Anhang zur wissenschaftlichen Begründung der 15. Aktualisierung der STIKO-Empfehlung zur COVID-19-Impfung
(Impfempfehlung für 5- bis 11-jährige Kinder)

Inhalt

1. Extraktionen der Studiendaten für den systematischen Review zur Wirksamkeit und Sicherheit der COVID-19-Impfstoffe (BNT162b2 (BioNTech/Pfizer)

	Description
Vaccine	
Vaccine name	BNT162b2
Vaccine composition	modRNA encoding prefusion spike glycoprotein (P2 S), lipid nanoparticle (LNP) composition.
Vaccine manufacturer & develloper	BioNTech/Pfizer
Vaccine type	mRNA
number and timing of doses, route	2 doses à 10 µg, 0, 21d, i.m.
other vaccine charcteristics/information	Frozen storage at -90°C to -60°C; post thawing refrigerated storage at 2-8°C for up to 10 weeks After dilution with 0.9% sodium chloride, storage at 2°C to 25°C for up to 12 hours
Study	C4591007 (Phase 1/2/3), Phase 1 not further described
Reference	• Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. DOI: 10.1056/NEJMoa2116298 • FDA Briefing Document, EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 5 through 11 years of age, Vaccines and Related Biological Products Advisory Committee Meeting, October 26, 2021 • Clinicaltrials.gov/ct2/show/NCT04816643
Study period	Study ongoing; Cohort 1: enrolment from June 7 to June 19, 2021 (data cutoff in September 2021); Cohort 2: randomization from August 15 2021 (data cutoff in October 2021)
Study design	Phase 2/3, randomized (2:1 ratio), placebo-controlled, observer-blind, safety, immunogenicity, and efficacy study in healthy individuals. Phase 1 not further reported.
Primary efficacy and immunogenicity endpoints	• SARS-CoV-2 neutralizing titers
Primary safety endpoint	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Randomization and ratio	Use of interactive Web-based system; 2:1
Blinding	The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. All participants and study personnel, with the exception of those preparing or administering the injections, were unaware of group assignments.
Countries	Study participants aged 5-11 years: USA, Finland, Poland, Spain; Comparison group for safety and immunogenicity (aged 16-25 years, from study C4591001): USA, Argentina, Brazil, Germany, South Africa, Turkey
Comparator	Study participants aged 5-11 years: placebo (saline) (normal saline (0.9% sodium chloride solution for injection)) Comparison group for safety and immunogenicity: aged 16-25 years, from study C4591001, vaccinated with 30 µg BNT162b2
Funding	BioNTech/Pfizer
Conflict of interest	Completed disclosure forms are available as supplement from https://www.nejm.org/doi/full/10.1056/NEJMoa2116298#disclosures; in brief: EB, RF, YM, GP, ES, KT, EW received topic-related grants or contracts; YM, FM are members of the Data and Safety Monitoring Board of Pfizer, FM also of Moderna; BP received topic-related consultancy fees; TB, DC, LC, PD, WG, AG, KJ, NK, KK, SL, HM, IM, JP, CS, UzS, KS, XX are employed by Pfizer; DC, PD, WG, KJ, NK, KK, SL, HM, IM, KS hold stocks from Pfizer;

