, and incorrect index date of medical events (Table 3). Those with moderate risk of bias were downgraded for study design (cohort) which raises concerns around source population from which the exposed and non-exposed were sampled from, and lack of an objective method to ascertain vaccination status and accounting for the non-immune period implying evidence of residual bias.

Table 3: ROBINS-I ASSESSMENTS FOR OBSERVATIONAL STUDIES

ROBINS domains	Bias in selection of participants into study	Bias in classification of interventions				Bias due to confounding				Bias in measurment of outcomes	
Amir 1	Moderate Risk	Low Risk	Low Risk	Low Risk	No information	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk
Dorabawila	Moderate Risk	Low Risk	Low Risk	Low Risk	No information	Moderate Risk	Serious Risk	Low Risk	Serious Risk	Low Risk	Serious Risk
Fleming-Dutra	Low Risk	Serious Risk	Low Risk	Moderate Risk	Low Risk	No information	Low Risk	Low Risk	Low Risk	Low Risk	Serious Risk
Fowlkes	Moderate Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	No information	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk
Klein	Low Risk	Low Risk	Low Risk	Serious Risk	Low Risk	No information	Serious Risk	Low Risk	Low Risk	Low Risk	Serious Risk
Price	Low Risk	Moderate Risk	Moderate Risk	Low Risk	Low Risk	No information	Serious Risk	Low Risk	Low Risk	Low Risk	Serious Risk
Simmons	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk	Serious Risk	Low Risk	Low Risk	Low Risk	Serious Risk
Shi	Moderate Risk	Low Risk	Low Risk	Low Risk	No information	Moderate Risk	Serious Risk	Moderate Risk	Low Risk	Low Risk	Serious Risk
Sacco	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk
Hause	Serious Risk	Low Risk	Low Risk	No information	No information	No information	No information	No information	No information	No information	Serious Risk
Cohen-Stavi (McMaster)	Moderate Risk	Serious Risk	Moderate Risk	Moderate Risk	Low Risk	Moderate Risk	Low Risk	Serious Risk	Low Risk	Low Risk	Serious Risk

EFFECTS OF THE INTERVENTION

The GRADE Evidence Profile Table 6 and Table 7 and Summary of Findings in Table 8 and Table 9 summarise the effects of the intervention for each of the following outcomes. We sought data from the included studies on vaccine efficacy, safety, and effectiveness in children with comorbidities, but this was not available.

Randomised controlled trials:

One study by Walter *et al.* (8) evaluated safety and efficacy of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine in children aged 5-11 years.

1. Symptomatic laboratory confirmed COVID-19

   There were 3/1514 cases of COVID-19 infection in the two-dose BNT162b2 group (0.20%) and 16/747 in the placebo group (2.14%). Two-dose BNT162b2 vaccine compared to placebo may result in small reduction in COVID-19 infection ≥7 days after the second dose, Risk Ratio (RR) 0.09 (95% CI 0.03 to 0.32), n = 2,261, moderate certainty evidence. In absolute terms, this is 19 fewer cases per 1,000 vaccines delivered (ranging from 15 to 21 fewer cases). Vaccine efficacy: 91% (95% confidence interval [CI] 68%-97%).

2. Hospitalisation due to COVID-19

   This outcome was not reported.

3. COVID-19 related death

   This outcome was not reported.

4. Serious adverse events

   Phase 1: 16 participants received two 10-µg doses of BNT162b2 vaccine. There were no serious adverse events reported.

   Phase 2-3: Serious adverse events were reported in 0.1% of BNT162b2 recipients (2/1,518) and 0.1% of placebo recipients (1/750), from the first dose to one month after the second dose. Three serious adverse events in two participants were reported by the cut-off date (a median of 2.3 months' follow-up); all three (post-injury abdominal pain and pancreatitis in a placebo recipient and arm fracture in a BNT162b2 recipient) were unrelated to the vaccine or placebo. No deaths or adverse events leading to withdrawal were reported. Low certainty evidence that there may be little or no difference in the occurrence of serious adverse events.

5. Adverse events

Phase 1: Most reported local reactions were mild to moderate, and all were transient. Adverse events from the first dose through one month after the second dose were reported by 43.8% (7/16) of participants who received two 10-µg doses of BNT162b2.

Phase 2: From the first dose through 1 month after the second dose, adverse events were reported by 10.9% (166/1,518) of BNT162b2 recipients and 9.2% (69/750) of placebo recipients RR 1.19 (95% CI 0.91 to 1.55), moderate certainty evidence.

There were more local reactions and systemic events reported in BNT162b2 recipients than placebo recipients. As reported: "The reactions and events reported were generally mild to moderate, lasting 1 to 2 days. Injection-site pain was the most common local reaction, occurring in 71% to 74% of BNT162b2 recipients. Fatigue and headache were the most frequently reported systemic events. Lymphadenopathy was reported in 10 BNT162b2 recipients (0.9%) and 1 placebo recipient (0.1%). No myocarditis, pericarditis, hyper-sensitivity, or anaphylaxis in BNT162b2 recipients was reported. Four rashes in BNT162b2 recipients (observed on the arm, torso, face, or body, with no consistent pattern) were related to vaccination; the rashes were mild and self-limiting, and onset was typically 7 days or more after vaccination".

Observational studies (n=11)

1. Symptomatic laboratory confirmed COVID-19

Overall, two-dose BNT162b2 vaccine compared to placebo may result in a small reduction in COVID-19 infection (day 14-90), Odds Ratio (OR) 0.46 (95% CI 0.23 to 0.93), 4 studies, n = 3,096,179, low certainty evidence. That is an absolute effect of 137 fewer cases per 1,000 vaccines given (ranging from 15 fewer to 214 fewer cases). Vaccine effectiveness: 54% (95% confidence interval [CI] 7%-77%). Four studies; Cohen-Stavi *et al.* (22), Fleming-Dutra *et al.* (17), Fowlkes *et al.* (11) and Sacco *et al.* (23) had available event/total group data to evaluate this outcome. Figure 2 shows the forest plot for this comparison.

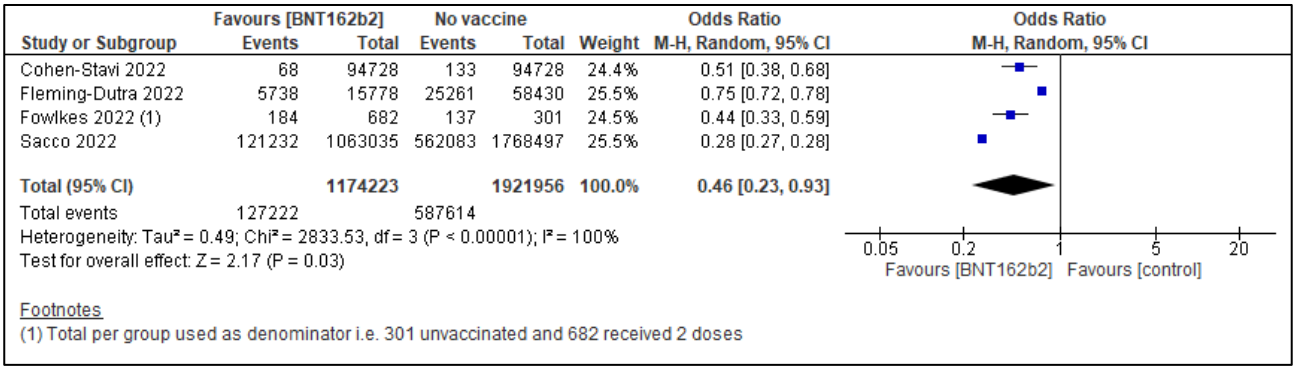

Figure 2: FOREST PLOT OF COMPARISON 2 BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES VS NO VACCINE: OBSERVATIONAL STUDIES, SYMPTOMATIC LABORATORY CONFIRMED COVID-19

Two studies data were not meta-analysed due to the methods of reporting of their data but found similar results. In a study by Amir *et al.* (21), of 691,591 children aged 5-10 years; the proportion of infection in the unvaccinated group was 1.45% (10,048/691,921) *vs*. 0.11% (743/691,921) in the internal control group and 0.08% (576/691,921) in the two-dose group. Unvaccinated children aged 5 to 10 years had a 2.4-fold higher risk of infection compared to the 2-dose BNT162b2 recipients (day 14 to 35 days after 2nd dose) RR 2.4 (95% CI, 2.2, 2.6). Another study by Dorabawila *et al.* (9) of 365,502 children aged 5-11 years who were fully vaccinated; the proportion of infections in vaccinated children was 4.42%

(16,146/365,502). From 13 December 2021 to 30 January 2022, vaccine effectiveness (VE) against cases declined from 68% (95% CI: 63%, 72%) to 12% (95% CI: 6%, 16%) in this age group.

2. Hospitalisation due to COVID-19

Two-dose BNT162b2 vaccine compared to placebo may result in small reduction in the number of hospitalisations (day 21-90) (Odds Ratio (OR) 0.36 (95% CI 0.19 to 0.69), 5 studies, n = 3,022,159, moderate certainty evidence). That is an absolute effect of 3 fewer hospitalization per 10,000 children who receive a vaccination (from 2 fewer to 4 fewer hospitalisations).

Vaccine effectiveness: 64% (95% CI 31%-81%). Five studies; Klein *et al.* (18), Price *et al.* (12), Shi *et al.* (20), Cohen-Stavi *et al.* (22) and Sacco *et al.* (23) had available event/total group data to evaluate this outcome. Figure 3 shows the forest plot for this comparison.

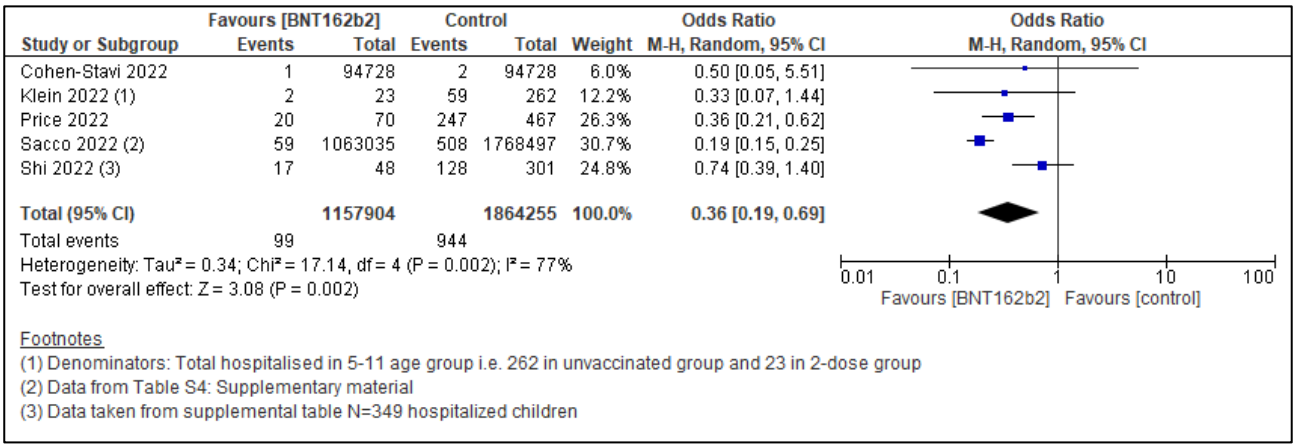

Figure 3: FOREST PLOT OF COMPARISON 2 BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES VS NO VACCINE: OBSERVATIONAL STUDIES, HOSPITALISATIONS

Two studies data were not meta-analysed due to the methods of reporting of their data but found similar results. In a study by Dorabawila *et al.* (9) of 365,502 children aged 5-11 years who were fully vaccinated; from 13 December 2021 to 30 January 2022, VE against hospitalisation declined from 100% (95% CI: -189%, 100%) to 48% (95% CI: -12%, 75%). The study by Simmons *et al.* (24) of 753 children aged 4-11 years who were diagnosed with COVID-19 in the study period, one vaccine dose was shown to be 32% effective against hospitalization (adjusted odds ratio [aOR] 0.68 [95% CI: 0.28-1.49]). In the two-dose vaccine group, <5 patients were hospitalized.

