Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung zur COVID-19-Impfung

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1. Syntax der Suchstrategie für den systematischen Reviews zur Wirksamkeit und Sicherheit der COVID-19-Impfung

Die systematische Literaturrecherche erfolgte in der COVID-19 Literaturdatenbank der Bibliothek des RKI. Diese erfasst sämtliche COVID-19-relevanten Einträge in den Datenbanken Pubmed und Embase (inkl. Medline) sowie auf den Pre-Print Servern ArRvix, BioRvix, ChemRvix, MedRvix, Preprints.org, ResearchSquare und SSRN.

Suchstrategie in der RKI-Datenbank (Datum der Suche: 04.01.2021)
The following searches will be combined with the terms "vaccin*" and "immuniz*" and the brand names of the respective vaccines.

Search Syntax PubMed 1:
("Severe Acute Respiratory Syndrome Coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "covid 19 diagnostic testing" [Supplementary Concept] OR "covid 19 drug treatment" [Supplementary Concept] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 vaccine" [Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[tiab] OR ncov*[tiab] OR covid*[tiab] OR sars-cov-2[tiab] OR "sars cov 2"[tiab] OR "SARS Coronavirus 2"[tiab] OR "Severe Acute Respiratory Syndrome CoV 2"[tiab] OR "Wuhan coronavirus"[tiab] OR "Wuhan seafood market pneumonia virus"[tiab] OR "SARS2"[tiab] OR "2019-nCoV"[tiab] OR "hcov-19"[tiab] OR „novel 2019 coronavirus“[tiab] OR "2019 novel coronavirus*"[tiab] OR „novel coronavirus 2019*“[tiab] OR "2019 novel human coronavirus*"[tiab] OR „human coronavirus 2019“[tiab] OR "coronavirus disease-19"[tiab] OR "corona virus disease-19"[tiab] OR "coronavirus disease 2019"[tiab] OR "corona virus disease 2019"[tiab] OR "2019 coronavirus disease"[tiab] OR "2019 corona virus disease"[tiab] OR „novel coronavirus disease 2019“[tiab] OR „novel coronavirus infection 2019“[tiab] OR "new coronavirus*"[tiab] OR "coronavirus outbreak"[tiab] OR "coronavirus epidemic"[tiab] OR "coronavirus pandemic"[tiab] OR "pandemic of coronavirus"[tiab]) AND ("2019/12/01"[PDAT] : "2099/12/31"[PDAT])Search Syntax PubMed 2: ("wuhan"[tiab] or china[tiab] or hubei[tiab]) AND ("Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "covid 19 diagnostic testing"[Supplementary Concept] OR "covid 19 drug treatment"[Supplementary Concept] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 vaccine"[Supplementary Concept] OR "coronavirus*"[tiab] OR "corona virus*"[tiab] OR ncov[tiab] OR covid*[tiab] OR sars*[tiab])Search Syntax Embase 1: ('severe acute respiratory syndrome coronavirus 2':ti, ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'covid 19'/exp OR ncov*:ti, ab OR covid*:ti, ab OR 'sars cov 2':ti, ab OR 'sars-cov-2':ti, ab OR 'sars coronavirus 2':ti, ab OR 'sars coronavirus 2'/exp OR 'severe acute respiratory syndrome cov 2':ti, ab OR 'wuhan coronavirus':ti, ab OR 'wuhan seafood market pneumonia virus':ti, ab OR sars2:ti, ab OR '2019-ncov':ti, ab OR 'hcov-19':ti, ab OR 'novel 2019 coronavirus':ti, ab OR '2019 novel coronavirus*':ti, ab OR 'novel coronavirus 2019'/exp OR '2019 novel human coronavirus*':ti, ab OR 'human coronavirus 2019':ti, ab OR 'coronavirus disease-19':ti, ab OR 'corona virus disease-19':ti, ab OR 'coronavirus disease 2019':ti, ab OR 'coronavirus disease 2019'/exp OR 'corona virus disease 2019':ti, ab OR '2019 coronavirus disease':ti, ab OR 'novel coronavirus 2019*':ti, ab OR 'novel coronavirus disease 2019':ti, ab OR 'novel coronavirus infection 2019':ti, ab OR '2019 corona virus disease':ti, ab OR 'new coronavirus*':ti, ab OR 'coronavirus outbreak':ti, ab OR 'coronavirus epidemic':ti, ab OR 'coronavirus pandemic':ti, ab OR 'pandemic of coronavirus':ti, ab OR 'severe acute respiratory syndrome coronavirus 2 vaccine'/exp OR 'covid 19 vaccine'/exp) AND 2020:pySearch Syntax Embase 2: (wuhan:ti, ab OR china:ti, ab OR hubei:ti, ab) AND ('severe acute respiratory syndrome coronavirus 2':ti, ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'covid*':ti, ab OR 'covid 19'/exp OR 'covid 19' OR coronavirus*:ti, ab OR 'corona virus*':ti, ab OR ncov:ti, ab OR covid*:ti, ab OR sars*:ti, ab OR 'sars coronavirus 2'/exp)

2. Syntax der Suchstrategie für den Umbrella-Review zu Risikofaktoren schwere COVID-19 Erkrankung (Hospitalisierung) und Mortalität

(letzte Suche: 11.12.2021).

Search Syntax PubMed 1:
("Severe Acute Respiratory Syndrome Coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "covid 19 diagnostic testing" [Supplementary Concept] OR "covid 19 drug treatment" [Supplementary Concept] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 vaccine" [Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[tiab] OR ncov*[tiab] OR covid*[tiab] OR sars-cov-2[tiab] OR "sars cov 2"[tiab] OR "SARS Coronavirus 2"[tiab] OR "Severe Acute Respiratory Syndrome CoV 2"[tiab] OR "Wuhan coronavirus"[tiab] OR "Wuhan seafood market pneumonia virus"[tiab] OR "SARS2"[tiab] OR "2019-nCoV"[tiab] OR "hcov-19"[tiab] OR „novel 2019 coronavirus“[tiab] OR "2019 novel coronavirus*"[tiab] OR „novel coronavirus 2019*“[tiab] OR "2019 novel human coronavirus*"[tiab] OR „human coronavirus 2019“[tiab] OR "coronavirus disease-19"[tiab] OR "corona virus disease-19"[tiab] OR "coronavirus disease 2019"[tiab] OR "corona virus disease 2019"[tiab] OR "2019 coronavirus disease"[tiab] OR "2019 corona virus disease"[tiab] OR „novel coronavirus disease 2019“[tiab] OR „novel coronavirus infection 2019“[tiab] OR "new coronavirus*"[tiab] OR "coronavirus outbreak"[tiab] OR "coronavirus epidemic"[tiab] OR "coronavirus pandemic"[tiab] OR "pandemic of coronavirus"[tiab]) AND ("2019/12/01"[PDAT] : "2099/12/31"[PDAT])

Search Syntax PubMed 2:
("wuhan"[tiab] or china[tiab] or hubei[tiab]) AND ("Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "covid 19 diagnostic testing"[Supplementary Concept] OR "covid 19 drug treatment"[Supplementary Concept] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 vaccine"[Supplementary Concept] OR "coronavirus*"[tiab] OR "corona virus*"[tiab] OR ncov[tiab] OR covid*[tiab] OR sars*[tiab])

