Anhang zur wissenschaftlichen Begründung der 9. Aktualisierung der STIKO-Empfehlung zur COVID-19-Impfung

(Impfempfehlung für 12- bis 17-jährige Kinder und Jugendliche)

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 30 µg, 0, 21d, i.m.
other vaccine charcteristics/information	storage at 2-8°C up to 31 days
Study	Phase 2/3
Reference	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.
Study period	October 15, 2020, and January 12, 2021
Study design	Phase 2/3, randomized (1:1 ratio), placebo-controlled, observer-blind, efficacy study in healthy individuals.
Efficacy and immunogenicity endpoints	first primary end point was the **efficacy** of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who did not have evidence of previous SARS-CoV-2 infection, as well as in all vaccinated participants; Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-yearold participants was an **immunogenicity objective**.
Primary safety endpoint	primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose
Randomization and ratio	use of Interactive Response Technology für randomization; 1:1
Blinding	The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded. Unblinded administrator. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.
Countries	participants aged 12-15 years: USA, for comparison group (aged 16-25 years): USA, Argentina, Brazil, Germany, South Africa, Turkey
Comparator	placebo (normal saline (0.9% sodium chloride solution for injection)) and comparison group (aged 16-25 years) for safety and immunogenicity vaccinated with BNT162b2
Funding	BioNTech/Pfizer
Conflict of interest	Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
Inclusion criteria	Eligible participants were healthy or had stable preexisting disease (including hepatitis B, hepatitis C, or human immunodeficiency virus infection).
Exclusion criteria	Persons with a previous clinical or virologic Covid-19 diagnosis or SARS-CoV-2 infection, previous coronavirus vaccination, diagnosis of an immunocompromising or immunodeficiency disorder, or treatment with immunosuppressive therapy (including cytotoxic agents and systemic glucocorticoids) were excluded.
Participants (study groups)	The safety population included all participants who received at least one dose of BNT162b2 or placebo. The reactogenicity subset included all 12-to-15-year-old participants and a subset of 16-to-25-year-old participants (those who received an e-diary to record reactogenicity events). Immunogenicity was assessed in a random subset of participants in each age cohort with the use of a simple random-sample selection procedure.
Age of participants	12 to 15 years; comparison group 16 to 25 years

Sex (% male)	BNT162b2: 50,1%; placebo 51,8%
Duration of follow-up after vaccination	1308 participants (58%) had at least 2 months of follow-up after their second vaccine dose.
Type of follow-up after vaccination	e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration;
Initial no. of participants included	2306 adolescents 12 to 15 years of age were screened for inclusion, and 2264 underwent randomization across 29 U.S. sites
Sample size	an accurate sample size to assess vaccine efficacy could not be calculated before the start of the trial, given uncertainties about the incidence of SARS-CoV-2 infection
Final no. of participants analyzed for each endpoint	2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo
Confounders adjusted for	not reported
Safety assessment	solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in the publication.
Safety -- definitions	
local reactions	
local reactions: pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for severe pain
local reactions: swelling	Grade 1: D>2.0 cm to 5.0 cm (5 to 10 measuring device units) Grade 2: >5.0 cm to 10.0 cm (11 to 20 measuring device units) Grade 3: >10 cm (≥21 measuring device units) Grade 4: Necrosis or exfoliative dermatitis
local reactions: redness	Grade 1: D>2.0 cm to 5.0 cm (5 to 10 measuring device units) Grade 2: >5.0 cm to 10.0 cm (11 to 20 measuring device units) Grade 3: >10 cm (≥21 measuring device units) Grade 4: Necrosis
systemic reactions (fever, myalgia, nausea, fatigue, …)	
Vomiting	Grade 1: 1-2 times in 24 hours Grade 2: >2 times in 24 hours Grade 3: Requires IV hydration Grade 4: Emergency room visit or hospitalization for hypotensive shock
Diarrhea	Grade 1: 2 to 3 loose stools in 24 hours Grade 2: 4 to 5 loose stools in 24 hours Grade 3: 6 or more loose stools in 24 hours Grade 4: Emergency room visit or hospitalization for severe diarrhea
Headache	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for headache
Fatigue/ tiredness	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for fatigue/ tiredness
Chills	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for chills
New or worsened muscle pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for new or worsened muscle pain
New or worsened joint pain	Grade 1: Does not interfere with activity Grade 2: Interferes with activity Grade 3: Prevents daily activity Grade 4: Emergency room visit or hospitalization for new or worsened joint pain
Fever	Fever is defined as an oral temperature of ≥38.0 °C