3. COVID-19 related death

Two-dose BNT162b2 vaccine compared to placebo may have little or no impact on mortality (day 84) (Odds Ratio (OR) 0.33 (95% CI 0.02 to 6.93), one study, n = 2,831,532, low certainty evidence). This outcome was reported in the Sacco *et al.* (22) study. There were two deaths in the unvaccinated group (0.0001%, n=1,768,497).

4. Serious adverse events

One study by Hause *et al.* (19) reported on adverse events, but there was no comparator group in this study. The results are described in detail in Table 4. The CDC reviewed adverse events following BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine administration reported to the Vaccine Adverse Event Reporting System (VAERS), a passive vaccine safety surveillance system, and adverse events and health impact assessments reported to “v-safe”, a voluntary smartphone-based safety surveillance system for

adverse events after COVID-19 vaccination, in United States (US) for the period 3 November – 19 December 2021. There were 2.4% (100/4,249) serious adverse events reported to VAERS. These included fever, vomiting, and increased troponin levels. As reported: "*There were 12 serious reports of seizure. Among 15 preliminary reports of myocarditis identified during the analytic period, 11 were verified (by provider interview or medical record review) and met the case definition for myocarditis. VAERS received two reports of death during the analytic period; both are under review. These deaths occurred in two females, aged 5 and 6 years, both of whom had complicated medical histories and were in fragile health before vaccination. None of the data suggested a causal association between death and vaccination*". This is considered very low certainty evidence.

5. Adverse events

   One study by Hause *et al.* (19) reported on adverse events, but there was no comparator group in this study. The results are described in detail in Table 4. There were 97.6% (4,149/4,249) VAERS reports for non-serious adverse events. The most reported non-serious events were related to vaccine administration (some without any adverse event), including no adverse event (n=1,157; 27.9%), product preparation issue (n=925; 22.3%), and incorrect dose administered (n=675; 16.3%). Other systemic effects included, vomiting, fever, headache, syncope, dizziness, fatigue, nausea and urticaria.

   In the period 3 November – 19 December 2021, v-safe enrolled 42,504 children aged 5-11 years who received BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine. Second dose data was available for 70.3% (n=29,899) children. Systemic reactions such as abdominal pain, myalgia, chills diarrhoea, fever, fatigue, headache, nausea and rash were more frequently reported during the week after administration of the second dose (n=12,223; 40.9%). This is also considered very low certainty evidence.

CONCLUSION

On balance the available evidence demonstrated a small absolute benefit in prevention of incident COVID-19 cases and hospitalisation if a two-dose BNT162b2 vaccine is offered to children aged 5-11 years, compared to placebo low certainty evidence). The availability and cost of the paediatric vaccine is yet to be confirmed. We did not find data on vaccine efficacy, safety and effectiveness in children aged 5-11 years with comorbidities, i.e., while there were no data to indicate vaccine effectiveness in this specific group of children, neither could we find evidence that the vaccine has no effect.

Triggers for updating the current review would be emergence of new data that will change the direction or strength and certainty of recommendations in terms of effectiveness and safety of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine.

REVIEWERS

Gregory Hussey, Rudzani Muloiwa, Andy Parrish, Andy Gray, Karen Cohen, SA GRADE: Tamara Kredo, Sumayyah Ebrahim, Ntombifuthi Blose, Natasha Gloeck, Ameer Hohlfeld, Yusentha Balakrishna.

DECLARATION OF INTERESTS

TK (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network. TK, SE, NB, AH and NG are partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies). SE (Cochrane South Africa, SAMRC and School of Clinical Medicine at University of KwaZulu-Natal (UKZN).

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Table 4: CHARACTERISTICS OF INCLUDED STUDIES

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
RANDOMISED CLINICAL TRIAL					
Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, *et al*. Evaluation of the BNT162b2 covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. 2022; 368:35-46. DOI: 10.1056/NEJMoa2116298	Setting and design Phase 1 dose-level identification study and Phase 2 – 3 safety, immunogenicity and efficacy double-blind randomised controlled trial across 81 sites in the United States, Spain, Finland and Poland Participants were randomly assigned (interactive web-based system) 2:1 ratio to receive 2 doses, 21 days apart. Dominant Variant(s) Delta Follow-up duration (days) 30-90 Funding Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04816643.	Sample size **Phase 2-3 trial** Healthy children aged 5 to 11 years (N= 2,285 were randomised, intervention n= 1,528, comparator n= 757) The number that received injections was n=2,268, 1,517 to intervention, 751 to comparator. One patient erroneously got vaccine instead of placebo, so numbers were 1,518 and 750. Immunobridging subset: **Aged 5 to 11 years** n=485 (intervention group n=322, comparator group n=163) **Comparison 16 to 25 years** N=350 (intervention (BNT162b2 30 mcg group) n=300, comparator group n=50) Inclusion criteria: • Children aged 5 to 11 years • No or stable pre-existing conditions	Intervention BNT162b2 vaccine (10µg), 2 doses, 21 days apart Control Saline placebo, 2 doses, 21 days apart	Primary outcome(s) • Safety/Adverse events • Percentage reporting local reactions within 7 days of dose • Percentage reporting systemic events within 7 days of dose • Percentage reporting adverse events up to 1 month after the last dose • Percentage reports serious adverse events up to 6 months after the last dose • Immunogenicity • Elicited by site investigational staff: in selected-dose participants, immunobridging of SARS-CoV-2 serum neutralizing titres after 2 doses in participants 5 to 11 years to the geometric mean of SARS-CoV-2 serum neutralizing titres in participants aged 16 to 25 years in the C4591001 study, 1 month after the second dose • Measured at the central laboratory: in selected-dose participants, the difference in percentages of participants with sero-response in participants aged 5 to 11 years and participants aged 16 to 25 years from Phase 2/3 of the C4591001	Overall: Some concerns of bias Randomisation: low risk of bias Deviations from the intervention: some risk of bias Missing outcome data: low risk of bias Measurement of the outcome: low risk of bias Selection of the reported results: low risk of bias

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Ethics and informed consent Approved	Exclusion criteria: • Children with an immunocompromising or immunodeficiency disorder, a history of MIS-C or those receiving immunosuppressive therapy (including cytotoxic agents and systemic glucocorticosteroids) • Previous receipt of COVID-19 preventative treatments		study, 1 month after the second dose • Vaccine Efficacy: Estimated efficacy of vaccine in preventing SARS-CoV-2 infection *Results* *Phase 1* • From March 24 through April 14, 2021, a total of 50 children 5 to 11 years of age were screened for inclusion at four U.S. sites, and 48 received escalating doses of the BNT162b2 vaccine. Half the children were male, 79% were White, 6% were Black, 10% were Asian, and 8% were Hispanic or Latinx. The mean age was 7.9 years (Table S2) • On the basis of reactogenicity and immunogenicity, a dose level of 10 µg was selected for further study *Phase 2–3* • Overall, 52% were male, 79% were White, 6% were Black, 6% were Asian, and 21% were Hispanic or Latinx (Table 1). The mean age was 8.2 years; 20% of children had coexisting conditions (including 12% with obesity and approximately 8% with asthma), and 9% were SARS-CoV-2–positive at baseline	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
				• Adverse events ○ Local reactions: Injection site pain 71% to 74% of BNT162b2 recipients ○ Severe injection-site pain 0.6% of BNT162b2 recipients, 0% placebo recipients ○ Systemic effects: After 1st or 2nd dose of intervention, fever 8.3%, severe fatigue 0.9%. headache 0.3%, chills 0.1%, muscle pain 0.1% ○ Adverse events (from dose 1 up to 1 month after dose 2): Intervention n=166 (10.9%), Comparator n=69 (9.2%) ○ Serious adverse events (from dose 1 through to study cut-off) Intervention n=1 (0.1%) Comparator n=1 (0.1%) No discontinuation or mortality ○ Immunogenicity ○ Geometric mean ratio of neutralizing titres for 10 µg of BNT162b2 in 5-to-11-year-olds to that for 30 µg of BNT162b2 in 16-to-25-year-olds 1 month after the second dose was1.04 (95% CI 0.93 to 1.18) ○ Efficacy (with or without evidence of previous infection) ○ Among participants without evidence of previous	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
				SARS-CoV-2 infection, there were three cases of COVID-19 (with onset 7 days or more after the second dose) among BNT162b2 recipients and 16 among placebo recipients; the observed vaccine efficacy was 90.7% (95% CI, 67.7 to 98.3). ○ Among all participants with data that could be evaluated, regardless of evidence of previous SARS-CoV-2 infection, no additional cases were reported; the observed vaccine efficacy was 90.7% (95% CI, 67.4% to 98.3%) ○ No cases of severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C) were reported	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
OBSERVATIONAL STUDIES					
Amir O, Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Ash N, Alroy-Preis S, Huppert A, Milo R. Initial protection against Omicron in children and adolescents by BNT162b2. MedRxiv. 2022 Jan 1.	Setting and Design A prospective cohort study was conducted on data obtained from the Israeli Ministry of Health database. Data was extracted on 1,444,406 children aged 5-10 years and adolescents aged 12-15 years during the Omicron-dominated (sub-lineage BA.1) variant of SARS-CoV-2 period from December 26, 2021, through January 8, 2022 was predominant (10 January 10 through to 2 March 2022). Covariates adjusted for were age, sex, socioeconomic status, calendar week and exposure Dominant Variant/s Omicron Follow-up duration (days) 14-35 Funding Not stated	Sample size N = 691,921 children aged 5-10 years Children in the 5-10 age group were divided into three cohorts: those unvaccinated, those who received the second dose of vaccine at least 14 days previously, and an internal control cohort of those who received their first dose 3-7 days previously Inclusion criteria "children (age 5-10) and adolescents (12-15) who were either vaccinated or took at least one test (PCR or state-regulated antigen) before December 1st, 2021." Exclusion criteria • 11-year-old age cohort, as data included age in years only, and vaccination eligibility dates differed between 11 and 12 year-olds. Thus, some of the '11-year-old group' turned	Intervention BNT162b2 (two doses) received at least 14 days before Control Unvaccinated and an internal control cohort of those who received their first dose 3-7 days previously	Primary outcome(s) Adjusted rates of confirmed infection following two doses of the BNT162b2 vaccine in children aged 5-10 up to 35 days from the 2nd dose *Results* • Proportion of infection in the unvaccinated group: 1.45% (10,048/691,921), in the internal control group 0.11% (743/691,921) and 0.08% (576/691,921) in the 2-dose group • In children aged 5 to 10 years, being unvaccinated showed RR 2.4 (95% CI, 2.2, 2.6) of infection compared to BNT162b2 14 to 35 days after 2nd dose • In children aged 5 to 10 years, BNT162b2 3 to 7 days after 1st dose showed RR 2.3 (95% CI, 2, 2.5) of infection compared to BNT162b2 14 to 35 days after 2nd dose	ROBINS-I: Moderate Risk of bias Downgraded due to study design and accounting for non-immune period and positive Study design – moderate risk – data-linkage. The authors specified the non-immune period and checked for an effect but there WAS an effect (e.g., evidence of a reduction in an outcome of interest when there should not have been) = evidence of residual bias

