Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung zur COVID-19-Impfung (2. Aktualisierung)

Inhaltsverzeichnis

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. Unterschiede zur ersten Version des Umbrella-Reviews zu Risikofaktoren für Hospitalisierung und Krankenhaus-Mortalität aufgrund von COVID-19

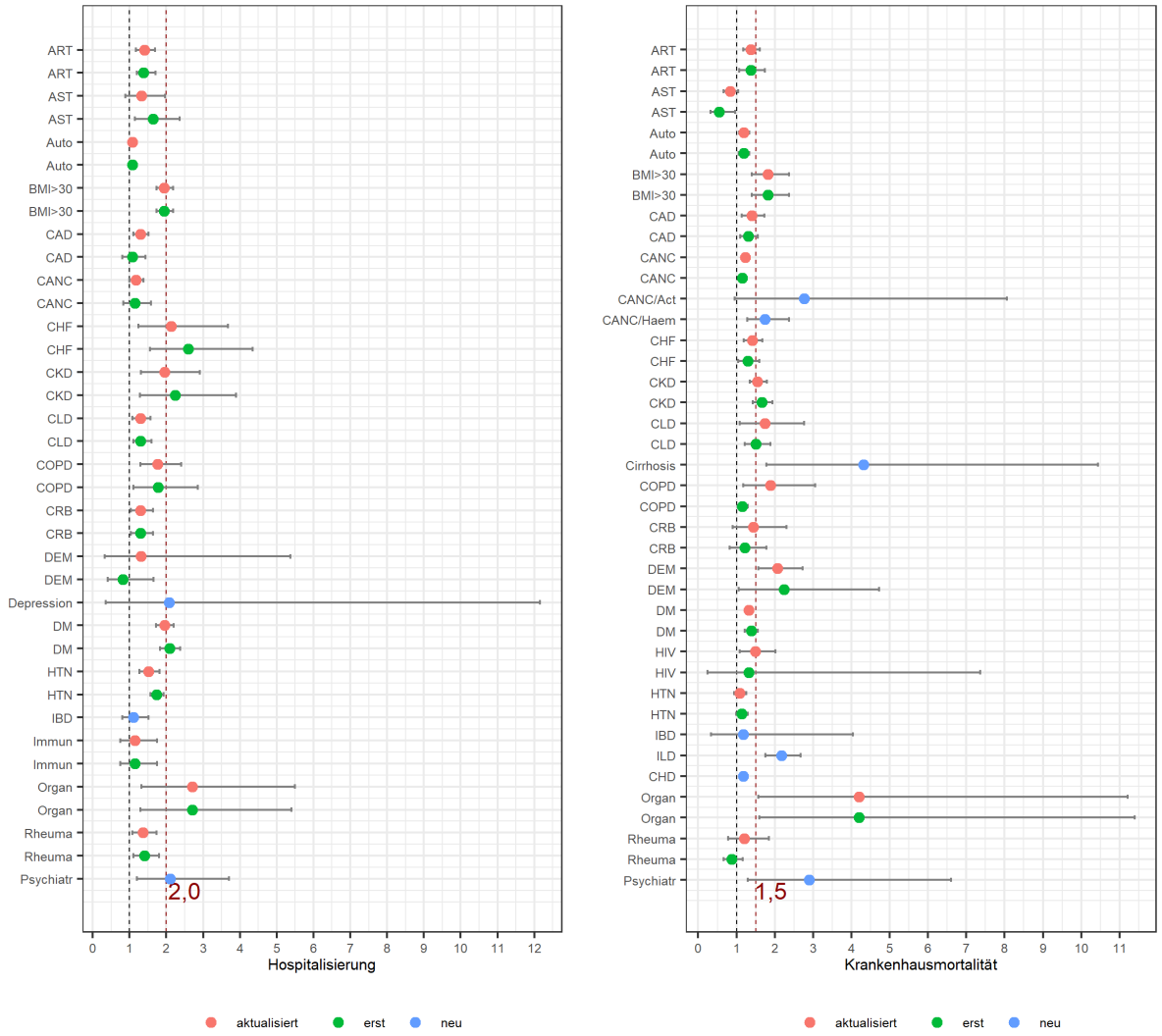

Abbildung 1: Vergleich der Risikoschätzer zwischen den Erhebungen.