	EL, OZ are employed by BioNTech; UgS, OZ hold stocks from BioNTech; JD was a paid site investigator of the trial (paid to employer); MR is national coordinator and/or PI of several industry-sponsored clinical vaccine trials; JP holds a meningococcal pentavalent vaccine patent; UgS, OR are fiduciary officers of BioNTech; EW is in the scientific advisory board of Vaxcyte; EK, PR have no relevant interests to disclose.
Inclusion criteria, as listed in the trial registration	1. "Male or female participants ≥6 months to <12 years of age, at the time of randomization, at Visit 1 for the dose-finding/selected-dose evaluation and for participants ≥5 to <30 years of age, at the time of randomization, at Visit 1 for the lower-dose evaluation. 2. Participants' parent(s)/legal guardian(s) and participants, as age appropriate, who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures. 3. Healthy participants who are determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study. Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in the therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. 4. Participants are expected to be available for the duration of the study and whose parent(s)/legal guardian can be contacted by telephone during study participation. 5. Negative urine pregnancy test for female participants who are biologically capable of having children. 6. Female participant of childbearing potential or male participant able to father children who is willing to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the last dose of study intervention if at risk of pregnancy with her/his partner; or female participant not of childbearing potential or male participant not able to father children. 7. The participant or participant's parent(s)/legal guardian is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written)."
Exclusion criteria, as listed in the trial registration	1. "Receipt of medications intended to prevent COVID-19. 2. Previous or current diagnosis of MIS-C. 3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. Note: This includes both conditions that may increase the risk associated with study intervention administration or a condition that may interfere with the interpretation of study results 4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s). 5. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination. 6. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus. Note: Stable type 1 diabetes and hypothyroidism are permitted. 7. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. 8. Female who is pregnant or breastfeeding. 9. Previous vaccination with any coronavirus vaccine. 10. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. 11. Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study.

	12. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation. 13. Previous participation in other studies involving study intervention containing LNPs. 14. Participants who are direct descendants (child or grandchild) of investigational site staff members or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members."
Participants (study groups)	• Safety population: all participants who received at least one study dose; • All-available immunogenicity: all randomized participants who received at least one study dose, and with at least 1 valid and determinate immunogenicity result after vaccination • Evaluable immunogenicity: all randomized participants who received both study doses per protocol, and with at least 1 valid and determinate immunogenicity result after blood sampling within appropriate window • Evaluable efficacy: all randomized participants who received both study doses per protocol
Age of participants	Median/Mean age: Cohort 1: 8.0 years (range 5–11)/ 8.2 years (SD 1.94) Cohort 2: baseline characteristics not provided Comparison group for safety and immunogenicity 16 to 25 years: 21.0 years (range 16–25)/ 20.9 years (SD 3.03)
Sex (% male)	Cohort 1: BNT162b2: 52,6%; placebo: 51,1%; Cohort 2: baseline characteristics not provided.
Duration of follow-up after vaccination	Cohort 1: 2256 participants (1510 in BNT162b2, and 746 in placebo group) (95.1%) had at least 2 months of follow-up after their second vaccine dose at data cutoff (September 6, 2021); Cohort 2: 2369 participants (1591 in BNT162b2, and 778 in placebo group) had a median FU of 2.4 weeks after their second dose at data-cutoff (October 8, 2021).
Type of follow-up after vaccination	Safety evaluations: events reported by the participant, parent(s) or legal guardian at each follow-up visit in the clinic, or by telephone (FUs scheduled for day 1 of first and second dose, 1 week after dose 2, 1 month after dose 2, 6 months after dose 2); • Reactogenicity events: monitored and recorded through the use of an electronic diary for 7 days after each dose; • Adverse events: from the first dose through 1 month after the second dose; • Serious adverse events: from the first dose through 6 months after the second dose. Immunogenicity evaluations: blood samples collected for a subset of participants at baseline and 1 month after the second dose Efficacy evaluations: from at least 7 days after second dose
Initial no. of participants included	Cohort 1: 2316 assessed for eligibility/2285 participants randomized (1528 assigned to BNT162b2, 757 assigned to placebo)/2268 received interventions/ 2256 completed 1-month FU after 2nd dose at data cut-off (1510 in BNT162b2 group, 746 in placebo group) • 17 participants (11 in BNT162b2 group and 6 in placebo group) did not receive intervention • 1 participant of placebo group received BNT162b2 in error for both doses • 11 participants (5 in BNT162b2 group and 6 in placebo group) withdrew from study; 4 participants (2 per group) before 1-month FU after 2nd dose • 3 participants turned 12 years of age during study period; data included until participants were unblinded Cohort 2: 2394 participants randomized (1598 assigned to BNT162b2, 796 assigned to placebo)/ 98.7% received both doses at data cut-off • 7 participants in BNT162b2 group did not receive vaccine (1591 included in safety population) • 1 participant in BNT162b2 group discontinued vaccination, due to AEs of pyrexia and neutropenia, 2 participants in BNT162b2 group before 1-month FU after 2nd dose
Sample size	Vaccine efficacy: 4500 participants aged 5-11 to provide approx.. 35.1% power to conclude true VE>30% with assumptions of true VE of 80%. Immunobridging success: 225 evaluable participants per age group (5-11 and 16-25 year olds) to provide 90.4% and 92.6% power to demonstrate immunobridging on the basis of the geometric mean ratio and the difference in seroresponse, respectively.
Final no. of participants analyzed for each endpoint	Cohort 1: • Safety population: 2268 • Immunogenicity: 264 5-11 year olds, 253 16-25 year olds • Efficacy: 2186 Cohort 2: Data verification in process, but not finished by the time the FDA briefing document was completed