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Ethics and Informed Consent The study was approved by the Institutional Review Board of the Sheba Medical Center.	12 before or during the study period • Persons who had documented positive PCR or state-regulated antigen results prior to the study period • Persons who had stayed abroad during the entire study period, or had received a vaccine different from BNT162b2 before the end of the study period			
Dorabawila V, Hoefer D, Bauer UE, Bassett M, Lutterloh E, Rosenberg E. Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the Emergence of the Omicron Variant. MedRxiv. 2022 Jan 1.	Setting and Design Data-linkage study in New York state, U.S; that included 1,539,762 person days of children aged 5-11 years and 151,005 person days of children aged 12-17 years, to estimate BNT162b2 vaccine effectiveness against COVID cases and hospitalizations during December, 2021- Jan, 2022; time and setting for VOC Omicron. Dominant Variant/s Omicron	Sample size N= 365,502 children aged 5-11 years were fully vaccinated Inclusion criteria Fully vaccinated children (defined as series completion + 14 days) Exclusion criteria Not stated	Intervention BNT162b2 (two doses) received at least 14 days before Control Unvaccinated children	Primary outcome(s) • Laboratory confirmed COVID-19 cases, defined as positive Nucleic Acid Amplification Test (NAAT) or antigen results • New COVID-19 hospital admissions *Results* • Proportion of infections in vaccinated children: 4.42% (16,146/365,502) and proportion of hospitalizations 0.01% (32/365,502) • From 13 December 2021 to 30 January 2022, among 365,502 children 5-11 years, vaccine effectiveness (VE) against cases declined from 68% (95% CI: 63%, 72%) to 12% (95% CI: 6%, 16%)	ROBINS-I: Serious risk of bias Downgraded as there was no adjustment for comorbidities, previously infected were not excluded

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Follow-up duration (days) 48 Funding The study did not receive any external funding Ethics and Informed Consent New York State Department of Health Institutional Review Board (IRB) determined this is a surveillance activity necessary for public health work, and therefore waived the need for IRB review.			• VE against hospitalization declined from 100% (95% CI: -189%, 100%) to 48% (95% CI: -12%, 75%) for those 5-11 years • For children aged 5-11 years, VE against cases declined from 65% (95% CI: 62%, 68%) to 12% (95% CI: 8%, 16%) by 28-34 days	
Fleming-Dutra KE, Britton A, Shang N, Derado G, Link-Gelles R, Accorsi EK, Smith ZR, Miller J, Verani JR, Schrag SJ. Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance. JAMA. 2022 May 13.	Setting and Design Test-negative case-control design in 49 states of the U.S among persons aged 5–15 years with COVID-19–like illness during Dec 26, 2021– Feb 21, 2022, including 74,208 tests from children 5 to 11 years of age and 47,744 tests from adolescents 12 to 15 years of age Dominant Variant/s Omicron	Sample size N= 74,208 children aged 5-11 years in the analytic data set: 58,430 unvaccinated and 15,778 vaccinated with 2 doses A test-negative, case-control analysis was conducted to estimate BNT162b2 VE against symptomatic infection. This analysis used rapid and laboratory based NAATs from children and adolescents aged 5 to 15 years reporting 1 or more	Intervention 2 BNT162b2 doses for children 5 to 11 years old Control Unvaccinated children "Cases and controls were considered unvaccinated if tests were from children and adolescents who received no COVID-19 vaccine before the SARS-CoV-2 test Cases and controls were considered vaccinated with 2 or	Primary outcome(s) Symptomatic SARS-CoV-2 infection determined by positive NAAT result in a person reporting COVID-19–like illness. The adjusted odds ratio (OR) for the association of prior vaccination and symptomatic SARS-CoV-2 infection was used to estimate VE: VE = (1 − OR) × 100%. *Results* • Among unvaccinated children, the proportion of positive cases was 43.23% (25,261/58,430) and among fully vaccinated children 36.37% (5,738/15,778)	ROBINS-I: Serious risk of bias Downgraded because vaccination status was assessed by questionnaire without confirmation by an additional method

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Follow-up duration (days) 90 Funding "Funding for the Increasing Community Access to Testing (ICATT) testing platform is provided by the US Department of Health and Human Services. Funding for this analysis was provided by the Centers for Disease Control and Prevention (CDC). *Role of the Funder/Sponsor*: The CDC was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. The CDC controlled publication decisions".	symptoms tested at the pharmacy chain from December 26, 2021, to February 21, 2022 (data downloaded February 22, 2022). The unit of analysis was tests because unique identifiers for individuals were not available. Inclusion criteria Cases were defined as those with positive SARS-CoV-2 NAAT results, and controls were those with negative NAAT results Exclusion criteria • Indeterminate test results • Missing assay type • Reported an immunocompromising condition (because COVID-19 vaccine recommendations differ for these individuals) • Unknown vaccination status • Vaccine product other than BNT162b2 • Receipt of 1 vaccine dose or receipt of the second or third dose	3 doses if tests were from children and adolescents who reported receiving the second or third dose 2 weeks or more before their SARS-CoV-2 test".	• A total of 30,999 test-positive cases and 43,209 test-negative controls were included from children 5 to 11 years of age • The median age among those with included tests was 10 years (IQR, 7-13); 61,189 (50.2%) were female, 75,758 (70.1%) were White, and 29,034 (25.7%) were Hispanic/Latino • At 2 to 4 weeks after dose 2, among children, the adjusted OR was 0.40 (95% CI, 0.35-0.45; estimated VE, 60.1% [95% CI, 54.7%-64.8%]) • During month 2 after dose 2, among children, the OR was 0.71 (95% CI, 0.67-0.76; estimated VE, 28.9% [95% CI, 24.5%-33.1%])	

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	Ethics and Informed Consent "This activity was determined to be public health surveillance as defined in 45 CFR §46.102(l) (US Department of Health and Human Services [HHS], Title 45 Code of Federal Regulations, §46 Protection of Human Subjects); thus, it was not submitted for institutional review board approval and informed consent was not needed."	within 2 weeks of the test date • Vaccination before the month of the recommendation by the Advisory Committee on Immunization Practices (for children 5-11 years, November 2021; for adolescents 12-15 years, May 2021 for the primary series and January 2022 for the booster dose) • Receipt of more than the authorized number of doses for non-immunocompromised individuals • Receipt of a third dose less than 4 months after the second dose (for adolescents 12-15 years) or inconsistent vaccination information (e.g., reported vaccine receipt but missing dose dates, reported no vaccine receipt but doses reported).			

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
Fowlkes AL, Yoon SK, Lutrick K, Gwynn L, Burns J, Grant L, Phillips AL, Ellingson K, Ferraris MV, LeClair LB, Mathenge C. Effectiveness of 2-dose BNT162b2 (Pfizer BioNTech) mRNA vaccine in preventing SARS-CoV-2 Infection among children aged 5–11 years and adolescents aged 12–15 years—PROTECT Cohort, July 2021–February 2022. Morbidity and Mortality Weekly Report. 2022 Mar 18; 71(11):422.	Setting and Design Prospective cohort in four states of US (Arizona, Florida, Texas, and Utah), of 1,364 participants between Jul 2021–Feb 2022; the PROTECT cohort included 1,052 children aged 5–11 years and 312 adolescents aged 12–15 years that were tested weekly for SARS-CoV-2; viral whole genome sequencing was assessed Covariates tested: Sociodemographic characteristics, health information, frequency of social contact, mask use, location, and local virus circulation Dominant Variant/s Omicron Follow-up duration (days) 82 Funding None stated Ethics and Informed Consent	Sample size N= 1,052 children aged 5-11 years 301 unvaccinated and 751 vaccinated with ≥1 vaccine dose (682 received 2 doses and 69 received 1 dose) Inclusion criteria Children aged <18 years Exclusion criteria • Children and adolescents aged 5–15 years with documented SARS-CoV-2 infection before enrollment or start of follow-up • Children who failed to complete weekly nasal swabs or were not in surveillance during the variant-specific follow-up period • Those who received a vaccine product other than Pfizer-BioNTech or had incomplete vaccination information	Intervention 2 BNT162b2 doses for children 5 to 11 years old Control Unvaccinated children	Primary outcome(s) Symptomatic and asymptomatic SARS-CoV-2 infections *Results* • The study sample comprised 1,364 participants, including 1,052 (77%) children aged 5–11 years and 312 (23%) adolescents aged 12–15 years • Overall, 76% of participants lived in Arizona, 52% were female, 76% were White, 34% were Hispanic, and 10% had at least one chronic medical condition • Of 381 SARS-CoV-2 infections among children aged 5–11 years, 352 (93%) were Omicron infections • Proportion of children infected per group: 2 dose recipients (28.8%, 184/640) and unvaccinated (40.8%, 137/336)* • BNT162b2 showed after 2nd dose VE 31% (95% CI, 9 to 48) at 14-82 days, in children age 5 to 11 years against infection *"Vaccination status varied with time, therefore, contributing participants in vaccination categories do not equal the number of participants in the study because participants could contribute to	ROBINS-I: Moderate risk of bias Downgraded due to study design, and because parents or legal guardians provided the participants' vaccination history confirmed by immunization registries

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	"This study was reviewed by CDC and approved by the institutional review boards at participating sites or under a reliance agreement with Abt Associates institutional review board and was conducted consistent with applicable federal law and CDC policy."			more than one vaccination category."	
Hause AM, Baggs J, Marquez P, Myers TR, Gee J, Su JR, Zhang B, Thompson D, Shimabukuro TT, Shay DK. COVID-19 vaccine safety in children aged 5–11 years—United States, November 3–December 19, 2021. Morbidity and Mortality Weekly Report. 2021 Dec 12; 70(51-52):1755.	Setting and Design Data linkage study. The CDC reviewed adverse events after receipt of Pfizer-BioNTech COVID-19 vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), a passive vaccine safety surveillance system co-managed by CDC and FDA, and adverse events and health impact assessments reported to v-safe, a voluntary smartphone-based safety surveillance system for adverse events after COVID-19 vaccination, during November 3–December 19, 2021	Sample size N= 4,249 reports of adverse events: VAERS N= 29,899 children with 2nd dose information for v-safe Inclusion criteria Children aged 5-11 years who received at least 1-dose of Pfizer-BioNTech COVID-19 vaccine Exclusion criteria Not stated	Intervention 2 BNT162b2 doses for children 5 to 11 years old Control Nil	Primary outcome(s) • Adverse events • Health impact assessments *Results* • VAERS received and processed 4,249 reports of adverse events • The median age was 8 years, and 1,896 (44.6%) reports were for males • Overall, 4,149 (97.6%) VAERS reports were for non-serious events, and 100 (2.4%) were for serious events • The most commonly reported non-serious events were related to vaccine administration (some without any adverse event), including no adverse event (n=1,157; 27.9%), product preparation issue (n=925;	ROBINS-I: Serious risk of bias Downgraded due to study design, no information available for many domains Cohort with any concerns = serious (passive surveillance, subject to reporting biases and underreporting)