ART, arrhythmia or atrial fibrillation; AST, asthma; Auto, autoimmune condition; BMI>30, obesity and overweight; CAD, coronary artery disease or ischemic heart disease; CANC, cancer (any cancer, active or history); CANC/Act, active cancer (any cancer not in remission); CANC/Haem, haematological malignancy; CHF, congestive heart failure; CKD, chronic kidney disease or reduced renal function; CLD, chronic liver disease; CRB, cerebrovascular or stroke; DEM, dementia; DM, diabetes; HTN, hypertension; ILD, interstitial lung disease; IBD, Inflammatory bowel disease; Immun, immunodeficiency; Organ, organ transplant history; Psychiatr ,psychiatric diseases (severe depression, schizophrenia, bipolar disorder); Rheuma, rheumatological disease.

4. Unterschiede zu Risikofaktoren zu Krankenhausmortalität aus dem Umbrella-Review und der Bevölkerungsmortalität aus der Studie von Williamson et. al. (1)

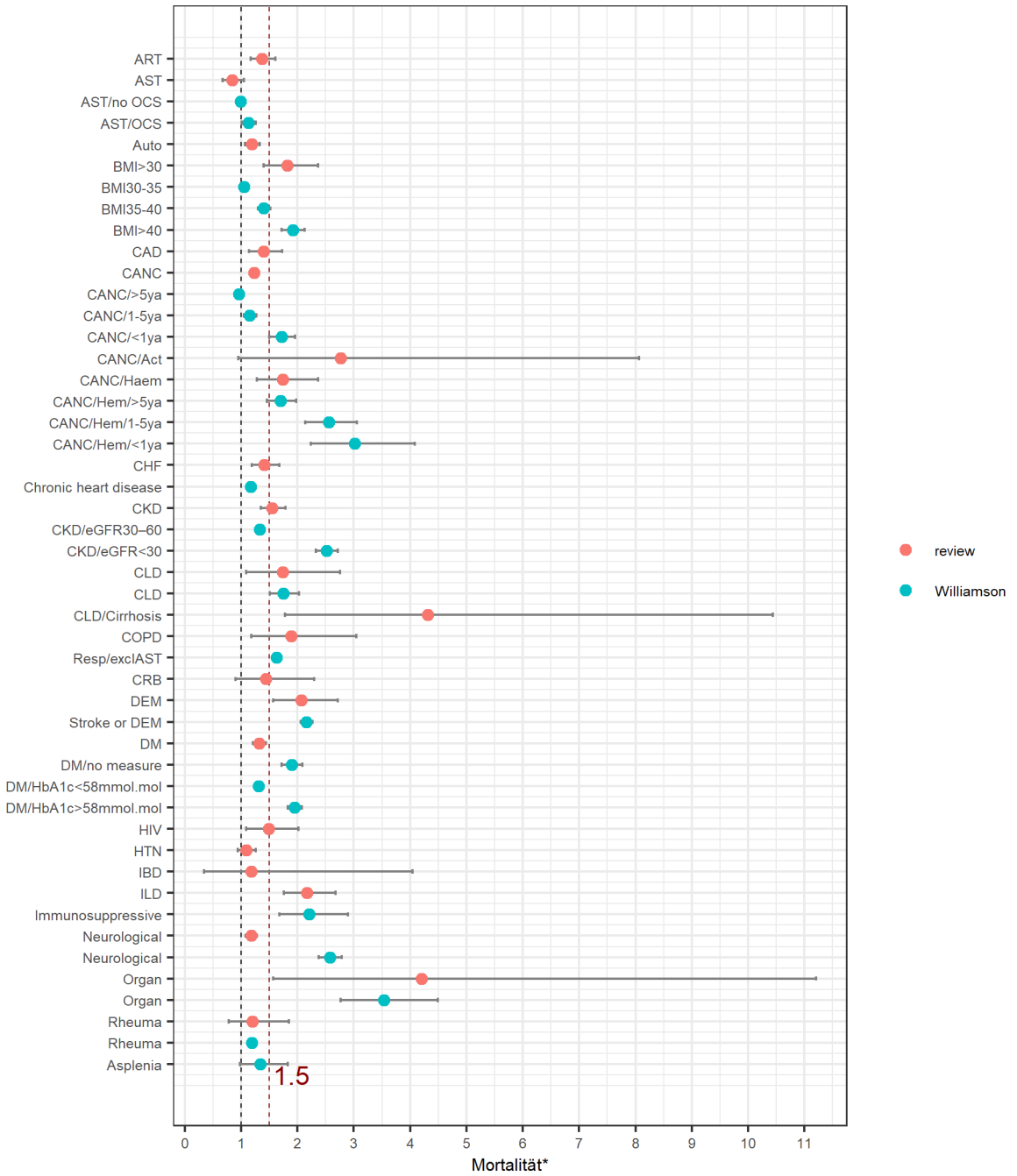

Abbildung 2: Vergleich der Risikoschätzer zwischen den Ergebnissen aus dem *umbrella review* (Krankenhausmortalität) und Williamson et al. (Bevölkerungsmortalität)