Confounders adjusted for	vaccine efficacy adjusted for surveillance time (defined as the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point)
Safety assessment	Cohort 1: 95% of participants had at least 2 months of available follow-up safety data after the second dose Cohort 2: NR; only selected safety outcomes reported
Safety -- definitions	
local reactions	
Pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Swelling	Grade 1: 0.5 cm to 2.0 cm (1 to 4 caliper units) Grade 2: >2.0 cm to 7.0 cm (5 to 14 caliper units) Grade 3: >7.0 cm (>14 caliper units) Grade 4: Necrosis or exfoliative dermatitis
Redness	Grade 1: 0.5 cm to 2.0 cm (1 to 4 caliper units) Grade 2: >2.0 cm to 7.0 cm (5 to 14 caliper units) Grade 3: >7.0 cm (>14 caliper units) Grade 4: Necrosis or exfoliative dermatitis
systemic reactions (fever, nausea, fatigue, …)	
Vomiting	Grade 1: 1 to 2 times in 24 hours Grade 2: >2 times in 24 hours Grade 3: Requires IV hydration Grade 4: ER visit or hospitalization
Diarrhea	Grade 1: 2 to 3 loose stools in 24 hours Grade 2: 4 to 5 loose stools in 24 hours Grade 3: ≥ 6 loose stools in 24 hours Grade 4: ER visit or hospitalization
Headache	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Fatigue	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Chills	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Muscle pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Joint pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
Fever	Grade 1: 38.0°C to 38.4°C Grade 2: >38.4°C to 38.9°C Grade 3: >38.9°C to 40.0°C Grade 4: >40.0°C
adverse events	Any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
serious adverse events	Any AE as defined above that: a. Results in death b. Is life-threatening c. Requires inpatient hospitalization or prolongation of existing hospitalization d. Results in persistent disability/incapacity e. Is a congenital anomaly/birth defect f. Other situations, as defined in the trial protocol