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Dominant Variant/s Omicron Follow-up duration (days) 82 Funding None stated Ethics and Informed Consent "This study was reviewed by CDC and approved by the institutional review boards at participating sites or under a reliance agreement with Abt Associates institutional review board and was conducted consistent with applicable federal law and CDC policy."			22.3%), and incorrect dose administered (n=675; 16.3%) • The most commonly reported conditions and diagnostic findings among the 100 reports of serious events were fever (n=29; 29.0%), vomiting (n=21; 21.0%), and increased troponin (n=15; 15.0% • There were 12 reports of seizure • Among 15 preliminary reports of myocarditis identified during the analytic period, 11 were verified (by provider interview or medical record review) and met the case definition for myocarditis • VAERS received two reports of death during the analytic period; both are under review. These deaths occurred in two females, aged 5 and 6 years, both of whom had complicated medical histories and were in fragile health before vaccination. None of the data suggested a causal association between death and vaccination • v-safe enrolled 42,504 children aged 5–11 years who received Pfizer-BioNTech COVID-19 vaccine; second dose information was available for 29,899 (70.3%) of these children. During the week after receipt of dose 1, local	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
				(n=23,290; 54.8%) and systemic (n=14,734; 34.7%) reactions were frequently reported; systemic reactions were more frequently reported during the week after dose 2 (n=12,223; 40.9%) than dose 1 • The most frequently reported reactions after either dose were injection site pain, fatigue, and headache. Fever was more frequently reported after dose 2 (n=4,001; 13.4%) than dose 1 (n=3,350; 7.9%) • Approximately 5.1% of parents reported that their child was unable to perform normal daily activities on the day after receipt of dose 1, and 7.4% after receipt of dose 2.	
Cohen-Stavi CJ, Magen O, Barda N, Yaron S, Peretz A, Netzer D, Giaquinto C, Judd A, Leibovici L, Hernán MA, Lipsitch M. BNT162b2 Vaccine Effectiveness against Omicron in Children 5 to 11 Years of Age. New England Journal of Medicine. 2022 Jun 29.	Setting and design Data linkage study. An observational cohort study was conducted emulating a target trial using observational data from Clalit Health Services (CHS), the largest integrated payer–provider health care Organisation in Israel. Children aged 5 to 11 years of age who were vaccinated on or after November 23, 2021, when vaccination	Sample size N= 189,456 After matching, the final study population comprised 94,728 vaccinated children and 94,728 unvaccinated matched controls "A total of 156,898 children covered by CHS were vaccinated during the study period; of these children, 136,127 were eligible for the study. Of 136,127 eligible children who had been vaccinated, 108,904 (80%) were successfully	Intervention 2 BNT162b2 doses for children 5 to 11 years old Control Unvaccinated children	Primary outcome(s) • Documented SARS-CoV-2 infection: A PCR confirmed infection • Symptomatic Covid-19: ○ A PCR-confirmed infection with report of symptoms during the PCR referral/during the follow-up in the community setting/COVID-19 related hospitalization. ○ Existing symptoms were considered when the physician or nurse checked the "symptomatic" option in the EHR, or when the following	ROBINS-I: Serious risk of bias Downgraded because authors did not reported methods for confirming vaccination but it is highly suspected that they used a linked database

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	became available for this age group in Israel were enrolled. Each vaccinated child was matched with an unvaccinated control on the date of vaccination (the recruitment date). The study period ended on January 7, 2022, when a new testing policy was implemented in Israel. <u>Dominant Variant/s</u> Omicron <u>Follow-up duration (days)</u> 42 <u>Funding</u> "Supported by the European Union through the VERDI project (Grant number, 101045989), the U.K. Medical Research Council (grant number, MC_UU_00004/03), and the Morris-Singer Fund. The funding institutions did not dictate the design of the study, have access to the data, or influence the decision to submit the	matched and included in at least one of the study groups: 94,728 were included in the vaccinated group, of whom 79,448 were originally included as members in the vaccinated group and 15,280 were initially matched as members of the unvaccinated group and then were re-matched as members of the vaccinated group after receiving their first dose. On each day of recruitment, all newly vaccinated children who met the inclusion criteria were matched one to one with eligible unvaccinated children on the basis of age, sex, population sector, residential area, number of influenza vaccines received in the past 5 years, overweight status, and number of diagnosis codes in the patient's medical record that were considered by the physician to represent chronic conditions." <u>Inclusion criteria</u>		specific symptoms were recorded: Fever or chills, cough, shortness of breath or difficulty breathing, sore throat, headache, weakness, congestion or runny nose, myalgia, nausea or vomiting, diarrhea, abdominal pain, loss of taste or smell, inability to eat or drink *Results* • The median age of the children in the study population was 8 years (interquartile range, 7 to 10), and in each study group, 49% (66,164/136,127) of the children were female and 17% (15,802/94,728) were overweight or obese per group • Other co-morbidities reported were cancer, chronic kidney disease, heart disease, cerebrovascular disease, neurological disease, liver disease, asthma, diabetes mellitus, immunosuppression, hypertension and solid-organ transplantation • Vaccine effectiveness against documented infection was 17% (95% CI, 7 to 25) at 14 to 27 days after the first dose and 51% (95% CI, 39 to 61) at 7 to 21 days after the second dose • Vaccine effectiveness against symptomatic Covid-19 was 18% (95% CI, −2 to 34) at 14 to 27 days after the first dose and 48%	

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	manuscript for publication". <u>Ethics and Informed Consent</u> "This study was approved by the institutional review board at CHS, and an exemption from the requirement for informed consent from the participants was granted".	• Children aged 5 to 11 years of age at the time of recruitment • Had at least 12 months of continuous membership in CHS before recruitment • Had no previous PCR, serology, or antigen test that was positive for SARS-CoV-2 • Had a valid residence location and assignment to a population sector • Were not homebound because of medical reasons • Had no interaction with the health care system (physician appointment, hospitalization, or laboratory testing) in the 3 days preceding the recruitment date, since such interaction would potentially be an indication of a developing case of symptomatic Covid-19. <u>Exclusion criteria</u> Not stated		(95% CI, 29 to 63) at 7 to 21 days after the second dose • The between-group risk differences after the second vaccine dose (D7-21) were estimated to be 1,905 events per 100,000 persons (95% CI, 1,294 to 2,440) for documented infections and 599 events per 100,000 persons (95% CI, 296 to 897) for symptomatic Covid-19.	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
Klein NP, Stockwell MS, Demarco M, Gaglani M, Kharbanda AB, Irving SA, *et al*. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated emergency department and urgent care encounters and hospitalizations among non-immunocompromised children and adolescents age 5 to 17 years – VISION network, 10 states, April 2021 – January 2022. MMWR. 2022; 71(9):352-8. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7109e3.htm	Setting and design: A case-control test-negative design of 39,217 emergency department (ED) and urgent care (UC) encounters and 1699 hospitalizations between children and adolescents aged 5 to 17 years with COVID-19 like illness, across ten states in the United States (US) between 9 April 2021 to 29 January 2022, comparing the odds of a positive SARS-CoV-2 test result between vaccinated* and unvaccinated patients using multivariable logistic regression models Dominant variant(s) Omicron and Delta Follow-up duration (days) 14-67	Sample size N=9,181 (Unvaccinated n=8,599; two doses Pfizer-BioNTech (14 to 149 days earlier) n=582) Inclusion criteria Children aged 5 to 11 years with COVID-19 like illness presenting to emergency department (ED) or urgent care (UC) Exclusion criteria: • Vaccinated before CDC recommendation date for their age group • Received a 3rd dose before booster doses were recommended for their age group • Received a booster dose <5 months after dose 2 • Received 1 or >3 doses of the vaccine • If <14 days had elapsed since receipt of dose 2 or <7 days since dose 3 • Patients who were likely immunocompromised on diagnostic codes	Intervention Children vaccinated with 2 doses of Pfizer-BioNTech vaccine 10 µg Comparator Unvaccinated children	Primary outcome(s) Estimated vaccine effectiveness (VE) in ED/UC encounters and hospitalisation *Results (Vaccine effectiveness)* • ED/UC encounters during Delta or Omicron predominance Unvaccinated n=8,599, SARS-CoV-2 test positive n=2,652 (30.8%) Two doses n=582, SARS-CoV-2 test positive n=124 (21.3%). VE 46% (95% CI 24% to 61%) • ED/UC encounters during Omicron predominance Unvaccinated n=5,938, SARS-CoV-2 test positive n=2,409 (40.6%) Two doses n=468, SARS-CoV-2 test positive n=118 (24.3%). VE 51% (95% CI 30% to 65%) • Hospitalised during Delta or Omicron predominance Unvaccinated n=262, SARS-CoV-2 test positive n= 59 (22.5%) Two doses n=23, SARS-CoV-2 test positive n=2 (8.7%). VE 74% (95% CI -35% to 95%)	ROBINS-I: Serious risk of bias Downgraded because the index date for each medical event was defined as the date of the most recent positive or negative result prior to the medical event (14 days before admission) OR the date of the medical event

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Funding: CDC, the VISION Network includes Baylor Scott & White Health (Texas), Columbia University Irving Medical Center (New York), HealthPartners (Minnesota and Wisconsin), Intermountain Healthcare (Utah), Kaiser Permanente Northern California (California), Kaiser Permanente Northwest (Oregon and Washington), Regenstrief Institute (Indiana), and University of Colorado (Colorado) Ethics: reviewed and approved by institutional review boards at participating sites or under agreement with the Westat, Inc, institutional review board. *Vaccinated defined as received at least 2 doses ≥ 14 days earlier or 3 doses ≥ 7 days earlier)				