Search Syntax Embase 1:
('severe acute respiratory syndrome coronavirus 2':ti,ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'covid 19'/exp OR ncov*:ti,ab OR covid*:ti,ab OR 'sars cov 2':ti,ab OR 'sars-cov-2':ti,ab OR 'sars coronavirus 2':ti,ab OR 'sars coronavirus 2'/exp OR 'severe acute respiratory syndrome cov 2':ti,ab OR 'wuhan coronavirus':ti,ab OR 'wuhan seafood market pneumonia virus':ti,ab OR sars2:ti,ab OR '2019-ncov':ti,ab OR 'hcov-19':ti,ab OR 'novel 2019 coronavirus':ti,ab OR '2019 novel coronavirus*':ti,ab OR 'novel coronavirus 2019'/exp OR '2019 novel human coronavirus*':ti,ab OR 'human coronavirus 2019':ti,ab OR 'coronavirus disease-19':ti,ab OR 'corona virus disease-19':ti,ab OR 'coronavirus disease 2019':ti,ab OR 'coronavirus disease 2019'/exp OR 'corona virus disease 2019':ti,ab OR '2019 coronavirus disease':ti,ab OR 'novel coronavirus 2019*':ti,ab OR 'novel coronavirus disease 2019':ti,ab OR 'novel coronavirus infection 2019':ti,ab OR '2019 corona virus disease':ti,ab OR 'new coronavirus*':ti,ab OR 'coronavirus outbreak':ti,ab OR 'coronavirus epidemic':ti,ab OR 'coronavirus pandemic':ti,ab OR 'pandemic of coronavirus':ti,ab OR 'severe acute respiratory syndrome coronavirus 2 vaccine'/exp OR 'covid 19 vaccine'/exp) AND 2020:py

Search Syntax Embase 2:
(wuhan:ti,ab OR china:ti,ab OR hubei:ti,ab) AND ('severe acute respiratory syndrome coronavirus 2':ti,ab OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'covid*':ti,ab OR 'covid 19'/exp OR 'covid 19' OR coronavirus*:ti,ab OR 'corona virus*':ti,ab OR ncov:ti,ab OR covid*:ti,ab OR sars*:ti,ab OR 'sars coronavirus 2'/exp)

Manual search in: ArRvix, BioRvix, ChemRvix, MedRvix, Preprints.org, ResearchSquare und SSRN

3. Extraktionen der Studiendaten für den systematischen Review zur Wirksamkeit und Sicherheit der COVID-19-Impfstoffe

3.1. BNT162b2 (BioNTech/Pfizer) (1)

	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 characteristics/information	storage at -70°C
Study	Phase 2/3
Reference	Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine. 2020.
Study period	start: 27th July, 2020; data cut off for publication: 14th November, 2020; study is ongoing
Study design	Phase 2/3, multicenter, multinational, randomized (1:1 ratio), placebo-controlled, observer-blind, efficacy study in healthy individuals.
First and second primary efficacy 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 had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose second primary end point was efficacy in participants with and participants without evidence of prior infection
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
Endpoint for power calculation	confirmed COIVD-19 Illness (accrual of 164 cases for VE calculation)
Randomization and ratio	use of Interactive Response Technology for 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	USA, Argentina, Brazil, (South Africa, Turkey, Germany)
Comparator	placebo (normal saline (0.9% sodium chloride solution for injection))
Funding	BioNTech/Pfizer

Conflict of interest	Dr. Absalon, Dr. Bailey, Dr. Cooper, Dr. Dormitzer, Dr. Gruber, Dr. Gurtman, Dr. Jansen, Dr. Kalina, Dr. Kitchin, Dr. Koury, Dr. Li, Dr. Lockhart, Dr. Mather, Dr. Perez, Dr. Pérez Marc, Dr. Roychoudhury, Dr. Swanson, Dr. Tresnan reports personal fees from Pfizer Inc, outside the submitted work; Dr. Hammitt reports grants from Pfizer, during the conduct of the study; grants from Merck, grants from Novavax, outside the submitted work; Dr. Polack reports personal fees from JANSSEN, grants from NOVAVAX, INC, personal fees from BAVARIAN NORDIC A/S, personal fees from PFIZER, personal fees from SANOFI, personal fees from REGENERON, personal fees from MERCK, personal fees from MEDIMMUNE, personal fees from VIRBIO, personal fees from ARKBIO, personal fees from DAIICHI SANKYO, outside the submitted work. Dr. Thomas reports other from Pfizer, during the conduct of the study; personal fees from Merck, personal fees from Sanofi, personal fees from Takeda, personal fees from Themisbio, personal fees from Janssen, outside the submitted work; Dr. Frenck, Dr. Moreira, Dr. Nell, Dr. Sahin, Dr. Schaefer, Dr. Unal, Dr. Tureci, Dr. Zerbini has nothing to disclose.
Inclusion criteria	Male or female participants ≥16 years; Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Capable of giving personal signed informed consent. Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
Exclusion criteria	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. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection; Women who are pregnant or breastfeeding. Previous vaccination with any coronavirus vaccine. 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 (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. Receipt of blood/plasma products or immunoglobulin, from 60 days. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation. Previous participation in other studies involving study intervention containing lipid nanoparticles. Investigator site staff 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)	Main Safety Population: BNT162b2 (N=18,860); Placebo (N=18,846); Efficacy: The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
Age of participants	≥16 years of age [stratified as ≤55 or >55 years of age]
Sex (% male)	50,6%
Duration of follow-up after vaccination	median follow-up time at publication: 2 months; planned: 24-26-month follow-up after 2nd vaccination
Type of follow-up after vaccination	subset of the first 8183 participants randomized in Phase 2/3: 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	44.820 participants were screened; 43.548 underwent randomization

Sample size	For Phase 2/3, the VE evaluation will be the primary objective. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being non evaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.
Final no. of participants analyzed for each endpoint	37.706 received vaccine or placebo and had median follow-up of 2 months
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	
Effectiveness assemssment	
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 hospitalization AND mechanical ventilation	n.a.
COVID-19 related death	n.a.
Confirmed severe COVID-19	Confirmed **severe COVID-19**: confirmed COVID-19 and presence of at least 1 of the following: • Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg); • Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); • Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors); • Significant acute renal, hepatic, or neurologic dysfunction*; • Admission to an ICU; • Death.

	* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.
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	numbers not reported, only %; N=8183
Number (%) with pain: vaccine vs. comparator	1st dose: 16-55 years: 83% : 14% ; >55 years: 71% : 9% 2nd dose: 16-55 years: 78% : 12% ; >55 years: 66% : 8%
Number (%) with tenderness: vaccine vs. comparator	not reported
Number (%) with Erythema/redness: vaccine vs. comparator	1st dose: 16-55 years: 5% : 1% ; >55 years: 5% : 1% 2nd dose: 16-55 years: 6% : 1% ; >55 years: 7% : 1%
Number (%) with Induration/swelling: vaccine vs. comparator	1st dose: 16-55 years: 6% : 0% ; >55 years: 7% : 1% 2nd dose: 16-55 years: 6% : 0% ; >55 years: 7% : 1%
Number (%) with systemic reactions (myalgia, nausea, fatigue, …)	not reported
Number (%) with fever: vaccine vs. comparator	16-55 years: 1st dose: 4% : 1% ; 2nd dose: 16% : 0% >55 years: 1st dose: 1% : 0% 2nd dose: 11% : 0%
Number (%) with fatigue/ tiredness: vaccine vs. comparator	16-55 years: 1st dose: 47% : 33% ; 2nd dose: 59% : 23% >55 years: 1st dose: 34% : 23% 2nd dose: 51% : 17%
Number (%) with headache: vaccine vs. comparator	16-55 years: 1st dose: 42% : 34% ; 2nd dose: 52% : 24% >55 years: 1st dose: 25% : 18%; 2nd dose: 39% : 14%
Number (%) with chills: vaccine vs. comparator	16-55 years: 1st dose: 14% : 6% ; 2nd dose: 35% : 4% >55 years: 1st dose: 6% : 3%; 2nd dose: 23% : 3%
Number (%) with vomiting: vaccine vs. comparator	16-55 years: 1st dose:1 % : 1% ; 2nd dose: 2% : 1% >55 years: 1st dose: 0% : 1%; 2nd dose: 1% : 0%
Number (%) with diarrhea: vaccine vs. comparator	16-55 years: 1st dose: 11% : 12% ; 2nd dose: 10% : 8% >55 years: 1st dose: 8% : 7%; 2nd dose: 8% : 6%
Number (%) with myalgia: vaccine vs. comparator	16-55 years: 1st dose: 21% : 11% ; 2nd dose: 37% : 8% >55 years: 1st dose: 14% : 8%; 2nd dose: 29% : 5%
Number (%) with joint pain: vaccine vs. comparator	16-55 years: 1st dose: 11% : 6% ; 2nd dose: 22% : 5% >55 years: 1st dose: 9% : 6%; 2nd dose: 19% : 4%
Number (%) with use of antipyretic medication: vaccine vs. comparator	16-55 years: 1st dose: 28% : 14% ; 2nd dose: 45% : 13% >55 years: 1st dose: 20% : 12%; 2nd dose: 38% : 10%
Number (%) with serious adverse events: vaccine vs. comparator	all SAE: 126 (0,6%) : 111 (0,5%); classified as vaccine related: 4 (<0,01%) : 0 (-); graded as severe: 71 (0,3%) : 68 (0,3%); life threatening 21 (0,1) : 23 (0,1)
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 occurrence 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	Number of cases among population of study arm; VE with 95%CI: all: 8/17.411 : 162/17.511; VE 95,0 (90,0-97,9) 16-55 years: 5/9.897 : 114/9.955; VE: 95,6 (89,4-98,6) >55 years: 3/7.500 : 48/7.543; VE: 93,7 (80,6-98,8) ≥65 years: 1/3.848 : 19/3.880; VE: 94,7 (66,7-99,9) ≥75 years: 0/774 : 5/785; VE: 100,0 (-13,1-100,0)
Number (%) with COVID-19 hospitalization: vaccine vs. comparator	not reported; severe COVID-19 was used as proxy: 1/21.314 : 4/21.259; VE: 75,0 (-152,6-99,5)
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	none
Number (%) with COVID-19 after 1st and before 2nd dose: vaccine vs. comparator	all: 39/21.314 : 82/21.258; VE: 52,4 (29,5-68,4)
COVID-19 occurence at least 7 days after 2. doses in participants *with and without* evidence of infeciotn	all: 9/18.559 : 169/18.708; VE: 94,6 (89,9-97,3)

3.2. mRNA-1723 (Moderna)(2)

Vaccine	
Vaccine name	COVID-19 Vaccine Moderna (mRNA-1273)
Vaccine composition	100 µg lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine: a synthetic messenger ribonucleic acid (mRNA) encoding the prefusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus
Vaccine manufacturer & develloper	ModernaTX, Inc.
Vaccine type	mRNA-vaccine
number and timing of doses, route	2 doses á 100µg (0,5ml), 28 days apart, i.m.
other vaccine charcteristics/information	vaccine must be stored at -25° to -15°C; after thawing vials can be stored refrigerated between 2°C to 8°C for up to 30 days; unopened vials may be stored between 8° to 25°C for 12 hours
Study	Study mRNA-1273-P301 (Phase 3)
Reference	Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020. Publication of the Food and Drug Administration (FDA): Moderna-COVID-19 Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum (FDA) https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiu46Hi-_LtAhXL_aQKHXHrAd0QFjAAegQIBBAC&url=https%3A%2F%2Fwww.fda.gov%2Fmedia%2F144673%2Fdownload&usg=AOvVaw1TzrvHbv3ybQ-kWXjW8Kie
Study period	The study enrollment (1st trial injection between July 27 and October 23,2020) and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. Planned follow-up approximately 24-26 months after second dose for each participant;
Study design	Phase 3, ongoing randomized (1:1 ratio), stratified, observer-blind, placebo-controlled multi-center study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection.
First and second primary efficacy endpoints	**Primary endpoint** was efficacy of mRNA-1273 to prevent protocol-defined **COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1**). COVID-19 is defined as symptomatic disease based on the following criteria: • TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR • ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND • NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. **Secondary endpoint:** **Severe COVID-19: (**Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg); OR Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); OR Evidence of shock (SBP<90 mm Hg, DBP <60 mm Hg, or requiring vasopressors) OR Significant acute renal, hepatic, or neurologic dysfunction OR Admission to an ICU OR Death **• COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine** **• Death due to COVID-19** **• COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)**
Primary safety endpoint	• Solicited local and systemic ARs through 7 days after each dose of IP. • Unsolicited AEs through 28 days after each dose of IP. • Medically attended adverse events (MAAEs) or AEs leading to withdrawal through the entire study period. • Serious AEs (SAEs)throughout the entire study period.
Endpoint for power calculation	confirmed COVID-19 cases; 151 cases for final VE calculation

Randomization and ratio	centralized Interactive Response Technology (IRT); ratio 1:1; 3 strata (Age and health risk for severe COVID-19 is used as stratification factor for randomization); 30418 randomized (vaccine group=15208, placebo group=15210)
Blinding	observer-blinded study; Vaccine is a white to off-white, sterile, preservative-free frozen suspension differing from the placebo.
Countries	99 sites across the United States
Comparator	placebo ((normal saline (0.9% sodium chloride solution for injection))
Funding	Moderna TX, Inc.
Conflict of interest	See https://www.nejm.org/doi/suppl/10.1056/NEJMoa2035389/suppl_file/nejmoa2035389_disclosures.pdf
Inclusion criteria	Male or female participants ≥ 18 years of age, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19. (Women in childbearing age: negative pregnancy test and contraception.) Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.
Exclusion criteria	Acute illness, pregnancy or breastfeeding; known history of SARS-CoV-2 infection; Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine; Known or suspected allergy or history of anaphylaxis, or significant adverse reaction to the vaccine or its excipients. Bleeding disorder; Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV positive participants with CD4 count ≥350 cells/mm3 and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy [ART] are permitted]). Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent). Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.
Participants (study groups)	Participants **(N=30,351)** were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo (n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: **18 to <65 years of age and not at risk for progression to severe COVID-19**, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers.
Age of participants/ Ethnicity	Mean (range): mRNA-1273 vaccine group: 51,4 (18-95); placebo group: 51,3 years (18-95); individuals ≥65 years of age: mRNA-1273 vaccine group24,8%; placebo group: 24,7%.
Sex (% male)	52,2%
Duration of follow-up after vaccination	As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received **one dose** of vaccine or placebo was **100%**, and the proportion of participants who received **two doses** was **96%**. Median follow-up **after dose 2 was 64 days (range 0-97 days)**. The proportion of participants with at **least 56 days of follow-up after dose 2 was 61%**. Proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups.
Type of follow-up after vaccination	Weekly contacts with the participant via a combination of telephone calls and completion of an eDiary. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of **27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2** were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination.