*Mortalität: Williamson et al. (1)berichten Hazard Ratios für COVID-19-bedingten Tod in der Allgemeinbevölkerung unabhängig vom SARS-CoV-2-Status. Der *umbrella review* berichtet die Risikoschätzer für COVID-19-bedingten Tod bei Patienten, die mit COVID-19 ins Krankenhaus aufgenommen wurden (Krankenhausmortalität).

ART, arrhythmia or atrial fibrillation; AST, asthma; Auto, autoimmune condition; BMI>30, obesity and overweight; CAD, coronary artery disease or ischemic heart disease; CANC, cancer (any cancer, active or history); CANC/Act, active cancer (any cancer not in remission); CANC/Hem, haematological malignancy; CHF, congestive heart failure; CKD, chronic kidney disease or reduced renal function; CLD, chronic liver disease; CRB, cerebrovascular or stroke; DEM, dementia; DM, diabetes; HTN, hypertension; ILD, interstitial lung disease; IBD, Inflammatory bowel disease; Immun, immunodeficiency; OCS, oral corticosteroid; Organ, organ transplant history; Resp/exclAST, respiratory diseases excluding asthma; Rheuma, rheumatological disease; ya, years ago (diagnosed).

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

5.1. BNT162b2 (BioNTech/Pfizer) (2)

	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)

5.2. mRNA-1723 (Moderna)(3)

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%)