Effectiveness -- definitions	
COVID-19	Definition of confirmed COVID-19 included the presence of ≥1 symptom: • Fever; • New or increased cough; • New or increased shortness of breath; • Chills; • New or increased muscle pain; • New loss of taste or smell; • Sore throat; • Diarrhea (≥3 loose stools per day); • Vomiting. and being SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period (either at the central laboratory or at a local testing facility using an acceptable test).
COVID-19 hospitalization	n.a.
COVID-19 hospitalization on intensive care	n.a.
COVID-19 related death	n.a.
Confirmed severe COVID-19	Diagnosis of severe COVID-19 included confirmed COVID-19 and the presence of ≥1 of the following: • Clinical signs at rest indicative of severe systemic illness (respiratory rate and heart rate as shown in the supplementary table, SpO2 ≤92% on room air of >50% FiO2 to maintain ≥92%, or PaO2/FiO2 <300 mmHg) • Respiratory failure (needing high-flow oxygen, including continuous positive airway pressure, bilevel positive airway pressure, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) • Evidence of shock or cardiac failure (systemic blood pressure <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain blood pressure in the normal range • Significant acute renal failure (serum creatinine ≥2 × upper limit of normal [ULN] for age or 2-fold increase in baseline creatinine • Significant gastrointestinal/hepatic failure (total bilirubin ≥4 mg/dL or ALT 2 × ULN for age) • Significant neurological dysfunction (Glasgow Coma Scale score ≤11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline) • Intensive care unit admission • Death
MIS-C	Confirmed MIS-C was per the CDC MIS-C case definition: • An individual <21 years of age presenting with fever (≥38°C for ≥24 hours or report of subjective fever lasting ≥24 hours); AND • Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; AND • Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement: o Cardiac (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia); o Renal (eg, acute kidney injury); o Respiratory (eg, pneumonia, ARDS, pulmonary embolism); o Hematologic (eg, elevated bilirubin, elevated liver enzy,es, or diarrhea); o Dermatologic (eg, rash, mucocutaneous lesions); o Neurological (eg, CVA, aseptic meningitis, encephalopathy); AND • No alternative plausible diagnosis; AND • Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR • COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

VE calculation	The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group.
Immunogenicity -- definitions	
Seroresponse	increase in titers by a factor of at least 4 from baseline or by titers that were at least 4 times the lower limit of quantitation if the baseline measurement was less than the lower limit of quantitation
Immunobridging success	lower limit of the 95% CI for the difference in percentages of participants (5–11 years minus 16–25 years) with seroresponse was greater than -10%
Safety -- results	
Number (%) with any adverse events from first dose to 1 month after second dose: vaccine vs. comparator	Cohort 1: 10.9% vs. 9.2% Cohort 2: not reported
Number (%) with any adverse events from first dose to 1 month after second dose that were considered related to the intervention: vaccine vs. comparator	Cohort 1: 3.0% vs. 2.1% Cohort 2: not reported
Safety – results, local events	
Number (%) with any local reactions: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 76.1% vs. 33.9% 2nd dose: BNT162b2 vs. placebo: 73.0% vs. 32.0% Cohort 2: not reported
Number (%) with redness: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 14.7% vs. 5.7% 2nd dose: BNT162b2 vs. placebo: 18.5% vs. 5.4% Cohort 2: not reported
Number (%) with swelling: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 10.5% vs. 2.7% 2nd dose: BNT162b2 vs. placebo: 15.3% vs. 2.7% Cohort 2: not reported
Number (%) with pain at injection site: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 74.1% vs. 31.3% 2nd dose: BNT162b2 vs. placebo: 71.0% vs. 29.5% Cohort 2: not reported
Safety -- results**, systemic events and use of medication**	
Number (%) with any systemic events: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 47.3% vs. 44.6% 2nd dose: BNT162b2 vs. placebo: 51.4% vs. 36.7% Cohort 2: not reported
Number (%) with fever: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 3% vs. 1% 2nd dose: BNT162b2 vs. placebo: 7% vs. 1% Cohort 2: not reported
Number (%) with fatigue: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 33.6% vs. 31.3% 2nd dose: BNT162b2 vs. placebo: 39.4% vs. 24.3% Cohort 2: not reported
Number (%) with headache: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 22.4% vs. 24.1% 2nd dose: BNT162b2 vs. placebo: 28.0% vs. 18.6% Cohort 2: not reported
Number (%) with chills: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 4.6% vs. 4.7% 2nd dose: BNT162b2 vs. placebo: 9.8% vs. 4.3% Cohort 2: not reported
Number (%) with vomiting: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 2.2% vs. 1.5% 2nd dose: BNT162b2 vs. placebo: 1.9% vs. 0.8% Cohort 2: not reported
Number (%) with diarrhea: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 5.9% vs. 4.1% 2nd dose: BNT162b2 vs. placebo: 5.3% vs. 4.7% Cohort 2: not reported
Number (%) with muscle pain: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 9.1% vs. 6.8% 2nd dose: BNT162b2 vs. placebo: 11.7% vs. 7.4%