adverse events	AEs from Dose 1 to 1 months after last dose; An AE is 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	SAEs from Dose 1 to 6 months after the last dose; Grade 1-4 (mild, moderate, severe, life-threatening); An SAE is defined as any untoward medical occurrence that, at any dose: 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: (see protocol)
Effectiveness -- definitions	
COVID-19	Confirmed **COVID-19**: presence of at least 1 of the following symptoms and 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): • 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; • Vomiting. The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html): • Fatigue; • Headache; • Nasal congestion or runny nose; • Nausea.
COVID-19 hospitalization	n.a.
COVID-19 hospitalization on intensive care	n.a.
COVID-19 related death	n.a.
Confirmed severe COVID-19	n.a.
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.
Safety -- results	
Number (%) with local reactions: vaccine vs. comparator	
Number (%) with pain: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 86% : 23% ; 16-25 years vs. placebo: 83% : 16% 2nd dose: 12-15 years vs. placebo: 79% : 18% ; 16-25 years vs. placebo: 78% : 12%
Number (%) with tenderness: vaccine vs. comparator	not reported
Number (%) with Erythema/redness: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 6% : 1% ; 16-25 years vs. placebo: 6% : 1% 2nd dose: 12-15 years vs. placebo: 5% : 1% ; 16-25 years vs. placebo: 6% : 0
Number (%) with Induration/swelling: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 7% : 1% ; 16-25 years vs. placebo: 8% : 1% 2nd dose: 12-15 years vs. placebo: 5% : 1% ; 16-25 years vs. placebo: 7% : 0
Number (%) with systemic reactions (myalgia, nausea, fatigue, …)	
Number (%) with fever: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 10% : 1% ; 16-25 years vs. placebo: 7% : 1% 2nd dose: 12-15 years vs. placebo: 20% : 1% ; 16-25 years vs. placebo: 17% : 0
Number (%) with fatigue/ tiredness: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 60% : 41% ; 16-25 years vs. placebo: 60% : 39% 2nd dose: 12-15 years vs. placebo: 66% : 25% ; 16-25 years vs. placebo: 66% : 23%
Number (%) with headache: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 55% : 35% ; 16-25 years vs. placebo: 54% : 37% 2nd dose: 12-15 years vs. placebo: 65% : 24% ; 16-25 years vs. placebo: 61% : 24%
Number (%) with chills: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 28% : 10% ; 16-25 years vs. placebo: 25% : 9% 2nd dose: 12-15 years vs. placebo: 42% : 7% ; 16-25 years vs. placebo: 40% : 4%
Number (%) with vomiting: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 3% : 1% ; 16-25 years vs. placebo: 2% : 2% 2nd dose: 12-15 years vs. placebo: 3% : 1% ; 16-25 years vs. placebo: 3% : 2%