Initial no. of participants included	mRNA-1273 vaccine group: 15,181; placebo group 15,170
Sample size	The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.30,000 participants, 151 cases for final analysis.
Final no. of participants analyzed for each endpoint	30,420 participants underwent randomization; 30,351 participants were included in safety analysis; per protocol analysis for efficacy endpoints: 14,073 placebo group and 14,134 mRNA-1273-group
Confounders adjusted for	not reported
Safety assessment	Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries. • Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR. • AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study. • Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study. • Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study. • Abnormal vital sign measurements. • Physical examination findings. • Pregnancy and accompanying outcomes.
Safety -- definitions	
local reactions	
local reactions: pain	Grade 1-4 (protocol page 75-) Grade 3: any use of Rx pain reliever/prevents daily activity Grade 4: requires E.R. visit or hospitalization
local reactions: Erythema and Swelling/Induration	Grade 1-4 (protocol page 75-) Grade3: >100mm/>10cm; Grade 4:necrosis/exfoliative dermatitis
local reactions: Axillary Swelling/Tendernessipsilateral to the vaccination arm	Grade 1-4 (protocol page 75-) Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
systemic reactions (fever, myalgia, nausea, fatigue, …)	
Vomiting	Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
Headache	Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
Fatigue/ tiredness	Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
Chills	Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization
Myalgia	Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
Arthralgia	Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
Fever	Grade 3: ≥39.0 – ≤40.0°C Grade 4: >40.0°C

adverse events	Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), or any event already present that worsened after exposure. Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose • AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
serious adverse events	•Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.
adverse events of special interest (AESI) according to CEPI criteria (e.g. enhanced COVID-19, Guillain-Barrée Syndrom)	
Effectiveness -- definitions	
Effectiveness assemssment	
SARS-CoV-2 infection	RT-PCR confirmation of SARS-CoV-2 infection; SARS-CoV-2 infection is defined by seroconversion
COVID-19	COVID-19 with RT-PCR confirmation of SARS-CoV-2 infection: •The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND • The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
COVID-19 hospitalization	n.a.
COVID-19 hospitalization on intensive care	n.a.
COVID-19 hospitalization AND mechanical ventilation	n.a.
COVID-19 related death	There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.
Confirmed severe COVID-19	Case of confirmed COVID-19 plus at least one of the following: • Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg); • Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); • Evidence of shock (SBP<90 mm Hg, DBP <60 mm Hg, or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction; • Admission to an ICU; • Death
VE calculation	VE is calculated as 1-hazard ratio (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model.
Safety -- results	Safety data from a November 11, 2020 of 30,351 participants ≥18 years of age with a median of 7 weeks of follow-up after the second dose. On December 7, 2020, additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2 were submitted. The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ≥65 years of age as compared to younger participants. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. Mean duration: 2.6 days after first dose, 3.2 days after 2. dose.

Number (%) with local reactions: vaccine vs. comparator	any local AR: 1st dose 84.2% vs. 19.8%; 2nd dose: 88.6% vs.18.8% grade 3 local AR: 1st dose 4% vs. 0.3%; 2nd dose 7.4% vs. 0.4% No reports of Grade 4 local reactions after any dose across groups. Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts.
Number (%) with pain: vaccine vs. comparator	Pain: 1st dose 83.7% vs 17.5% (Grade 3: 3.2% vs. 0.2%); 2nd dose 88.2% vs 17.0% (Grade 3: 4.6% vs 0.2%). 18-65: Pain: 1st dose 86.9% vs 19.1% (Grade 3: 3.2% vs 0.2%); 2nd dose 90.1% vs 18.8% (Grade 3: 4.6% vs 0.2%). >65: Pain: 1st dose 74.0% vs 12.8% (Grade 3: 1.3% vs 0.9%); 2nd dose 83.4% vs 11.9% (Grade 3: 2.7% vs 0.5%).
Number (%) with swelling: vaccine vs. comparator	Swelling at injection side: 1st dose 6.1% vs. 0.3% (Grade 3: 0.5% vs. <0.1%); 2nd dose 12.2% vs. 0.3% (Grade 3: 1.7% vs.<0.1%) Axillary swelling or tenderness: 1st dose 11.6% vs 5.0% (Grade 3: 0.3% vs. 0.1%); 2nd dose 16.0% vs. 4.3% (Grade 3: 0.4% vs. <0.1%). 18-65: swelling: 1st dose 6.7% vs. 0.3% (Grade 3: 0.5% vs <0.1%); 2nd dose 12.6% vs 0.3% (Grade 3: 1.7% vs <0.1%). >65: swelling: 1st dose 4.4% vs. 0.5% (Grade 3: 0.5% vs <0.1%); 2nd dose 10.8% vs 0.4% (Grade 3: 1.9% vs 0.2%).
Number (%) with Erythema/redness: vaccine vs. comparator	Redness: 1st dose 2.8% vs. 0.4% (Grade 3: 0.3% vs <0.1%); 2nd dose 8.6% vs 0.4% (Grade 3: 2.0% vs 0.1%).
Number (%) with lymphadenpathy: vaccine vs. comparator	18-65: axillary swelling and tenderness (lymphadenopathy): 1st dose 11.6% vs. 5.0% (Grade 3: 0.3% vs 0.1%); 2nd dose 16.0% vs 4.3% (Grade 3: 0.4% vs <0.1%). >65: 1st dose 6.1% vs. 4.1% (Grade 3: 0.3% vs 0.4%); 2nd dose 8.4% vs 2.5% (Grade 3: 0.6% vs 0.2%).
Number (%) with systemic reactions (myalgia, nausea, fatigue, …)	any systemic AR: 1st dose 54.9% vs. 42.2%; 2nd dose: 79.4% vs.36.5% Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients and at higher rates of systemic reactions after the 2nd dose than the 1st dose. Any grade: 1st dose 54.9% vs 42.2% (Grade 3 2.9% vs. 2.0%); 2nd dose: 79.3% vs 36.5% (Grade 15.7%vs. 2.0%). Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever). Median duration after any dose was 2 days. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1. 18-65: any systemic reaction: 1st dose 57.0% vs. 44.4% (Grade 3: 3.2% vs 2.21%/Grade 4: <0.1 % vs.<0.1%); 2nd dose 81.9% vs 38.4% (Grade 3: 17.4% vs 2.1%/Grade 4: <0.1 % vs.<0.1%). >65: any systemic reaction: 1st dose 48.3% vs. 35.6% (Grade 3: 2.2% vs 1.7%/Grade 4: 0% vs. 0%); 2nd dose 71.9% vs 31.1% (Grade 3: 10.8% vs 1.6%/Grade 4: <0.1 % vs.<0.1%).
Number (%) with fever: vaccine vs. comparator	Fever: after 1st dose 0.8% vs. 0.3% and after 2nd dose 15.6% vs. 0.3% Grade 3: <0.1% of vaccine recipients after dose 1 and 1.3% after dose 2. Grade 4: by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. 18-65: fever: 1st dose 0.9% vs. 0.3% (Grade 3: <0.1% vs. <0.1%/Grade 4: <0.1 % vs.<0.1%); 2nd dose 17.4% vs. 0.4% (Grade 3: 1.6% vs. <0.1%/Grade 4: <0.1 % vs.<0.1%). >65: fever: 1st dose 0.3% vs. 0.2% (Grade 3: <0.1% vs. <0.%/Grade 4: 0% vs. <0.1%); 2nd dose 10.2% vs. 0.1% (Grade 3: 0.5% vs. 0%/Grade 4: <0.1 % vs.<0.1%).
Number (%) with nausea/Vomiting: vaccine vs. comparator	18-65: Nausea/Vomiting: 1st dose 9.4% vs. 8.0% (Grade 3: <0.1% vs <0.1%); 2nd dose 21.3% vs 7.3% (Grade 3: <0.1% vs <0.1%). >65: Nausea/Vomiting: 1st dose 5.2% vs. 4.4% (Grade 3: 0.1% vs 0.1%); 2nd dose 11.8% vs 3.6% (Grade 3: 0.3% vs <0.1%).
Number (%) with chills: vaccine vs. comparator	Chills after any dose: 43.4% vs. 9.5% (Grade 3: 1.3% vs. 0.2%). 18-65: chills: 1st dose 9.2% vs. 6.4% (Grade 3: 0.1% vs <0.1%); 2nd dose 48.3% vs 5.9% (Grade 3: 1.5% vs 0.1%). >65: chills: 1st dose 5.4% vs. 4.0% (Grade 3: 0.2% vs 0.2%); 2nd dose 30.6% vs 4.1% (Grade 3: 0.8% vs <0.1%)
Number (%) with headache: vaccine vs. comparator	Headache after any dose: 63.0% vs.36.5% (Grade 3: 5.5% vs. 2.2%); 1st dose 32.7% vs. 26.6%; 2nd dose 58.6% vs. 23.4% 18-65: headache: 1st dose 35.4% vs. 29.0% (Grade 3: 1.9% vs 1.4%); 2nd dose 62.8% vs 25.4% (Grade 3: 5.0% vs 1.2%).