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
Price AM, Olson SM, Newhams MM, Halasa NB, Boom JA, Sahni LC, *et al*. BNT162b2 protection against the Omicron variant in children and adolescents. N Engl J Med. 2022; 386 (2):1899:090. DOI: 10.1056/NEJMoa2202826	Setting and Design A case-control, test-negative design at 31 hospitals across 23 states in the US between 1 July 2021 and 17 February 2022. Vaccine effectiveness estimated by comparing the odds of antecedent vaccination among hospitalized patients (aged 5 to 11 and 12 to 18 years who had laboratory confirmed COVID-19 and control patients without COVID-19. Case patients were identified through review of hospital admission logs or electronic medical records. Matched control patients were selected from among the patients hospitalized at the same institution as case patient, were in the same age category as the case patient and were hospitalized within 4 weeks before or after date of admission for the case patient.	Sample size N=537 (cases n=267; controls n=270) Inclusion criteria • Patients hospitalized with COVID-19 as the primary reason for admission or with a clinical syndrome consistent with acute COVID-19 (one or more: fever, cough, shortness of breath, loss of smell and or taste, gastrointestinal symptoms, receipt of respiratory support or new pulmonary findings on chest x-ray or other imaging) • All cases: positive SARS-CoV-2 reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or antigen test result within 10 days after symptoms onset or 72 hours of hospital admission • Control: hospitalized with a negative SARS-CoV-2 RT-PCR or antigen test, with or	Intervention Vaccinated with BNT162b2, 10µg, 2 doses, at least 14 days before onset of illness Control Unvaccinated	Primary outcome(s) • Vaccine effectiveness against COVID-19–associated hospitalization • Vaccine effectiveness against a gradient of disease severity *Results* • Among case patients in this age group, the median age was 8 years, and 82% had at least one underlying health condition • Among the control patients, the median age was 8 years, and 73% had at least one underlying condition • Among the 267 case patients, 20 (7%) were fully vaccinated and 247 (93%) were unvaccinated (Table 1) • Vaccine effectiveness in children 5 to 11 years against hospitalisation (Omicron predominance) Among 267 case patients: 20 (7%) were fully vaccinated and 247 (93%) were unvaccinated. VE 68% (95% CI 42% to 82%) • Vaccine effectiveness in children 5 to 11 years against a gradient of disease severity Not assessed, sample size limitations	ROBINS-I: Serious Risk of bias Downgraded to serious as the authors didn't excluded or analyse separately participants with prior COVID-19 infection (concerns about infectivity and risk-taking/health-seeking behavior)

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Dominant Variant(s) Omicron-predominant period Follow-up duration (days) 14-88 Funding Funded by the Centers for Disease Control and Prevention (CDC) Ethics and informed consent "The surveillance protocol was reviewed by the Centers for Disease Control and Prevention (CDC) and other participating institutions and was determined to be public health surveillance and not subject to informed-consent requirements; this review was conducted in accordance with applicable federal laws and CDC policy".	without COVID-19-associated symptoms. Exclusion criteria • SARS-CoV-2 test more than 10 days after illness onset or more than 72 hours after hospital admission • Partiallv vaccinated patients • Vaccinated 0 to 13 days prior to symptom onset • Vaccination status unknown • Received mRNA-1273 (Moderna) or Ad26.COV2.S (Johnson & Johnson) vaccines • Patients admitted for reasons not related to COVID-19 who had positive SARS-CoV-2 test during admission • Patients who had received a 3rd dose of BNT162b2 as sample size was not sufficient for an evaluation of booster protection.			

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
Shi DS, Whitaker M, Marks KJ, Anglin O, Milucky J, Patel K, *et al*. Hospitalizations of children aged 5 – 11 years with laboratory-confirmed COVID-19 – COVID-NET, 14 states, March 2020 – February 2022. MMWR. 2022; 71(16):574:81. DOI: 10.15585/mmwr.mm7116e1	Setting and Design Data- linkage study - hospitalisation rates in children aged 5 to 11 years between 1 March 2020 and 28 February 2022. Data extracted from the COVID-19-Associated Hospital Surveillance Network (COVID-NET) to describe characteristics of COVID-19 associated hospitalization among children aged 5 to 11 years throughout the pandemic, with focus on the period of early Omicron predominance (19 December 2021 to 28 February 2022). Dominant Variant(s) Pre-Delta to Delta to Omicron Follow-up duration (days) 60 Funding Not reported	Sample size N=1475 (pre-Delta n=596, Delta predominant n=482, Omicron predominant **n=397**) In December 2021 to February 2022, due to a surge in hospitalisations, some sites examined clinical data on a representative sample of hospitalized children. The sample included 1,252 (86%) of 1,475 children with positive SARS-CoV-2 tests, with complete clinical data available for 595 of 596 (99.8%), 438 of 468 (93.6) and 219 of 225 (97.3%) Inclusion criteria • 5 to 11 years of age • COVID-19 associated hospitalization Exclusion criteria Not stated	Intervention Pfizer BNT162b2 vaccine, 10 µg, 2 doses, last dose more than 14 days prior to positive SARS-CoV-2 test Control Not vaccinated Definitions Vaccinated children aged 5–11 years were defined as those who had received the final dose in their primary series ≥14 days before receiving a positive SARS-CoV-2 test result associated with their hospitalization. Children who had received only 1 vaccine dose ≥14 days before the SARS-CoV-2 test date or had received a single dose of vaccine <14 days before the positive SARS-CoV-2 test results were considered partially vaccinated; these children were grouped with unvaccinated children	Primary outcome(s) • Hospitalisation rates in the pre-Delta, Delta predominant and Omicron predominant waves • Length of hospital stay • Requirement of ICU admission • Non-invasive or invasive ventilation *Results (Omicron predominant period)* • Median age was 8 years, interquartile range (IQR): 6-10 years • 218 males (54.9%) and 179 females (45.1%) • Total number of Hospitalized children n=397 Unvaccinated 87% No underlying medical conditions (30%) Admitted to ICU 19% • In a subset of patients from 11 states (19 Dec 2021-28 Feb 2022)**: N=349, vaccinated n=301, unvaccinated n=48). Of these, primary reason for admission likely COVID-19 related: Unvaccinated n=128/301 (42.5%). Vaccinated n=17/48 (35.4%) • Cumulative hospitalization rate	ROBINS-I: Serious risk of bias Downgraded due to study design, calendar time not adjusted for (accounting for calendar time reduces bias due to differences in vaccine accessibility and risk of exposure over time), previously infected not excluded

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Ethics and informed consent "This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy".			Unvaccinated 19.1 per 100,000 population Vaccinated 9.2 per 100,000 population • Length of hospital stay Unvaccinated median=3 days (IQR) 1-5 days, vaccinated median=2 (IQR 1-4 days) (p=0.36) • ICU admission Unvaccinated n=36/301 (11.96%), vaccinated n=4/48 (8.33%), p=0.57 • Bilevel positive airway pressure (BiPAP) or Continuous positive airway pressure (CPAP) Unvaccinated n=11/301 (3.65%), Vaccinated n=0 • High flow nasal cannula Unvaccinated n=8/301 (2.66%), Vaccinated n=0 • Invasive mechanical ventilation Unvaccinated n=10/301 (3.32%), Vaccinated n=0 • In hospital death n=0 in both vaccinated and unvaccinated groups **Supplemental table data	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
Simmons AE, Amoako A, Grima AA, Murison KR, Tuite AR, Fisman DN. Vaccine Effectiveness Against Hospitalization Among Adolescent and Pediatric SARS-CoV-2 Cases in Ontario, Canada [Internet]. MedRxiv [Preprint]. 2022 [cited 29 Jun 2022]. DOI: https://doi.org/10.1101/2022.03.24.22272919	Setting and Design Age and time-matched nested case-control design between 28 May 2021 and 10 January 2022 in 1,441 paediatric and adolescent patients aged 4 to 17 years old. Confirmed SARS-CoV-2 cases identified through Ontario's Public Health Case and Contact Management Solution (CCM). Vaccine information was identified from the Ontario COVaxON database. These databases were linked through a "pseudo-health card number" identifier that is present in both datasets. For each hospitalized patient, 10 non-hospitalized patients were matched by age and case-onset date using the near-neighbor matching procedure to improve precision. Dominant Variant(s) Delta to Omicron	Sample size N=1,441 children aged 4-17 years: Hospitalised SARS-CoV-2 cases n=131. Non-hospitalised SARS-CoV-2 cases n=1,310 **Children aged 4-11 n=753** Inclusion criteria • Age 4 to 17 years old • SARS-CoV-2 positive test Exclusion criteria SARS-CoV-2 cases where the patient had had three vaccine doses as the study population was not eligible for a 3rd dose at the time of the study.	Intervention Pfizer BNT162b2 vaccine, 10 µg, 2 doses, last dose more than 14 days prior to positive SARS-CoV-2 test Control Not vaccinated Definitions • One dose vaccinated: "14 or more days after the first vaccine dose was administered" • Two dose vaccinated: "14 or more days after the second vaccine dose was administered" • Unvaccinated: not vaccinated or "during the first 13 days after the date that the first vaccine was administered"	Primary outcome(s) Hospitalization due to SARS-CoV-2 *Results* *Whole cohort* • One vaccine dose was shown to be 37% effective against hospitalization among SARS-CoV-2 cases (adjusted odds ratio [aOR] = 0.63 [95% CI: 0.33, 1.13]) • In contrast, two doses were 59% (aOR = 0.41 [95% CI: 0.21, 0.77]) effective at preventing hospitalization among SARS-CoV-2 cases *Ages 4 to 11 (n=753)* • Unvaccinated: aOR 1.00 (95% CI *reference category)* • One dose: aOR 0.68 (95% CI 0.28 to 1.49) • Two doses: 5 SARS-CoV-2 cases occurred in this patient group that were vaccinated with 2 doses, and <5 patients were hospitalized	ROBINS-I: Serious risk of bias Downgraded because there is no clarity about inclusion of participants with prior COVID-19 infection

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
	Follow-up duration (days) Not stated Funding "AES is supported by the University of Toronto Connaught International Doctoral Scholarship. This research is supported by a grant to DNF from the Canadian Institutes for Health Research (2019 COVID-19 rapid researching funding OV4-170360)". Ethics and informed consent Ethics approval received from the Research Ethics Board of the University of Toronto (#00031358)				
Sacco C, Manso M Del, Mateo-Urdiales A, Rota MC, Petrone D, Riccardo F, *et al*. Articles Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5-11 years in Italy: a retrospective analysis of	Setting and Design Data linkage study; a retrospective population analysis, that assessed vaccine effectiveness against SARS-CoV-2 infection and severe COVID-19, defined as an infection leading to hospitalisation or death, by linking the national	Sample size N=2,965,918 (n=1,063,035 two doses, n= 134,386 one dose, and n= 1,768,497 unvaccinated) Inclusion criteria Italian children aged 5–11 years without a previous	Intervention Partial – 1 dose BNT162b2 Fully vaccinated – 2 doses BNT162b2 Control Unvaccinated	Primary outcome(s) • SARS-CoV-2 infections (the incidence of notified SARS-CoV-2 infection (asymptomatic or symptomatic) • Severe COVID-19 (defined as a SARS-CoV-2 infection resulting in hospital admission or death within 28 days) *Results* adjusted for age and sex*	Risk of Bias (ROBINS-I): Moderate risk of bias Downgraded due to study design

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
January-April, 2022. Lancet 2022;400:97–103. https://doi.org/10.1016/S0140-6736(22)01185-0.	COVID-19 surveillance system and the national vaccination registry. <u>Dominant variant</u> Omicron <u>Follow-up duration (days)</u> 84 <u>Funding</u> "No funding source for this study." <u>Ethic and Informed Consent</u> Not reported	diagnosis of infection were eligible <u>Exclusion criteria</u> • Children with inconsistent vaccination data • Diagnosed with SARS-CoV-2 infection before the start date of the study or without information on the municipality of residence		○ N=1,063,035 (35.8%) children had completed the primary cycle of two doses, n= 134,386 (4.5%) had received one dose, and n= 1,768,497 (59.6%) were unvaccinated • Proportion of children infected per group: 2 dose recipients (11.4%, 121,232/1,063,035); partly vaccinated (62.1%, 83,441/134,386) and unvaccinated (31.8%, 562,083/336) IRR: Infection • Unvaccinated group (426.9 per 100 000 person-days [95% CI 425.8–428.1]) • Fully vaccinated group 234.5 per 100 000 person-days [233.2–235.8] Overall, 644 children had severe COVID-19 and required hospitalisation (15 of whom were admitted to an ICU; two died; all were unvaccinated) IRR: Severe COVID-19 (hosp. or death) • Unvaccinated group (0.6 per 100,000 person-days) • Fully vaccinated group (0.3 per 100,000 person-days	

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS	RISK OF BIAS
				No age gradient was observed with children aged 5 years having a similar rate (0.40 per 100,000 person-days) to those aged 11 years (0.41 per 100,000 person-days. *VE data* Adjusted vaccine effectiveness against SARS-CoV-2 infection was higher in the fully vaccinated group (29.4% [95% CI 28.5–30.2]) than in those in the partly vaccinated group (27.4% [26.4–28.4). The adjusted vaccine effectiveness against severe COVID-19 was 38.1% (95% CI 20.9–51.5) in the partly vaccinated group and 41.1% (22.2–55.4) in the fully vaccinated group. Vaccine effectiveness against SARS-CoV-2 infection peaked at 0–14 days after full vaccination (38.7% [95% CI 37.7–39.7]); vaccine effectiveness then declined to 21·2% (19.7–22.7) at 43–84 days after the second dose.	