5.3. AZD1222 (AstraZeneca) (4, 5)

Vaccine	Description
Vaccine name	**AZD1222 (previously referred to as ChAdOx1 nCoV-19) / AstraZeneca**
Vaccine composition	sterile, clear to slightly opaque solution, practically free from visible particles, with a label-claim volume of 5 ml. Dose formulation: 10 mM histidine, 7.5% (w/v) sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) polysorbate 80, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6.
Vaccine manufacturer & developer	ChAdOx1 nCoV-19 was manufactured and vialed by Advent (Pomezia, Italy), and additional batches produced by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK).
Vaccine type	non-replicating ChAdOx1 Vector Vaccine: AZD1222 is a recombinant replication-deficient chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein antigen gene (spike protein; nCoV-19)
number and timing of doses, route	2 doses i.m. into the deltoid of the non-dominant arm 4 weeks apart (d1 and d29) non-replicating ChAdOx1 Vector Vaccine; either 5 × 1010 viral particles (nominal, ± 1.5 × 1010 vp) AZD1222 (n = approximately 20 000) or MenACWY-conjugate vaccine or saline placebo (n = approximately 10 000) 1459 (53·2%) of 2741 participants in COV002 in the LD/SD group received a second dose at least 12 weeks after the first (median 84 days, IQR 77—91) and only 22 (0·8%) received a second dose within 8 weeks of the first. The median interval between doses for the SD/SD group in COV002 was 69 days (50–86). Conversely, the majority of participants in COV003 in the SD/SD group (2493 [61·0%] of 4088) received a second dose within 6 weeks of the first (median 36 days, 32–58).
Storage	Unopened vials of AZD1222 vials must be stored at 2-8 °C (36-46 °F) for the duration of assigned shelf-life and must not be frozen.
Study	Phase 1/2, 2/3 and 3 studies in adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19//four ongoing single blinded (COOV001, COOV002, COOV003) or double blinded (COV005), randomized, controlled trials done across three countries: COV001 (phase 1/2; UK) protocol was modified to a two-dose regime, following an amendment on July 30, 2020, COV002 (phase 2/3; UK) is a continuing single-blind phase 2/3 study in the UK that began on May 28, 2020, and enrolled participants in 19 study sites in England, Wales, and Scotland in health and social care settings; Two dosage groups were included in COV002: participants who received a low dose of the vaccine ($2{\cdot}2 \times 10^{10}$ viral particles) as their first dose and were boosted with a standard dose (in the LD/SD group), and subsequent cohorts who were vaccinated with two standard-dose vaccines (SD/SD group).protocol was amended on June 5, 2020, resulting in enrolment of two distinct groups with different dosing regimens with no pause in enrolment; LD/SD cohort (aged 18–55 years) was enrolled over 11 days between May 31 and June 10, 2020. SD/SD cohort (aged 18–55 years) was enrolled from June 9 to July 20, 2020. Subsequently, enrolment of older age cohorts began (from Aug 8, 2020, for participants aged 56–69 years and from Aug 13, 2020, for participants aged ≥70 years), all of whom were assigned to two standard doses (SD/SD cohort).COV003 (phase 3; Brazil) COV003 is a continuing single-blind phase 3 study in Brazil that began on June 23, 2020., 18 years or older, and this trial included individuals with stable pre-existing health conditions. COV005 (phase 1/2; South Africa) double-blind phase 1/2 study in South Africa in healthy adults aged 18–65 years living without HIV that began on June 28, 2020. All four studies included participants who received two doses, with a booster dose incorporated into the three trials6 that were initially designed to assess a single-dose of ChAdOx1 nCoV-19 compared with control (COV001, COV002, and COV003) after review of the antibody response data from COV001.
Reference	**Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. The Lancet. 2020.**// Public assessment report Authorization for Temporary Supply (https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiIg5D0lJbuAhUQuqQKHSgpBC8QFjAAegQIBxAC&url=https%3A%2F%2Fassets.publishing.service.gov.uk%2Fgovernment%2Fuploads%2Fsystem%2Fuploads%2Fattachment_data%2Ffile%2F949772%2FUKPAR_COVID_19_Vaccine_AstraZeneca_05.01.2021.pdf&usg=AOvVaw2VQktTrdpmZI_1hMqQB2Jh)