	>65: headache: 1st dose 24.5% vs. 19.3% (Grade 3: 1.4% vs. <0.9%); 2nd dose 46.4% vs 17.9% (Grade 3: 3.0% vs. 0.9%).
Number (%) with fatigue/ tiredness: vaccine vs. comparator	Overall: 68.5% vs. 36.1%. After any dose, Grade 3: 9.6% vs. 1.3%. Grade 4 fatigue was reported by 1 vs. 0. After 1st dose any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after 2nd dose by 65.3%/9.7% of vaccine recipients. 18-65: Fatigue: 1st dose 38.5% vs. 28.8% (Grade 3: 1.1% vs <0.7%/Grade 4: <0.1 % vs.<0%); 2nd dose 67.6% vs 24.5% (Grade 3: 10.6% vs 0.8%/Grade 4: 0% vs.0%). >65: Fatigue: 1st dose 33.3% vs. 22.7% (Grade 3: 0.8% vs <0.6%); 2nd dose 58.4% vs 19.6% (Grade 3: 6.9% vs 0.6%).
Number (%) with myalgia: vaccine vs. comparator	Myalgia after any dose: 59.6% vs. 20.1% (Grade 3: 8.6% vs. 0.6%) 18-65: Myalgia: 1st dose 23.7% vs. 14.3% (Grade 3: 0.6% vs 0.3%); 2nd dose 6.1% vs 12.7% (Grade 3: 10.0% vs. 0.4%). >65: Myalgia: 1st dose 19.8% vs. 11.8% (Grade 3: 0.5% vs 0.2%); 2nd dose 46.9% vs 10.8% (Grade 3: 5.6% vs. 0.3%).
Number (%) with joint pain: vaccine vs. comparator	Arthralgia after any dose: 44.8% vs. 17.2% 18-65: Arthralgia: 1st dose 16.6% vs. 11.6% (Grade 3: 0.4% vs 0.3%); 2nd dose 45.2% vs 10.5% (Grade 3: 5.8% vs 0.3%). >65: Arthralgia: 1st dose 16.4% vs. 12.2% (Grade 3: 0.3% vs 0.2%); 2nd dose 34.9% vs 1078% (Grade 3: 3.4% vs 0.2%).
Number (%) with serious adverse events: vaccine vs. comparator	The frequency of serious adverse events was low (1.0%in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%). 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling.
Number (%) with adverse events of special interest (AESI) according to CEPI criteria (e.g. enhanced COVID-19, Guillain-Barrée Syndrom)	Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group.
Pregnancies	Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.
Effectiveness -- results	Primary Endpoint, COVID-19 Starting 14 days after the second dose
Number (%) with SARS-CoV-2 infection: vaccine vs. comparator	not reported
Number (%) with COVID-19: vaccine vs. comparator	All participants: vaccine group: 11/14,134; placebo group 185/14,073 VE: 94.1% (89.3%, 96.8%) 18 to <65: vaccine group: 7/10,551; placebo group 156/10,521VE: 95.6% (90.6%–97.9%) 65 and older: vaccine group 4/3583; placebo group 29/3552 VE 86.4% (61.4%–95.2%) 75 and older: vaccine group 0/623; placebo group 3/676 VE 100% (-) Age and risk for severe COVID-19** 18 and <65 and not at risk: vaccine group 5/8,396; placebo group 121/8,403 VE: 95.9% (90.0%-98.3%) 18 and <65 and at risk: vaccine group 2/2,155; placebo group 35/2,118 VE: 94.4% (76.9%-98.7%) >65: vaccine group 4/3,583; placebo group 29/3,552 VE: 86.4% (61.4%-95.2%)

Number (%) with COVID-19 hospitalization: vaccine vs. comparator	not reported; severe COVID-19 was used as proxy: Severe COVID-19: all vaccine group 0/1,4134; placebo group: 30/1,4073 VE: 100% (-)
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	vaccine group 0/14,134; placebo group 1/14,073 VE 100% (-)
Number (%) with COVID-19 after 1st and before 2nd dose: vaccine vs. comparator	After dose 1, before dose 2: 7/996 vs. 39/1079 VE: 50.2% (55.2%, 92.5%) 14 days after dose 1, before dose 2: 2/14,550 vs. 35/14.598 VE: 94.0% (76.0%-99.0%)

4. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie des BNT162b2-Impfstoffs von BioNTech (1)

Tabelle 1: Risk of BIAS-Bewertung der Phase-3-Zulassungsstudie des BNT162b2-Impfstoffs von BioNTech (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]	some concerns[2]	low	low	some concerns
Severe COVID-19 (als proxy für Hospitalisierung)	low	low[1]	some concerns[2]	low	low	some concerns
Lokalreaktionen (local reactions)	low	some concerns[3]	some concerns[2]	low	low	some concerns
Systemische Reaktionen (systemic events)	low	some concerns[3]	some concerns[2]	low	low	some concerns
Schwere Impfstoffnebenwirkungen (serious adverse events)	low	some concerns[3]	some concerns[2]	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] Ein beträchtlicher Teil der randomisierten Studienpopulation (beider Studienarme), der zudem deutlich größer ist als die Gesamtzahl der Ereignisse, ging nicht in die Auswertung ein. Das *reporting* ist hier unklar, so dass eine Verzerrung nicht komplett ausgeschlossen werden kann.