Number (%) with diarrhea: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 8% : 7% ; 16-25 years vs. placebo: 11% : 11% 2nd dose: 12-15 years vs. placebo: 6% : 4% ; 16-25 years vs. placebo: 8% : 5%
Number (%) with myalgia: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 24% : 13% ; 16-25 years vs. placebo: 27% : 14% 2nd dose: 12-15 years vs. placebo: 32% : 8% ; 16-25 years vs. placebo: 41% : 10%
Number (%) with joint pain: vaccine vs. comparator	1st dose: 12-15 years vs. placebo: 10% : 7% ; 16-25 years vs. placebo: 13% : 5% 2nd dose: 12-15 years vs. placebo: 16% : 5% ; 16-25 years vs. placebo: 22% : 4%
Number (%) with use of antipyretic medication: vaccine vs. comparator	1st dose: 12-15 years vs. placebo:37 % : 10% ; 16-25 years vs. placebo: 32% : 11% 2nd dose: 12-15 years vs. placebo: 51% : 9% ; 16-25 years vs. placebo: 46% : 12%
Number (%) with serious adverse events: vaccine vs. comparator	Lymphadenopathy was reported in 9 of 1131 BNT162b2 recipients (0.8%) and in 2 of 1129 placebo recipients (0.2%) who were 12 to 15 years of age, as compared with in 1 of 536 BNT162b2 recipients (0.2%) and in no placebo recipients who were 16 to 25 years of age; Few participants in any cohort (≤0.4% through 1 month after dose 2) had serious adverse events, and none were considered by the investigators to have been vaccine-related. No thromboses or hypersensitivity adverse events or vaccine-related anaphylaxis was seen.
Number (%) with adverse events of special interest (AESI) according to CEPI criteria (e.g. enhanced COVID-19, Guillain-Barrée Syndrom)	not reported
Efficacy-- results	Covid-19 occurance at least 7 days after 2. doses in participants without evidence of infection
Number (%) with SARS-CoV-2 infection: vaccine vs. comparator	not reported
Number (%) with COVID-19: vaccine vs. comparator (without proof of prior infection)	0 cases vs. 16 cases; VE: 100% (95% CI,75.3 to 100)
Number (%) with COVID-19 hospitalization: vaccine vs. comparator	no cases in either group
Number (%) with COVID-19 hospitalization on intensive care: vaccine vs. comparator	no cases in either group
Number (%) with COVID-19 hospitalization AND mechanical ventilation: vaccine vs. comparator	no cases in either group
Number (%) with COVID-19 related death: vaccine vs. comparator	no cases in either group
Number (%) with COVID-19 after 1st and before 2nd dose: vaccine vs. comparator	3 cases vs. 12 cases; VE:75%; 95% CI, 7.6 to 95.5
Covid-19 occurance at least 7 days after 2. doses in participants *with and without* evidence of infection	0 cases vs. 18 cases; VE: 100% (95% CI, 78.1 to 100)
Immunogenicity 12 to 15 years vs. 16 to 25 years	
Geometric Mean 50% Neutralizing Titer (95% CI)	12 to 15 years (n=190) vs. 16 to 25 years (n=170): 1239.5 (1095.5–1402.5) vs. 705.1 (621.4–800.2)
Geometric Mean Ratio (95% CI)	12 to 15 years (n=190) vs. 16 to 25 years (n=170): 1.76 (1.47–2.10); meaning non-inferiority

2. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie für Comirnaty (BNT162b2-Impfstoffs) von BioNTech für 12- bis 15-jährige Kinder und Jugendliche

Tabelle 1: Risk of BIAS-Bewertung der Phase 3-Zulassungsstudie für Comirnaty (BNT162b2-Impfstoffs) von BioNTech für 12- bis 15-jährige Kinder und Jugendliche (1)

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]	low	low	low	some concerns
Lokalreaktionen (local reactions)	low	some concerns[2]	low	low	low	some concerns
Systemische Reaktionen (systemic events)	low	some concerns[2]	low	low	low	some concerns
Schwere Impfstoffnebenwirkungen (serious adverse events)	low	some concerns[2]	low	low	low	some concerns

[1] Teile des Studienpersonals waren nicht verblindet (z.B. Personen, die Impfungen verabreichten). Es wurde eingeschätzt, dass dies keinen oder nur einen vernachlässigbaren Einfluss auf das Verzerrungsrisiko für diesen Endpunkt hatte.

[2] 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.

3. GRADE Evidenzprofil: Impfung mit Comirnaty (BNT162b2) von BionTech/Pfizer gegen COVID-19 bei 12-17-jährigen Kindern und Jugendlichen

Soll 12- bis 17-jährige Jugendliche eine Impfung mit Comirnaty (BNT162b2) von BionTech/Pfizer zum Schutz vor COVID-19 empfohlen werden?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with the BionTech/Pfizer vaccine	No vaccination	Relative (95% CI)	Absolute		
COVID-19 (lab-confirmed); without evidence of prior infection; 12-15 yrs (follow-up median 2 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/1005 (0%)	16/978 (1.6%)	RR 0.03 (0.49 to 0)	16 fewer per 1000 (from 8 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Hospitalisation due to COVID-19 - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Death due to COVID-19 - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Local reaction (example: pain at injection site in age group 12-15 yrs) (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	971/1127 (86.2%)	263/1127 (23.3%)	RR 3.69 (3.31 to 4.11)	628 more per 1000 (from 539 more to 726 more)	⊕⊕⊕ MODERATE	IMPORTANT
Systemic reaction (example: fatique in age group 12-15 yrs) (follow-up median 2 months)												

1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	677/1127 (60.1%)	457/1127 (40.6%)	RR 2.57 (2.29 to 2.89)	637 more per 1000 (from 523 more to 766 more)	⊕⊕⊕ MODERATE	IMPORTANT
Any serious adverse event (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	4/1127 (0.35%)	1/1127 (0.09%)	RR 0.02 (0.01 to 0.04)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕⊕ LOW	CRITICAL
ICU admission due to COVID-19 - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Intubation due to COVID-19 - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Adverse events of special interest - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] 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 to them.

[2] 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.