Table 5: CHARACTERISTICS OF PLANNED AND ONGOING STUDIES

TREATMENT (PER ARM)	SAMPLE SIZE	SEVERITY AT ENROLLMENT	SPONSOR	REGISTRATION NUMBER	FULL-TEXT LINK	SOURCE
(1) Bnt162b2 vs (2) Placebo	290	Healthy volunteers	BioNTech SE	EUCTR2020-005442-42-PL	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-005442-42/PL	COVID-nma website (www.covid-nma.com) 5 July 2022
Bio, NTech S. E. A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of an RNA Vaccine Candidate Against COVID-19 in Healthy Children <12 Years of Age (includes phase 2b)	15350	Healthy children and young adults	BioNTech SE	NCT04816643	https://clinicaltrials.gov/ct2/show/NCT04816643	Cochrane COVID-19 register (https://covid-19.cochrane.org/) 28 June 2022
National Vaccine, Institute. Safety and Immunogenicity of SARS-CoV-2 mRNA vaccine platform in Thai children aged 5-11 years (COVID19)	400	Good Health	National Vaccine Institute	TCTR20220125002	https://trialsearch.who.int/Trial2.aspx?TrialID=TCTR20220125002	Cochrane COVID-19 register (https://covid-19.cochrane.org/) 28 June 2022
STUDIES UNDER CONSIDERATION						
Tan SH, Cook AR, Heng D, Ong B, Lye DC, Tan KB. Effectiveness of BNT162b2 Vaccine against Omicron in Children 5 to 11 Years of Age. New England Journal of Medicine. 2022 Jul 20.	255,936	Healthy volunteers	None stated	N/A	https://www.nejm.org/doi/full/10.1056/NEJMoa2203209	https://www.nejm.org/doi/full/10.1056/NEJMoa2203209 20 July 2022

TABLES 6 (RCT) AND 7 (OBSERVATIONAL STUDIES): GRADE EVIDENCE PROFILES

Table 6: BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES COMPARED TO NO VACCINE FOR CHILDREN 5-11 YEARS FOR COVID-19 (RCT)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine	No vaccine	Relative (95% CI)	Absolute (95% CI)	
Symptomatic laboratory confirmed COVID-19											
1	randomised trials	not serious	not serious	not serious	serious[a]	none	3/1514 (0.2%)	16/747 (2.1%)	**RR 0.09** (0.03 to 0.32)	**19 fewer per 1,000** (from 21 fewer to 15 fewer)	⊕⊕⊕◯ Moderate
Hospitalisation - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
COVID-19 related death - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events											
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	*Phase 1*: 16 participants received two 10-µg doses of BNT162b2 vaccine. There were no serious adverse events reported. *Phase 2-3*: Serious adverse events were reported in 0.1% of BNT162b2 recipients (2/1,518) and 0.1% of placebo recipients (1/750), from the first dose to one month after the second dose.				⊕⊕◯◯ Low
Adverse events (local and systemic)											
1	randomised trials	not serious	not serious	not serious	serious[c]	none	166/1518 (10.9%)	69/750 (9.2%)	**RR 1.19** (0.91 to 1.55)	**17 more per 1,000** (from 8 fewer to 51 more)	⊕⊕⊕◯ Moderate

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

Explanations

a. Downgraded by one level for imprecision: Low number of events and short follow-up period. Fragility index calculated at 13: the number of patients required to lose statistical significance, https://clincalc.com/Stats/FragilityIndex.aspx

b. Downgraded by two levels for imprecision: Low number of events and short follow-up period

c. Downgraded by one level for imprecision: Wide confidence interval ranging from a 9% reduction in risk to a 55% increase in risk

Table 7: BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES COMPARED TO NO VACCINE FOR CHILDREN 5-11 YEARS FOR COVID-19 (OBSERVATIONAL)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine	no vaccine	Relative (95% CI)	Absolute (95% CI)	
Symptomatic laboratory confirmed COVID-19											
4	observational studies	serious[a]	not serious	not serious	serious[b]	none	127222/1174223 (10.8%)	587614/1921956 (30.6%)	**OR 0.46** (0.23 to 0.93)	**137 fewer per 1,000** (from 214 fewer to 15 fewer)	⊕⊕◯◯ Low
Hospitalisation											
5	observational studies	serious[c]	not serious	not serious	not serious	none	99/1157904 (0.0%)	944/1864255 (0.1%)	**OR 0.36** (0.19 to 0.69)	**3 fewer per 10,000** (from 4 fewer to 2 fewer)	⊕⊕⊕◯ Moderate
COVID-19 related death											
1	observational studies	not serious	not serious	not serious	very serious[d]	none	0/1063035 (0.0%)	2/1768497 (0.0%)	**OR 0.33** (0.02 to 6.93)	**0 fewer per 100,000** (from 0 fewer to 1 more)	⊕⊕◯◯ Low
Serious adverse events											
1	observational studies	very serious[e]	not serious	serious[f]	serious[g]	none	Hause 2021: There were 2.4% (100/4,249) serious adverse events reported to Vaccine Adverse Event Reporting System (VAERS).				⊕◯◯◯ Very low
Adverse events (non-serious)											
1	observational studies	very serious[e]	not serious	serious[f]	serious[g]	none	Hause 2021: Of the adverse events reported, there were 97.6% (4,149/4,249) VAERS reports for non-serious adverse events, and 2.4% were serious.				⊕◯◯◯ Very low

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

Explanations

a. Downgraded by one level for serious risk of bias (ROB): Fowlkes and Sacco assessed as moderate ROB; Cohen-Stavi and Fleming-Dutra assessed as serious ROB

b. Downgraded by one level: serious imprecision, wide confidence interval ranging from 15 to 214 fewer cases per 1,000

c. Downgraded by one level for serious risk of bias (ROB): Sacco assessed as moderate ROB; Klein, Price, Shi and Cohen-Stavi assessed as serious ROB

d. Downgraded by two levels for imprecision: low number of events, wide confidence interval ranging from 98% reduction to a 7-fold increase in risk

e. Downgraded by two levels for serious ROB: Passive surveillance, subject to reporting biases and/or underreporting

f. Downgraded by one level for indirectness: Passive surveillance, data on race/ethnicity not provided in >40% of VAERS reports

g. Downgraded by one level for imprecision: Passive surveillance, no comparison group

TABLES 8 (RCT) AND 9 (OBSERVATIONAL STUDIES): SUMMARY OF FINDINGS

Table 8: BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES COMPARED TO NO VACCINE FOR CHILDREN 5-11 YEARS FOR COVID-19 (RCT)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Symptomatic laboratory confirmed COVID-19	21 per 1,000	**2 per 1,000** (1 to 7)	**RR 0.09** (0.03 to 0.32)	2261 (1 RCT)	⨁⨁⨁◯ Moderate[a]	
Hospitalisation - not reported	-	-	-	-	-	
COVID-19 related death - not reported	-	-	-	-	-	
Serious adverse events	*Phase 1*: 16 participants received two 10-µg doses of BNT162b2 vaccine. There were no serious adverse events reported. *Phase 2-3*: Serious adverse events were reported in 0.1% of BNT162b2 recipients (2/1,518) and 0.1% of placebo recipients (1/750), from the first dose to one month after the second dose.			2268 (1 RCT)	⨁⨁◯◯ Low[b]	
Adverse events (local and systemic)	92 per 1,000	**109 per 1,000** (84 to 143)	**RR 1.19** (0.91 to 1.55)	2268 (1 RCT)	⨁⨁⨁◯ Moderate[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; **RR:** risk 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. Downgraded by one level for imprecision: Low number of events. Fragility index calculated at 13: the number of patients required to lose statistical significance, https://clincalc.com/Stats/FragilityIndex.aspx
b. Downgraded by two levels for imprecision: Low number of events
c. Downgraded by one level for imprecision: Wide confidence interval ranging from a 9% reduction in risk to a 55% increase in risk

Table 9: BNT162b2 (PFIZER-BIONTECH) COVID-19 VACCINE, 2 DOSES COMPARED TO NO VACCINE FOR CHILDREN 5-11 YEARS FOR COVID-19 (OBSERVATIONAL)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Symptomatic laboratory confirmed COVID-19	306 per 1,000	**168 per 1,000** (92 to 291)	**OR 0.46** (0.23 to 0.93)	3096179 (4 observational studies)	⊕⊕◯◯ Low[a,b]	
Hospitalisation	5 per 10,000	**2 per 10,000** (1 to 3)	**OR 0.36** (0.19 to 0.69)	3022159 (5 observational studies)	⊕⊕⊕◯ Moderate[c]	
COVID-19 related death	0 per 100,000	**0 per 100,000** (0 to 1)	**OR 0.33** (0.02 to 6.93)	2831532 (1 observational study)	⊕⊕◯◯ Low[d]	
Serious adverse events	Hause 2021: There were 2.4% (100/4,249) serious adverse events reported to Vaccine Adverse Event Reporting System (VAERS).			(1 observational study)	⊕◯◯◯ Very low[e,f,g]	
Adverse events (non-serious)	Hause 2021: There were 97.6% (4,149/4,249) VAERS reports for non-serious adverse events.			(1 observational study)	⊕◯◯◯ Very low[e,f,g]	

***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; **RR:** risk 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. Downgraded by one level for serious risk of bias (ROB): Fowlkes and Sacco assessed as moderate ROB; Cohen-Stavi and Fleming-Dutra assessed as serious ROB
b. Downgraded by one level: serious imprecision, wide confidence interval ranging from 15 to 214 fewer cases per 1,000
c. Downgraded by one level for serious risk of bias (ROB): Sacco assessed as moderate ROB; Klein, Price, Shi and Cohen-Stavi assessed as serious ROB
d. Downgraded by two levels for imprecision: low number of events, wide confidence interval ranging from 98% reduction in risk to a 7-fold increase in risk
e. Downgraded by two levels for serious ROB: Passive surveillance, subject to reporting biases and/or underreporting

f. Downgraded by one level for indirectness: Passive surveillance, data on race/ethnicity not provided in >40% of VAERS reports
g. Downgraded by one level for imprecision: Passive surveillance, no comparison group