[3] 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. GRADE Evidenzprofil: Vaccination with BNT162b2 (BionTech/Pfizer) against COVID-19 (1)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with BNT162b2	No vaccination	Vaccine efficacy (VE) or risk ratio (RR) (95% CI)	Absolute		
COVID-19 (lab-confirmed); with and without evidence of prior infection; all age groups (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/18559 (0.05%)	169/18708 (0.9%)	VE 94.6 (89.9 to 97.3)	9 fewer per 1000 (from 8 fewer to 9 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age 16-55 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/9897 (0.05%)	114/9955 (1.1%)	VE 95.6 (89.4 to 98.6)	11 fewer per 1000 (from 10 fewer to 11 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age >55 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/7500 (0.04%)	48/7543 (0.64%)	VE 93.7 (80.6 to 98.8)	6 fewer per 1000 (from 5 fewer to 6 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age >=65 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/3848 (0.03%)	19/3880 (0.49%)	VE 94.7 (66.7 to 99.9)	5 fewer per 1000 (from 3 fewer to 5 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age >=75 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/774 (0%)	5/785 (0.64%)	VE 100.0 (-13.1 - to 100.0)	6 fewer per 1000 (from 6 fewer to 13 more)	⊕⊕OO LOW	IMPORTANT
										-		
Hospitalisation due to COVID-19 (proxy: severe COVID-19; lab-confirmed); with and without evidence of prior infection; all age groups (follow-up median 2 months)												

1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	1/21314 (0.005%)	4/21259 (0.02%)	VE 75 (-152.6 to 99.5)	10 fewer per 10000 (from 15 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
Local reaction (example: pain at injection site after dose 1; age 16-55 years)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83%	14%	Calculation based on published data not possible		⊕⊕⊕O MODERATE	IMPORTANT
Systemic reaction (example: fatique after dose 1; age 16-55 years)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47%	33%	Calculation based on published data not possible		⊕⊕⊕O MODERATE	IMPORTANT
Any serious adverse event; all age groups (up to 14 weeks after dose 2)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/21621 (0.58%)	111/21631 (0.51%)	RR 1.13 (0.88 to 1.46)	1 more per 1000 (from 1 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
ICU admission due to COVID-19 – no evidence available												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Intubation due to COVID-19 - no evidence available												
0	-	-	-	-	-	-	-	-	-	--		CRITICAL
Death due to COVID-19 - no evidence available												
0	-	-	-	-	-	-		-	-	-		CRITICAL
Adverse events of special interest - no evidence available												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL

[1] exclusion of participants in both arms not completely transparently described; impact on results cannot definitely be excluded

[2] Wide 95% confidence interval

[3] severe COVID-19 used as proxy for hospitalization (indirectness regarding outcome)

[4] 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.

6. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie des mRNA-1723-Impfstoffs von Moderna (2)

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
Severe COVID-19 (als proxy für Hospitalisierung)	low	low[1]	some concerns[2]	low	low	some concerns
Tod	low	low[1]	some concerns[2]	low	low	some concerns
Lokalreaktionen (local reactions)	low	some concerns[3]	some concerns[2]	low	low	some concerns
Systemische Reaktionen (systemic events)	low	some concerns[3]	some concerns[2]	low	low	some concerns
Schwere Impfstoffnebenwirkungen (serious adverse events)	low	some concerns[3]	some concerns[2]	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 Ein beträchtlicher Teil der randomisierten Studienpopulation (beider Studienarme), der zudem deutlich größer ist als die Gesamtzahl der Ereignisse, ging nicht in die Auswertung ein. Das reporting ist hier unklar, so dass eine Verzerrung nicht komplett ausgeschlossen werden kann.

3 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.

7. GRADE Evidence Profile: Vaccination with mRNA-1273 (Moderna) against COVID-19(2)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with mRNA-1273	No vaccination	Vaccine efficacy (VE) or risk ratio (RR) (95% CI)	Absolute		
COVID-19 (lab-confirmed); without evidence of prior infection; all age groups (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/14134 (0.08%)	185/14073 (1.3%)	VE 94.1 (89.3 to 96.8)	13 fewer per 1000 (from 12 fewer to 13 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age 18-64 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/10551 (0.07%)	156/10521 (1.5%)	VE 95.6 (90.6 to 97.9)	14 fewer per 1000 (from 13 fewer to 15 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age >=65 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/3583 (0.11%)	29/3552 (0.82%)	VE 86.4 (61.4 to 95.2)	7 fewer per 1000 (from 5 fewer to 8 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
COVID-19 (lab-confirmed); without evidence of prior infection; age >=75 years (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/623 (0%)	3/676 (0.4%)	VE 100 (95%CI not calculated)	- (cannot be calculated)	⊕⊕⊕O MODERATE	IMPORTANT
Hospitalisation due to COVID-19 (proxy: severe COVID-19; lab-confirmed); without evidence of prior infection; all age groups (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/14134 (0%)	30/14073 (0.21%)	VE 100 (95%CI not calculated)	- (cannot be calculated)	⊕OOO VERY LOW	CRITICAL
Death due to COVID-19 (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/14134 (0%)	1/14073 (0.007%)	VE 100 (95%CI not calculated)	- (cannot be calculated)	⊕⊕OO LOW	CRITICAL

Local reaction (example: pain at injection site after dose 1) (follow-up median 2 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12690/15168 (83.7%)	2658/15155 (17.5%)	RR 5.0 (4.82 to 5.18)	702 more per 1000 (from 670 more to 733 more)	⊕⊕⊕O MODERATE	IMPORTANT
Systemic reaction (example: fatique after dose 1; age 16-55 years) (follow-up median 2 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5635/15168 (37.2%)	4133/15155 (27.3%)	RR 1.24 (1.22 to 1.27)	65 more per 1000 (from 60 more to 74 more)	⊕⊕⊕O MODERATE	IMPORTANT
Any serious treatment-emergent adverse event (follow-up median 2 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93/15184 (0.6%)	89/15165 (0.6%)	RR 1.0 (0.89 to 1.18)	0 more per 1000 (from 1 fewer to 1 more)	⊕⊕⊕O MODERATE	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] exclusion of participants in both arms not completely transparently described; impact on results cannot definitely be excluded

[2] severe COVID-19 used as proxy for hospitalization (indirectness regarding outcome)

[3] wide 95% confidence interval

[4] 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.

8. DECIDE-Tabelle

Evidence-to-Decision Tabelle: Soll der Bevölkerung eine Impfung gegen COVID-19 mit den COVID-19-Impfstoffen (BNT162b2 (BioNTech/Pfizer) bzw. mRNA-1273 (Moderna) empfohlen werden (1, 2)**?**

Impfziele:

- Verhinderung schwerer COVID-19-Verläufe (Hospitalisierung) und Todesfälle
- Schutz von Personen mit besonders hohem arbeitsbedingten SARS-CoV-2-Expositionsrisiko (berufliche Indikation)
- Verhinderung von Transmission sowie Schutz in Umgebungen mit hohem Anteil vulnerabler Personen und in solchen mit hohem Ausbruchspotenzial
- Aufrechterhaltung staatlicher Funktionen und des öffentlichen Lebens

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Problem	Hat das Problem Priorität?	☐ Nein ☐ Eher Nein ☐ Unklar ☐ eher Ja ☐ Ja ☐ Teils Nein / Teils Ja	Mit Stand 08.12.2020 sind in Deutschland über das IfSG Meldesystem folgende Anzahlen an Fällen übermittelt worden: • 1.197.709 COVID-19-Fälle seit Beginn der Pandemie • Kumulative Inzidenz: 1.440/100.000 • 82.000 Hospitalisierungen (7%) • 14.361Tote (1,5%) • 87% der Todesfälle ≥70 Jahre • 7-Tages-Inzidenz >100 in 279 Kreisen von insg. 412 • Altenpflegeheime von Ausbrüchen hinsichtlich Fallzahl und Mortalität besonders betroffen • 35.839 COVID-19 Fälle sind bisher intensivmedizinisch behandelt worden; davon sind 8.550 verstorben (24%)	Durch verschärftes Kontaktmanagement (Lock down) wird angestrebt, die Infektionswelle abzuflachen und die SARS-CoV-2-Ausbreitung zu verhindern. Die bisher ergriffenen Infektionsschutzmaßnahmen wirken sich in fast allen Lebensbereichen einschneidend auf die Bevölkerung aus, v. a. in den Bereichen des Gesundheitswesens, des sozialen Lebens und der Wirtschaft.