	Cohort 2: not reported
Number (%) with joint pain: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 3.3% vs. 5.5% 2nd dose: BNT162b2 vs. placebo: 5.2% vs. 3.6% Cohort 2: not reported
Number (%) with use of antipyretic medication: vaccine vs. comparator	Cohort 1: 1st dose: BNT162b2 vs. placebo: 14.4% vs. 8.3% 2nd dose: BNT162b2 vs. placebo: 19.7% vs. 8.1% Cohort 2: not reported
Number (%) with tenderness: vaccine vs. comparator	Not reported
Number (%) with Erythema/redness: vaccine vs. comparator	Not reported
Number (%) with Induration/swelling: vaccine vs. comparator	Not reported
Number (%) with systemic reactions (myalgia, nausea, fatigue, …)	Not reported
Number (%) with myalgia: vaccine vs. comparator	Not reported
Number (%) with lymphadenopathy: vaccine vs. comparator	Cohort 1: 0.9% vs. 0.1% Cohort 2: 0.4% vs. 0.4%
Number (%) with myocarditis: vaccine vs. comparator	Cohort 1: No events vs. not reported Cohort 2: not reported
Number (%) with pericarditis: vaccine vs. comparator	Cohort 1: No events vs. not reported Cohort 2: not reported
Number (%) with hypersensitivity: vaccine vs. comparator	Cohort 1: 0.92% vs. 0.53% Cohort 2: 0.57% vs. 0.51%
Number (%) with anaphylaxis: vaccine vs. comparator	Cohort 1: No events vs. not reported Cohort 2: not reported
Number (%) with serious adverse events: vaccine vs. comparator	Cohort 1: 0.1% (1 event [arm fracture] in 1 participant) vs. 0.1% (2 events [postinjury abdominal pain and pancreatitis] in 1 participant Cohort 2: 0.2% (3 events [1 infection of the knee, 1 foreign body ingestion, and 1 epiphyseal fracture] in 3 participants) vs. 0%
Number (%) with any adverse events of special interest (AESI) according to CEPI criteria (myocarditis, pericarditis, anaphylaxis)	Cohort 1: No cases in either group Cohort 2: No cases in either group
Efficacy-- results	Covid-19 occurrence at least 7 days after 2. doses in participants
Number (%) with SARS-CoV-2 infection: vaccine vs. comparator	not reported
Number (%) with COVID-19: vaccine vs. comparator (without proof of prior infection)	3 cases vs. 16 cases; VE: 90.7% (95% CI 67.7 to 98.3)
Number (%) with COVID-19: vaccine vs. comparator (total cohort, including participants with or without proof of prior infection)	3 cases vs. 16 cases; VE: 90.7% (95% CI 67.4 to 98.3)
Number (%) with severe COVID-19: vaccine vs. comparator	No cases in either group
Number (%) with MIS-C: vaccine vs. comparator	No cases in either group
Number (%) with COVID-19 hospitalization: vaccine vs. comparator	Not reported
Number (%) with COVID-19 hospitalization on intensive care: vaccine vs. comparator	Not reported
Number (%) with COVID-19 hospitalization AND mechanical ventilation: vaccine vs. comparator	Not reported
Number (%) with COVID-19 related death: vaccine vs. comparator	Not reported