APPENDIX 1: SEARCH STRATEGY

Guidelines: CDC [23 June 2022]
Search terms/strategy: "Child" and "vaccine"; COVID-19 section for "vaccine 5 to 11"
Output*:*
1. *Woodworth K, Moulia D, Collins J, Hadler S, Jones J, Reddy S, et al. The advisory committee on immunization practices' interim recommendation for the use of Pfizer-BioNTech COVID-19 vaccine in children aged 5 – 11 years – United States, November 2021. MMWR Morb Mortal Wkly Rep. 2021;70(45):1579-83. DOI: http://dx.doi.org/10.15585/mmwr.mm7045e1 (CDC)*
2. *Centers for Disease Prevention and Control [Internet]. COVID-19 vaccine recommendations for children and teens. [updated 19 June 2022, cited 23 June 2022]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccines-children-teens.html*

Guidelines: WHO [23 June 2022]
Search terms/strategy: "Child" and "vaccine"
Output*:* *World Health Organization [Internet]. Interim recommendations for the use of Pfizer-BioNTech COVID-19 vaccine BNT162b2, under emergency use listing: interim guidance [updated 21 January 2021; cited 23 June 2022]. Available from: https://apps.who.int/iris/handle/10665/351139*

Guidelines: JVIC [23 June 2022]
Search terms/strategy: "jcvi covid vaccine 5-11"
Output: *Joint Committee on Vaccination and Immunization [Internet]. JCVI statement on COVID-19 vaccination of children and young people: 22 December 2021. [published 22 Dec 2021; cited 23 Jun 2022]. Available from: https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-and-young-people/jcvi-statement-on-covid-19-vaccination-of-children-and-young-people-22-december-2021*

Living Review: McMaster Vaccine Effectiveness Review [23 June 2022]
(https://www.mcmasterforum.org/networks/covid-end/resources-specific-to-canada/for-decision-makers/scan-evidence-products)
Output*: https://www.mcmasterforum.org/docs/default-source/product-documents/living-evidence-syntheses/covid-19-living-evidence-synthesis-8.13---what-is-the-effectiveness-of-available-covid-19-vaccines-for-children-and-adolescents-including-variants-of-concern.pdf?sfvrsn=2428374_7*

Cochrane COVID-19 Study Register [23 June 2022]
Search strategy: Pfizer or BNT162b2 or BioNtech or Comirnaty
Output: 3805 studies with 4467 references (IMPORTED 4463 into EndNote)
Filtered EndNote results
Title – word begins with CHILD
OR
Abstract – word begins with CHILD
175 studies
Abstract – word begins with YOUNG
NOT
Abstract – contains WOMAN OR WOMEN OR ADULT OR PATIENTS OR WORK OR MALE OR MEN
12 studies of which none were relevant

COVID-nma [27 June 2022] (https://covid-nma.com/)
Search terms/ strategy: *Living Evidence Synthesis (Vaccine RCTs) -> Filter by author "Walter"*
Output:https://covidnma.com/vaccines/index.php?search_by=2&search_input=Walter&submit=Validate#moteur_recherche (n=1)

APPENDIX 2: AGREE-II SCORES FOR WHO SAGE AND CDC GUIDELINES

Appendix 2 - Table 1: Main Domain Item Scores per Rater for O795

GL ID	Title	Date	Full Reference	Rater	Domain 1: Scope & Purpose				Domain 3: Rigour of Development									Domain 6: Editorial Independence		
					Item 1	Item 2	Item 3	Domain 1 Total Item Score	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Domain 3 Total Item Score	Item 22	Item 23	Domain 6 Total Item Score
O795	Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing	2022-01-21	World Health Organization. (2022).Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1	Dina	7	7	7	21	4	6	3	6	6	3	4	5	37	7	7	14
O795	Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing	2022-01-21	World Health Organization. (2022).Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1	Charifa	6	6	6	18	4	5	3	5	4	5	5	4	35	7	6	13

Appendix 2 - Table 2: Remaining Domain Item Scores per Rater for O795

GL ID	Title	Date	Full Reference	Rater	Domain 2: Stakeholder Involvement				Domain 4: Clarity of Presentation				Domain 5: Applicability				
					Item 4	Item 5	Item 6	Domain 2 Total Item Score	Item 15	Item 16	Item 17	Domain 4 Total Item Score	Item 18	Item 19	Item 20	Item 21	Domain 5 Total Item Score
O795	Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing	2022-01-21	World Health Organization. (2022).Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1	Lucia	5	4	6	15	6	5	4	15	4	3	3	3	13
O795	Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing	2022-01-21	World Health Organization. (2022).Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1	Lara	4	2	4	10	5	3	4	12	2	2	2	2	8

Domain Scores for O795:

Domain 1: Scope & Purpose – 91.7%

Domain 2: Stakeholder Involvement – 52.8%

Domain 3: Rigour of Development – 58.3%

Domain 4: Clarity of Presentation – 58.3%

Domain 5: Applicability – 27.1%

Domain 6: Editorial Independence – 95.8%

Appendix 2 - Table 3: Main Domain Item Scores per Rater for O734

GL ID	Title	Date	Full Reference	Rater	Domain 1: Scope & Purpose				Domain 3: Rigour of Development									Domain 6: Editorial Independence		
					Item 1	Item 2	Item 3	Domain 1 Total Item Score	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Domain 3 Total Item Score	Item 22	Item 23	Domain 6 Total Item Score
O734	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021	2021-11-05	Centers for Disease Control and Prevention. (2021).The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021. Retrieved from https://www.cdc.gov/mmwr/volumes/70/wr/mm7045e1.htm	Zil	7	7	7	21	5	5	7	7	7	7	1	4	43	1	5	6
O734	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021	2021-11-05	Centers for Disease Control and Prevention. (2021).The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021. Retrieved from https://www.cdc.gov/mmwr/volumes/70/wr/mm7045e1.htm	Funeka	7	7	6	20	7	7	7	7	7	7	1	4	47	1	5	6

Appendix 2 - Table 4: Remaining Domain Item Scores per Rater for O734

GL ID	Title	Date	Full Reference	Rater	Domain 2: Stakeholder Involvement				Domain 4: Clarity of Presentation				Domain 5: Applicability				
					Item 4	Item 5	Item 6	Domain 2 Total Item Score	Item 15	Item 16	Item 17	Domain 4 Total Item Score	Item 18	Item 19	Item 20	Item 21	Domain 5 Total Item Score
O734	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021	2021-11-05	Centers for Disease Control and Prevention. (2021).The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021. Retrieved from https://www.cdc.gov/mmwr/volumes/70/wr/mm7045e1.htm	Lucia	6	6	2	14	5	4	1	10	4	2	4	2	12
O734	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021	2021-11-05	Centers for Disease Control and Prevention. (2021).The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021. Retrieved from https://www.cdc.gov/mmwr/volumes/70/wr/mm7045e1.htm	Tereza	6	6	3	15	4	4	1	9	6	2	6	1	15

Domain Scores for O734:

Domain 1: Scope & Purpose – 97.2%

Domain 2: Stakeholder Involvement – 63.9%

Domain 3: Rigour of Development – 77.1%

Domain 4: Clarity of Presentation – 36.1%

Domain 5: Applicability – 39.6%

Domain 6: Editorial Independence – 33.3%

APPENDIX 3: EVIDENCE TO DECISION FRAMEWORK

QUESTION

WHAT IS THE EFFECTIVENESS OF THE PFIZER-COMIRNATY VACCINE TO PREVENT MORBIDITY AND MORTALITY ASSOCIATED WITH COVID-19 IN CHILDREN AGED 5–11 YEARS OLD?	
POPULATION:	CHILDREN AGED 5-11 YEARS OLD
INTERVENTION:	PFIZER VACCINE
COMPARISON:	NO VACCINE OR PLACEBO
SETTING:	PUBLIC SECTOR SOUTH AFRICA
PERSPECTIVE:	PUBLIC HEALTH/ POPULATION

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial **X Small** ○ Moderate ○ Large ○ Varies ○ Don't know	See summary of findings tables below for findings from the RCT and observational studies for these outcomes. **RCT**	The committee noted that there is a small absolute benefit for children aged 5-11 years old. They discussed that children with underlying conditions that predispose them to severe COVID-19 may benefit more from vaccination, however there is no research evidence as yet to support this. The committee noted that these studies report on data prior to Omicron, i.e., conducted mainly during Delta variant period, so the effects in future VoC are less known i.e the actual benefit considering the unknown future VoC.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Symptomatic laboratory confirmed COVID-19	21 per 1,000	**2 per 1,000** (1 to 7)	**RR 0.09** (0.03 to 0.32)	2261 (1 RCT)	⨁⨁⨁◯ Moderate[a]	

Hospitalisation - not reported	-	-	-	-	-	
COVID-19 related death - not reported	-	-	-	-	-	

*__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; **RR:** risk ratio

OBSERVATIONAL STUDIES

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Symptomatic laboratory confirmed COVID-19	306 per 1,000	**168 per 1,000** (92 to 291)	**OR 0.46** (0.23 to 0.93)	3096179 (4 observational studies)	⨁⨁◯◯ Low[a,b]	
Hospitalisation	5 per 10,000	**2 per 10,000** (1 to 3)	**OR 0.36** (0.19 to 0.69)	3022159 (5 observational studies)	⨁⨁⨁◯ Moderate[c]	
COVID-19 related death	0 per 100,000	**0 per 100,000** (0 to 1)	**OR 0.33** (0.02 to 6.93)	2831532 (1 observational study)	⨁⨁◯◯ Low[d]	

*__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; **RR:** risk 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.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate **X Small** ○ Trivial ○ Varies ○ Don't know	See summary of findings tables below for findings from the RCT and observational studies for these outcomes. **RCT**	To note: the term “Trivial” is relevant when considering results of non-inferiority trials. The committee discussed that the undesirable effects are considered small.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Serious adverse events	*Phase 1*: 16 participants received two 10-µg doses of BNT162b2 vaccine. There were no serious adverse events reported. *Phase 2-3*: Serious adverse events were reported in 0.1% of BNT162b2 recipients (2/1,518) and 0.1% of placebo recipients (1/750), from the first dose to one month after the second dose.			2268 (1 RCT)	⨁⨁◯◯ Low[b]	
Adverse events (local and systemic)	92 per 1,000	**109 per 1,000** (84 to 143)	**RR 1.19** (0.91 to 1.55)	2268 (1 RCT)	⨁⨁⨁◯ Moderate[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; **RR:** risk ratio

OBSERVATIONAL STUDIES

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vaccine	Risk with BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine				
Serious adverse events	Hause 2021: There were 2.4% (100/4,249) serious adverse events reported to Vaccine Adverse Event Reporting System (VAERS).			(1 observational study)	⊕◯◯◯ Very low[e,f,g]	
Adverse events (non-serious)	Hause 2021: Of the adverse events reported, there were 97.6% (4,149/4,249) VAERS reports for non-serious adverse events, and 2.4% were serious.			(1 observational study)	⊕◯◯◯ Very low[e,f,g]	

*__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; **RR:** risk 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.