<table>
<tr><th></th><th>Kriterien</th><th>Bewertung</th><th>Stand der Wissenschaft / Evidenz</th><th>zusätzliche Hinweise</th></tr>
<tr><td rowspan="4">Nutzen und Risiken</td><td>Sind die zu erwartenden erwünschten Effekte groß?</td><td>☐ Nein
☐ Eher Nein
☐ Unklar
☐ Eher Ja
☐ Ja
☐ Teils Nein / Teils Ja</td><td>• Gepoolte Daten zur VE von BNT162b2 und mRNA-1273:
• Impfeffektivität gegen COVID-19 (alle Altersgruppen): 95,0% (95%CI: 91,0-97,0)
• Auch in der Altersgruppe ≥65 Jahre hohe Effektivität gegen COVID-19: 90,0% (95%CI: 74,0-96,0)
• Altersgruppe ≥75 Jahre: 88% (95% CI: 9-99)
• Effektivität gegen schwere COVID-19-Erkrankung: 96,0% (78,0-99)
• Bisher keine verlässlichen Daten aufgrund der seltenen Beobachtungen zu Verhinderung von ITS-Aufnahme oder Tod verfügbar
• Modellierung des RKI zeigt, dass durch die priorisierte Impfung von Personen im Alter von >=80 Jahren in den ersten 12 Wochen nach Einführung der Impfung 38.820 COVID-19-Fälle, 20.910 Hospitalisierungen und 3.830 COVID-19-bedingte Todesfälle verhindert werden können.</td><td>Durch die Priorisierung und die vorrangige Impfung von alten Menschen bzw. Pflegebedürftigen sollen zu Beginn des Impfprogramms vor allem schwere Krankheitsverläufe und Todesfälle verhindert werden.</td></tr>
<tr><td>Sind die zu erwartenden unerwünschten Effekte gering?</td><td>☐ Nein
☐ Eher Nein
☐ Unklar
☐ Eher Ja
☐ Ja
☐ Teils Nein / Teils Ja</td><td>• Lokalreaktionen: z.B. Schmerzen 83% bzw. 88% vs. 14% bzw. 17%
• Systemische Reaktionen: z.B. Abgeschlagenheit 47% bzw. 65% vs. 23 bzw. 33%
• Schwere UAWs: RR 1,13 (95%CI: 0,88-1,46) bzw. RR 1,0 (95%CI: 0,89-1,18)</td><td>Die Impfung ist vergleichsweise reaktogen. Es gab aber weder unter den Lokalreaktionen, noch unter den systemischen Reaktionen besondere Auffälligkeiten. Es gab in den Zulassungsstudien (Phase 1-3) keine Hinweise auf ein erhöhtes Risiko für schwere UAWs.</td></tr>
<tr><td>Sind die erwünschten Effekte groß in Relation zu den unerwünschten Effekten?</td><td>☐ Nein
☐ Eher Nein
☐ Unklar
☐ Eher Ja
☐ Ja
☐ Teils Nein / Teils Ja</td><td>Die Impfung hat (bei vergleichsweise hoher Reaktogenität) eine sehr hohe Effektivität in der Verhinderung von COVID-19 in allen untersuchten Altersgruppen. Die Modellierung zeigt, dass ein beträchtlicher Public-Health-Effekt erzielt werden kann.</td><td></td></tr>
<tr><td>Wie ist die Qualität der Evidenz?</td><td>Wirksamkeit der Intervention
☐ keine Studien
☐ sehr niedrig
☐ niedrig
☐ moderat
☐ hoch</td><td>Relative Bedeutung der wichtigsten Ergebnisse bzw. Endpunkte:<table><tr><th>Ergebnis</th><th>relative Bedeutung</th><th>GRADE</th></tr><tr><td colspan="3">Wirksamkeit der Intervention</td></tr><tr><td>SARS-CoV-2-Infektion (Transmission)</td><td>IMPORTANT</td><td>Keine Daten</td></tr></table></td><td>Die Evidenzqualität für den in den Zulassungsstudien untersuchten primären Endpunkt COVID-19 (Bewertung: IMPORTANT) war moderat (aufgrund Verzerrungsrisiko). Für den von der</td></tr>
</table>

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz			zusätzliche Hinweise
			COVID-19	IMPORTANT	MODERAT	STIKO als „kritisch“ (CRITICAL) für die Entscheidungsfindung bewerteten Endpunkte Hospitalisierung lag keine direkte Evidenz vor; es wurde der in der Studie untersuchte Endpunkt „severe COVID-19“ als indirekte Evidenz hierfür verwendet.
			COVID-19-Hospitalisierung	CRITICAL	SEHR GERING	
			COVID-19-Hospitalisierung (ITS-pflichtig)	CRITICAL	Keine Daten	
			COVID-19-Hospitalisierung (beatmungspflichtig)	CRITICAL	Keine Daten	
			COVID-19-bedingter Tod	CRITICAL	BNT162b2: Keine Daten/ mRNA-1273: GERING	
		Sicherheit der Intervention ☐ keine Studien ☐ sehr niedrig ☐ niedrig ☐ moderat ☐ hoch	Relative Bedeutung der wichtigsten Ergebnisse bzw. Endpunkte:			Die Sicherheitsendpunkte wurden alle aufgrund des Verzerrungsrisikos als moderate Evidenzqualität eingeschätzt.
			Ergebnis	**relative Bedeutung**	**GRADE**	
			Sicherheit der Intervention			
			Lokalreaktionen	IMPORTANT	MODERAT	
			Systemische Reaktionen	IMPORTANT	MODERAT	
			Schwere unerwünschte Ereignisse	CRITICAL	MODERAT	
Werte	Besteht erhebliche Unsicherheit darüber, ob die Intervention Akzeptanz in der Zielgruppe findet? (Nutzen-Risiko-Bewertung auf Patientenebene)	☐ Erhebliche Unsicherheit oder Variabilität ☐ Mögliche Unsicherheit oder Variabilität ☐ Eher keine Unsicherheit oder Variabilität ☐ Keine Unsicherheit oder Variabilität ☐ keine bekannten unerwünschten Endpunkte	Daten zur möglichen Akzeptanz sind weiter unten (S. 4 oben) zusammengefasst.			
Ressourcen	Sind die erforderlichen Ressourcen gering?	☐ Nein ☐ Eher Nein ☐ Unklar ☐ Eher Ja ☐ Ja ☐ Teils Nein / Teils Ja	Eine gesundheitsökonomische Analyse wurde bisher nicht durchgeführt, ist aber geplant.			Die Impfung wird durch den Bund finanziert und steht allen zu Impfenden kostenlos zur Verfügung.