Number (%) with COVID-19 after 1st and before 2nd dose: vaccine vs. comparator	Not reported
Covid-19 occurrence at least 7 days after 2. doses in participants *with and without* evidence of infection	Not reported
Immunogenicity 10 µg of BNT162b2 in 5 to 11 years vs. 30 µg of BNT162b2 in 16 to 25 years	
Geometric Mean 50% Neutralizing Titer (95% CI)	5 to 11 years (n=264) vs. 16 to 25 years (n=253): 1197.6 (1106.1-1296.6) vs. 1146.5 (1045.5-1257.2)
Geometric Mean Ratio (95% CI)	5 to 11 years (n=264) vs. 16 to 25 years (n=253): 1.04 (0.93–1.18); meaning immunobridging criterion met
Seroresponse	5 to 11 years (n=264) vs. 16 to 25 years (n=253): 99.2% (95% CI 97.3 to 99.9) vs. 99.2% (95% CI 97.2 to 99.9)
Relative seroresponse difference in percentage points (95% CI)	0.0% (95% CI -2.0 to 2.2); meaning immunobridging criterion met

2. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie für Comirnaty (BNT162b2-Impfstoffs) von BioNTech für 5- bis 11-jährige Kinder

Tabelle 1: Risk of BIAS-Bewertung der Phase 3-Zulassungsstudie für Comirnaty (BNT162b2-Impfstoffs) von Pfizer/BioNTech für 5- bis 11-jährige Kinder und Jugendliche

Endpunkt	Bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
COVID-19	low	low[1]	some concerns[2]	low	low	some concerns
Schwere COVID-19 Erkrankung oder Tod	low	low[1]	some concerns[3]	some concerns[4]	low	some concerns
PIMS	low	low[1]	some concerns[3]	some concerns[4]	low	some concerns
Lokalreaktionen (local reactions)	low	low[1]	low	some concerns[4]	low	some concerns
Systemische Reaktionen (systemic events)	low	low[1]	low	some concerns[4]	low	some concerns
Unerwünschte Ereignisse (adverse events)	low	low[1]	low	some concerns[4]	low	some concerns
Schwerwiegende Impfstoffnebenwirkungen (serious adverse events)	low	low[1]	low	low[5]	low	low
Unerwünschte Ereignisse von besonderem Interesse (adverse events of special interest)	low	low[1]	some concerns[3]	some concerns[4]	low	some concerns

[1] Teile des Studienpersonals waren nicht verblindet (z.B. Personen, die Impfungen verabreichten). Eine Person (0.1%) der Placebo-Gruppe erhielt fälschlicherweise bei beiden Injektionen den Impfstoff, ansonsten sind keine Abweichungen beschrieben. Es wurde eingeschätzt, dass dies keinen oder nur einen vernachlässigbaren Einfluss auf das Verzerrungsrisiko für diesen Endpunkt hatte.

[2] Daten für 1450/1514 (95.7%) der Interventionsgruppe und 736/747 (98.5%) der Placebogruppe, die beide Dosen erhielten vorhanden. Es wurde eingeschätzt, dass aufgrund der kleinen erwarteten Fallzahlen das Ergebnis durch fehlende Daten verzerrt sein könnte.

[3] In der beschriebenen Studienpopulation wurden keine Ereignisse beobachtet. Allerdings wird keine Referenz zur ausgewerteten Grundgesamtheit gegeben. Unter der Annahme, dass die Grundgesamtheit mit der ausgewerteten Population für die Effektivitäts-Endpunkte übereinstimmt (VE-Daten für 1450/1514 (95.7%) der Interventionsgruppe und 736/747 (98.5%) der Placebogruppe, die beide Dosen erhielten vorhanden) wird eingeschätzt, dass aufgrund der kleinen erwarteten Fallzahlen das Ergebnis durch fehlende Daten verzerrt sein könnte.