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low **X Low** **X Moderate** ○ High ○ No included studies		There was one large RCT; with eleven observational studies with consistent results on a small absolute benefit for reduced incidence of covid-19 and hospitalisation. Several important clinical outcomes were graded as low and other as moderate, therefore the committee considered the evidence ranging from low to moderate.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability **X Possibly no important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		*How much do people affected by the decision value to the outcomes/or what are their preferences? (Children, caregivers, health care providers)* The committee discussed that there is a lack of research evidence about this, but overall, the outcomes chosen (e.g. hospitalisation and death) are likely to be important. Further research about people preferences would be informative. It was discussed whether we could engage the HSRC to include questions about what people in South Africa value in their survey.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the comparison or the intervention **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The committee considered that the balance of effects probably favours the vaccination compared to non-vaccination for 5–11-year-olds.	Decision is based on the above criteria: small benefits, small harms, and a low to moderate certainty of the evidence.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies **X Don't know**	Current cost of the vaccine is not known <u>Comparative uptake with other EPI vaccines and assumed costs:</u> Historically, routine health services are not able to reach all in this age-group. Furthermore, it is estimated that there are about 8 million children in this age group, and if the vaccine was procured at the same price as the adult vaccine, this would amount to about R3 billion for 100% coverage. However, the current national coverage for dT vaccine is about 30% for 5 yo and 17% for 12 yo, with better coverage (about 80%) at schools which is a more expensive way of providing health coverage. Also, utilising multi-dose vials it is estimated that there would be 25% wastage.	Currently unknown. Vaccine providers are not yet willing to sell to private healthcare providers and are only willing to sell to governments. The NDoH could procure small amounts of vaccine on Section 21, if it is registered in the country. The company has been asked for a reference price using other countries with a similar population to ours as an example.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies **X Don't know**	No research evidence was presented.	The committee discussed that we are not certain whether there may be increased or decreased equity if the vaccine was made available for all 5-11 years old. It was noted that in the USA access for this age group resulted in an increase in equity on an age by having access to increased options to health care. This, however, must be balanced with cost, as it may result in opportunity cost from other health services where the benefit may be higher. There is no data for this in our setting.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	SA GRADE network conducted a rapid search of available qualitative evidence regarding vaccination for 5-11 year olds. We searched PubMed, Epistomonikos and	Overall, the committee agreed that acceptability is likely to vary.

○ Probably yes ○ Yes **X Varies** ○ Don't know	Google Scholar on 19 July 2022 and found eight qualitative studies. Results are summarized in Appendix 4. None of the studies were from South Africa/Africa. In summary, across studies, most participants (usually parents or caregivers) were unlikely to vaccinate their children for COVID-19 with common reasons being concerns around vaccine safety and efficacy, side-effects and feeling that it is not necessary.	Since this vaccination is not offered in South Africa, we do not have local data yet. However, it is noted that uptake of vaccination amongst those aged 12 and older has been modest. Further, the committee shared that Stats SA reports population estimates by 5-year age bands, which do not exactly match this target group – the 2021 estimate for 10-14 yo is 5 671 023 (https://www.statssa.gov.za/publications/P0302/P03022021.pdf). However, estimating the percentage uptake is going to be far more challenging – in the 12-17 yo group, a total of 2 619 936 doses have been administered to date, with only 725 236 being 2nd doses (https://sacoronavirus.co.za/latest-vaccine-statistics/). No estimate of coverage is provided, but there were estimated to be 4 909 941 15-19 yo in SA in mid-2021. Each birth cohort is about a million per year, and hasn't changed much for more than a decade (1 166 304 in 2021 vs . 1 192 033 in 2011). Furthermore, parental consent required would be required. It was mentioned that it would be beneficial is the HSRC could conduct local studies for data on the general feeling on vaccination in this age group.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes **X Varies** ○ Don't know	Not registered with SAHPRA, with no Section 21 approval. Cost of the vaccine is as yet not known locally. Preparation materials are the same as what is used currently for the adult vaccine. Special training of healthcare workers will be required as the paediatric formulation has a different dose for a specific population. The storage requirements are considerable and require deep cold.	The committee discussed the concern that the medicine is not yet registered; not available; no stock. With this in mind, the discussion focused on which groyup iof children may benefit most from this recommendation? A universal recommendation for all 5 to 11 year olds or targeting those children within this age band who are considered at-risk group? It is assumed the benefit of vaccination may be greater in children with co-morbidities, however, there may also be

		decreased benefit in those with comorbidities due to decreased immune response – there is no data on this, however. Other considerations discussed were: • Fractional dosing of the adult dose considering there is not a registered product at the moment. However, very small (0.01ml) dose and may be challenging to administer accurately, training would be required. • Vaccinating only selected patients, e.g. those considered at risk, and how would they be identified and how would the vaccine be sent to where they require it. This would affect the cost.

APPENDIX 4: Attitudes, perceptions, and views on acceptability of Parents around COVID-19 vaccination for their children

Worldwide, vaccination is considered as a critically important public health intervention for reducing childhood morbidity and mortality. However, in 2016 over 19 million children globally did not receive their full series of basic immunizations, with low- and middle-income countries bearing the largest proportion of partially and unvaccinated children. Reasons for poor vaccine coverage are multifactorial. One aspect is how different factors influence parental view and practices regarding routine childhood vaccinations.[1] Whilst COVID-19 vaccination does not form part of routine childhood vaccinations, parental attitudes and perceptions play an important role in vaccine hesitancy and should be explored.

I searched PubMed, Epistomonikos and Google Scholar on 19 July 2022. Seven primary research studies are summarised below.

In Poland[2], 4732 people completed a survey assessing attitudes of parents towards COVID-19 vaccination, as well as concerns around it. Respondents were predominantly women, aged 36 to 44 years, with higher education, residing in large cities. 31.4% of respondents were hesitant to get the COVID-19 vaccine for themselves, whilst 54.3% had already been vaccinated. Regarding the vaccination of their children, 44.1% of respondents indicated they were willing to vaccinate their children, while 25.8% were very opposed, not wanting to vaccinate their children at all. 5.8% indicated that they would consider vaccination after at least a few months. On a 10-point Likert scale assessing likelihood of vaccinating ones' child, the median score was 5.94 +- 3.86. The most common concerns included that vaccine preparations had not been adequately tested (56%), that complications may occur in the future (51.3%), and that the child would experience an adverse reaction to vaccination (47.3%).

In Quebec[3], drivers of vaccine hesitancy among parents of 5 to 11 years olds were explored through four focus groups with 28 vaccine-hesitant parents in November 2021. Of the 28 participants, seven intended to vaccinate their children whilst the rest were unwilling or unsure. Many parents felt that the risk of COVID-19 in children was low and as such vaccination was not necessarily that important.

"I have done some research and I can see that for children, it is quite okay if they catch COVID. [. . .] I don't have any fear as such for my children's health. (Parent, Focus Group no4, Nov 10, 2021)".

Parents with positive vaccination intentions were predominantly motivated by a desire to return to normality by contributing to decrease disease transmission through children and protect their children and society in general.

"But I'll be honest with you tonight, it's also to get rid of it that I want to vaccinate my children. I don't mind being politically correct, but at some point, you want to get it over with. (Parent, Focus Group no1, Nov 9, 2021)"

Reasons for refusing the vaccine included that it was not necessary (low risk of complications from COVID-19), concerns around vaccine safety, concerns around being able to participate in school activities if not vaccinated, and concerns around political pressure to vaccinate children.

" Why vaccinate children aged 5 to 11? That's the question. [. . .] We were asked to vaccinate to protect ourselves and others. We are 95% vaccinated. That's good. The people who need to protect are protected. Why are we asking our children to have this vaccine? For what purpose? In order to protect themselves? They are not at risk. To protect others? They are all already vaccinated. I'm sorry. There is no reason for our little ones to be vaccinated. (Parent, Focus Group no2, Nov 9, 2021)"

"I find it difficult that they [the children] have that burden to carry and I find it ungrateful, actually. I think it's using children. As was mentioned, we have 90% of the population vaccinated. I don't think that the small percentage of children between the ages of 5 and 11 is going to change the game to the point where everything can change. I have the impression that we are in something "political" and at this level, it bothers me a lot. (Parent, Focus Group no2, Nov 9, 2021) "

A further concern was the added weight that parents would need to make the decision since their children are too young to decide for themselves – parents with older children noted that the decision was easier as the child could understand and voice their opinion. A limitation of these focus groups included that only vaccine-hesitant parents were part of the focus groups.

A cross-sectional survey[4] (as part of the COVID-19 Parental Attitude Study (COVIPAS)) was developed to assess willingness of parents to vaccinate their children in Canada, Israel and the United States (US). A total of 797 surveys were completed for children under the age of 12 years, 17 were excluded as they were not completed by a parent and 60 were excluded where the willingness to vaccinate question was not answered. Willingness to vaccinate decreased over time in Canada from above to below 50%, remained steady in Israel (approximately 50%) and increased in the US from around 50% to 75%. The reason for the steady rate in Israel and increase in the US was hypothesized to be related to the speed and inclusivity of the countries' vaccination programmes.

In a survey among 819 parents in Jordan[5] investigating the prevalence of vaccine hesitancy, 30.2% of participants were willing to vaccinate their children. Perceived seriousness of COVID-19 in children, perceived degree of vaccine safety and efficacy in children, personal beliefs around the likelihood of children contracting COVID-19, adherence to other COVID-19 preventative measures, whether parents were already planning on vaccinating their child(ren), residential region, and average monthly income were all strong predictors associated with likelihood of vaccinating their children.

In a survey of 1745 parents in the US[6] around willingness to vaccinate their child(ren) and identifying specific parental concerns around vaccination, 28% indicated they were very likely to vaccinate their children against COVID-19, 18% indicated somewhat likely, 33% indicated very unlikely and 12% were unsure. Parents were more likely to agree to vaccination if they had older children, higher education, had already received a COVID-19 vaccine themselves, or had a Democratic political affiliation. Concerns centred around vaccine safety and side effects. In another survey across the US[7], 1381 vaccine-hesitant parents were recruited to explore COVID-19 vaccine hesitancy using Likert scales. Parents scored below the midpoint in rating their intentions to vaccinate their child(ren) (mean (m) = 3.55, Standard Deviation (SD) = 2.13) or themselves (m=3.58, SD=2.16). Level of education was an indicator of likelihood to vaccinate themselves or their children, with more educated parents more likely to vaccinate. Reasons for vaccine hesitancy were not explored.

In Japan[8], 1100 parents of children younger than 16 years responded to a survey around vaccine hesitancy. The average age of respondents' children was 7.4 years. Overall, 42.9% (n=472) of participants indicated willingness to vaccinate their children, whilst 42.7% were unsure and 14.4% did not want to vaccinate their child(ren) at all. Main reasons for being unsure included fears around potential vaccine side effects (84.9%), safety of the vaccine itself (54.7%), and lack of trust in vaccine efficiency (25.7%).

In summary, across studies, most participants were unlikely to vaccinate their children for COVID-19 with common reasons being concerns around vaccine safety and efficacy, side-effects and feeling that it is not necessary.

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APPENDIX 5: UPDATING OF A RAPID REPORT

Date	Signal	Rationale

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
V3	15Aug22	NEML MAC and VMAC	Not for use in the general population in this age group, but rather retain use for those in the high risk groups as outlined.