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Gleichheit	Hätte die Intervention aus Public Health Perspektive Auswirkung auf Ungleichgewichte bez. Gesundheit? (Würden Bevölkerungsgruppen von der Intervention benachteiligt?)	☐ Ungleichheit sicher verstärkt ☐ Ungleichheit eher verstärkt ☐ Unklar ☐ Ungleichheit eher verringert ☐ Ungleichheit verringert ☐ Teils / Teils	Die Impfempfehlung wurde unter Berücksichtigung ethischer Kriterien erarbeitet, die in einem von der STIKO gemeinsam mit der Nationalen Akademie Leopoldina und dem Deutschen Ethikrat erarbeiteten Dokument formulieren wurden. Es bestehen erhebliche Unterschiede zwischen einzelnen Bevölkerungsgruppen in Bezug auf das Risiko zu erkranken oder bei Erkrankung schwer zu erkranken oder zu versterben. Das höchste Risiko in Bezug auf die Mortalität besteht aufgrund eines hohen Alters. Im Folgenden sind Risikogruppen mit einem mehr als 2-fach erhöhten Risiko aufgeführt: • Alter >=80 Jahre pOR=16,9 (5,16-55,6) • Down-Syndrom HR=10,4 (7,08-15,2) • Alter 70-79 Jahre pOR=7,4 (2,97-18,4) • Organtransplantierte OR=4,2 (1,6-11,4) • Alter 60-69 Jahre pOR=2,8 (1,63-4,9) • Demenz pOR=2,2 (1,06-4,7) Durch die Impfung von Personengruppen mit einem signifikant erhöhten Risiko, an einer COVID-19 Erkrankung zu versterben, wird eine Ungleichheit adressiert. Internationale Studien zeigen, dass sozioökonomisch benachteiligte Menschen ein höheres Risiko für eine Infektion mit SARS-CoV-2 haben. Analysen aus Deutschland, die sich auf die erste Welle im Frühjahr 2020 beziehen, zeigen keinen eindeutigen Trend.	
Akzeptanz (Umsetzungsbereitschaft?)	Wird die Option / Empfehlung von Entscheidungsträgern akzeptiert?	☐ Nein ☐ Eher Nein ☐ Unklar ☐ Eher Ja ☐ Ja ☐ Teils Nein / Teils Ja	• 54% der Befragten (http://corona-monitor.de/) gaben zuletzt an, sich (eher) gegen COVID-19 impfen zu lassen. Mitte April waren es noch 79%, seitdem sinkt die Bereitschaft kontinuierlich ab (Stand: 10.11.20) • Die für Vertrauen in die Sicherheit und Effektivität der Impfung maßgebliche impfende Ärzteschaft befürwortet die Impfung • Verantwortungsgefühl für die Gemeinschaft triggert die Impfbereitschaft • ältere Personen und männliche Befragte geben eine höhere Impfbereitschaft an • Ab einer Impfeffektivität von ca. 80% steigt Impfbereitschaft deutlich an	

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Durchführbarkeit	Ist die Intervention (Impfempfehlung) umsetzbar?	☐ Nein ☐ Eher Nein ☐ Unklar ☐ Eher Ja ☐ Ja ☐ Teils Nein / Teils Ja	• Die verfügbaren Impfstoffe werden in verschiedenen Dosisbehältnissen zur Verfügung gestellt und haben unterschiedliche Lagerungs- und Kühlanforderungen. • Entsprechende Strukturen werden gerade von Bund und Ländern etabliert. • Die Erreichbarkeit von Personen im Alter >80 Jahre und BewohnerInnen in Alten- und Pflegeheimen stellt eine gewisse Herausforderung dar. • Zur Erreichbarkeit der Bewohner in Alten- und Pflegeheimen sind mobile Impfteams in den Bundesländern vorgesehen. • Ansonsten werden in der initialen Phase Impfungen in Impfzentren angeboten. • Medizinisches Personal kann ggf. in Krankenhäusern geimpft werden.	**BNT162b2** kann bei einer Temperatur von −70 ±10 °C bis zu 6 Monate gelagert werden; nach dem Auftauen kann das unverdünnte Konzentrat im Kühlschrank bei 2 bis 8 °C bis zu 5 Tage und bei Temperaturen <25 °C bis zu 2 h aufbewahrt werden. Zur Verdünnung des Der mit physiologischer Kochsalzlösung verdünnte Impfstoff muss in <6h verbraucht werden. Ein Mehrdosenbehältnis enthält 5 Dosen. **mRNA-1273** kann bei −20°C bis zu 6 Monaten gelagert werden. Im Kühlschrank kann der Impfstoff bei 2 bis 8 °C bis zu 30 Tagen aufbewahrt werden.

Empfehlung	Impfung der Bevölkerung (zunächst der durch die STIKO priorisierten Personengruppen; s. unten) mit den COVID-19-Impfstoffen BNT162b2 (BioNTech/Pfizer) oder mRNA-1723 (Moderna)				
Abwägen der Folgen	unerwünschte Folgen überwiegen klar gegenüber den gewünschten	unerwünschte Folgen überwiegen wahrscheinlich gegenüber den gewünschten	Unerwünschte und gewünschte Folgen sind im Gleichgewicht oder die Balance ist unklar	gewünschte Folgen überwiegen wahrscheinlich gegenüber den unerwünschten	gewünschte Folgen überwiegen klar gegenüber den unerwünschten
	☐	☐	☐	☐	☐
Empfehlung	Da in Bezug auf die Höhe des Risikos und die angestrebten Impfziele Unterschiede bestehen, empfiehlt die STIKO ein stufenweises Vorgehen. In der 1. Stufe sollten folgende Personengruppen geimpft werden: • BewohnerInnen von Senioren- und Altenpflegeheimen • Personen im Alter von ≥ 80 Jahren • Personal mit besonders hohem Expositionsrisiko in medizinischen Einrichtungen (z.B. in Notaufnahmen, in der medizinischen Betreuung von COVID-19 PatientInnen) • Personal in medizinischen Einrichtungen mit engem Kontakt zu vulnerablen Gruppen (z.B. in der Onkologie oder Transplantationsmedizin) • Pflegepersonal in der ambulanten und stationären Altenpflege • Andere Tätige in Senioren- und Altenpflegeheimen mit Kontakt zu den BewohnerInnen				
Begründung	• Mit der empfohlenen Impfstrategie kann angesichts der o.g. Limitationen ein Maximum an Public Health Impact erzielt werden. Da initial die COVID-19 Impfstoffe nur in sehr begrenzten Mengen zur Verfügung stehen wird, sollten diese dafür genutzt werden, möglichst schnell die Anzahl an Sterbefällen und schweren Krankheitsverläufen zu senken.				
Berücksichtigung spezieller (Unter)Gruppen	• Die von der STIKO empfohlene Priorisierung von Personengruppen wird bei Vorliegen neuer Evidenz, Zulassung weiterer Impfstoffe bzw. erhöhter Verfügbarkeit von Impfstoffdosen aktualisiert werden.				
Betrachtung zur Einführung / Umsetzung	s. oben				
Monitoring and Evaluation	• Durch das RKI wird ein System zum digitalen Impfquoten-Monitoring auf Bundesebene etabliert und durch regelmäßige Bevölkerungssurveys ergänzt. • Bevölkerungssurveys zum Monitoring der Impfakzeptanz und zu Impfbarrieren sind durch RKI und BZgA geplant. • Es erfolgt eine intensivierte Surveillance der Sicherheit der Impfung durch das Paul-Ehrlich-Institut. • Das RKI plant Studien zur Effektivität im Rahmen der breiten Anwendung (Post-Marketing Studien). • Des Weiteren wird der Zulassungsinhaber im Rahmen seiner Verpflichtungen Post-Marketing Studien zur Sicherheit und Wirksamkeit des Impfstoffs entsprechend Risk Management Plan durchführen. Es wird zudem erwartet, dass Universitäten und andere Forschungseinrichtungen Studien zur Evaluation der Impfung durchführen.				
Forschungsprioritäten	• Untersuchung der Verhinderung der Transmission von SARS-CoV2 durch die Impfung • Untersuchung der Verhinderung schwerer COVID-19 Erkrankungen durch die Impfung • Untersuchung der Langzeit-Wirksamkeit der Impfung (Schutzdauer) • Untersuchung der Langzeit-Sicherheit der Impfung				

9. Literatur zum Anhang

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020.
2. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020.