[4] Teile des Studienpersonals waren nicht verblindet (z.B. Personen, die Impfungen verabreichten). Da es sich um selbstberichtete Ereignisse handelt (elektronisches Studientagebuch), könnte eine mögliche Kenntnis der Gruppenzugehörigkeit (wissentlich oder unwissentlich durch Studienpersonal kommuniziert) das Berichten bzw. die Bewertung von Ereignissen durch einzelne Studienteilnehmer beeinflusst haben.

[5] Aufgrund des Schweregrads der Ereignisse und daher der objektiven Natur des Endpunktes wird davon ausgegangen, dass eine Beeinflussung der Endpunkterhebung durch eine mögliche Kenntnis der Gruppenzugehörigkeit äußerst unwahrscheinlich ist.

3. GRADE Evidenzprofil: Impfung mit Comirnaty (BNT162b2) von BionTech/Pfizer gegen COVID-19 bei 5-11-jährigen Kindern

Soll 5- bis 11-jährigen Kindern eine Impfung mit Comirnaty (BNT162b2) von BionTech/Pfizer zum Schutz vor COVID-19 empfohlen werden?

Population: Children, aged 5-11 years, without or with stable pre-existing condition

Intervention: BNT162b (2 doses à 10 µg, 21 days apart)

Comparison: Placebo (2 doses, 21 days apart)

Setting: community

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vaccination with the BionTech/Pfizer vaccine**	**No vaccination[a]**	**Relative (95% CI)**	**Absolute**		
COVID-19 (lab-confirmed); with or without evidence of prior infection; 5-11 yrs (follow-up 2 months)												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/1450 (0.2%)	16/736 (2.2%)	RR[b] 0.10 (0.03 to 0.33)	19 fewer per 1000 (from 15 fewer to 21 fewer)	⊕⊕⊕ MODERATE	IMPORTANT
Hospitalisation due to COVID-19 - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Death due to COVID-19												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	No cases observed in either group.				⊕⊕ LOW	CRITICAL
Any local reaction after first dose in age group 5-11 yrs (follow-up 7 days after injection)												

1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1150/1511 (76.1%%)	254/749 (33.9%)	RR 2.24 (2.02 to 2.49)	420 more per 1000 (from 345 more to 505 more)	⊕⊕⊕ MODERATE	IMPORTANT
Any systemic reaction after first dose in age group 5-11 yrs (follow-up 7 days after injection)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	715/1511 (47.3%)	334/749 (44.6%)	RR 1.06 (0.96 to 1.17)	26 more per 1000 (from 18 fewer to 75 more)	⊕⊕ LOW	IMPORTANT
Any serious adverse event (follow-up median 2 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[5]	none	4/3109 (0.13%)	1/1538 (0.07%)	RR 1.98 (0.22 to 17.69)	1 more per 1000 (from 0 fewer to 10 more)	⊕⊕⊕ MODERATE	CRITICAL
ICU admission due to COVID-19 – (measured as part of criteria for severe COVID-19)												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	No cases observed in either group.				⊕⊕ LOW	CRITICAL
Intubation due to COVID-19 – (measured as part of criteria for severe COVID-19)												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	No cases observed in either group.				⊕⊕ LOW	CRITICAL
Adverse events of special interest (incl. myocarditis, pericarditis, anaphylaxis) (follow-up 2 months)												
1	randomised trials	Serious[3]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	No cases observed in either group.				⊕⊕ LOW	CRITICAL

[a] The comparison group for the immunobridging-outcome was a random sample of 16 to 25 year olds drawn from the intervention group of the C4591001 study.

[b] RR: Risk Ratio

[c] RD: Relative difference

[1] Data were available for 95.1% of participants in intervention group, and 98.5% of participants in control group. However, due to the small number of expected cases, the result could be biased by missing data.

[2] No events in small study-size

[3] Part of study personnel was not blinded (incl. vaccine administrators). This could have had an impact on recognition of events/reactions by participants if information on allocation was communicated

[4] Confidence interval includes a potential benefit and harm for the intervention

[5] Very few evens in small study-size

Literatur:

1. Frenck RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021.