Study period	COV001(study (COV001) included efficacy cohort and the phase 2 and 3 studies (COV002, COV003, and COV005), began April 23, 2020, enrolled 1077 healthy volunteers aged 18–55 years/ COV002 is a continuing single-blind phase 2/3 study in the UK that began on May 28, 2020, and enrolled participants in 19 study sites in England, Wales, and Scotland. The LD/SD cohort (aged 18–55 years) was enrolled over 11 days between May 31 and June 10, 2020. The SD/SD cohort (aged 18–55 years) was enrolled from June 9 to July 20, 2020. Subsequently, enrolment of older age cohorts began (from Aug 8, 2020, for participants aged 56–69 years and from Aug 13, 2020, for participants aged ≥70 years), all of whom were assigned to two standard doses (SD/SD cohort). To test for asymptomatic infections, participants in COV002 in the UK were asked to provide a weekly self-administered nose and throat swab for NAAT testing from 1 week after first vaccination using kits provided by the UK Department of Health and Social Care (DHSC). COV003 began on June 23, 2020./ COV005 began on June 28, 2020 Participants will remain on study for 2 years following administration of the first dose of study intervention (Day 730). The cutoff date for inclusion in the analysis was Nov 4, 2020, and the data lock date was Nov 21, 2020.
Study design	Phase 1/2, 2/3 and 3 studies: Randomized, Double-blind, Placebo-controlled Multicenter Studies. The four trials are registered at ISRCTN89951424 (COV003) and ClinicalTrials.gov, NCT04324606 (COV001), NCT04400838 (COV002), and NCT04444674 (COV005) Each study had to meet prespecified criteria of having at least 5 cases eligible for inclusion in the primary outcome before a study was included in efficacy analyses. Neither COV001 or COV005 met these criteria and so are not included in the efficacy assessment for this interim analysis.
Endpoint for power calculation	COVID-19: SARS-CoV-2 RT-PCR-positive symptomatic illness (accrual of 75 cases for interim analysis, 150 for final analysis.
Randomization, ratio	Randomization lists using block randomization, stratified by study site and study group for COV001, COV002, and COV003. In COV005, the randomization list was held by the unmasked study pharmacist who prepared the vaccines for administration, with all other trial staff masked to group allocation.
Blinding	Preparation by the unblinded pharmacists. Neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD1222 and placebo are visually distinct prior to dose preparation (due to differences in container closure), IMP will be handled by an unblinded pharmacist (or designee in accordance with local and institutional regulations) at the study site. Once drawn into syringes for administration, AZD1222 and placebo are not visually distinct from each other.
Country	UK, Brazil, South Africa
Comparator	COV002: MenACWY; COV003: MenACWY as control for 1stdose and saline for 2nd dose; COV005: saline solution.
Primary endpoints	Efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age Safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age Reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age
Funding	UK Research and Innovation, National Institutes for Health Research (NIHR), Coalition for Epidemic Preparedness Innovations, Bill & Melinda Gates Foundation, Lemann Foundation, Rede D'Or, Brava and Telles Foundation, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and AstraZeneca.
Conflict of interest	Oxford University entered into partnership with AstraZeneca for development of ChAdOx1 nCoV-19. SCG is co-founder of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering this SARS-CoV-2 vaccine (PCT/GB2012/000467). TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was a consultant to Vaccitech for an unrelated project, during the conduct of the study. PMF is a consultant to Vaccitech during the conduct of the study. AJP is chair of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in discussions on COVID-19 vaccines, and is a member of WHO's SAGE. AJP is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this Article do not necessarily represent the views of the DHSC, JCVI, NIHR, or WHO. AVSH reports personal fees from Vaccitech, outside of the submitted work, and has a patent on ChAdOx1 licensed to Vaccitech (PCT/GB2012/000467), and might benefit from royalty income to the University of Oxford from sales of this vaccine by AstraZeneca and sublicensees. MS reports grants from NIHR and non-financial support from AstraZeneca, during the conduct of the study; and grants from Janssen, GlaxoSmithKline, Medimmune, Novavax, and MCM and grants and non-financial support from Pfizer, outside of the submitted work. CG reports personal fees from the Duke Human Vaccine

	Institute, outside of the submitted work. ADD reports grants and personal fees from AstraZeneca, outside of the submitted work. AF is a member of the JCVI and chair of the WHO European Technical Advisory Group of Experts. AF declares research grants from Pfizer, GlaxoSmithKline, Sanofi, Merck Sharp & Dohme, and Valneva, outside of the submitted work. JV, TLV, and IH are employees of AstraZeneca. The other authors declare no competing interests.
Inclusion criteria	Adult, ≥ 18 years of age at the time of consent; Healthy or have medically-stable chronic diseases who are not immunosuppressed, and are at increased risk for SARS-CoV-2 acquisition and COVID-19. Females only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening and vaccination.
Exclusion criteria	Participants were excluded from the primary efficacy analysis if they were seropositive at baseline or had no baseline result. Other exclusions included those with NAAT-positive swabs within 14 days after the second vaccination, or those who discontinued from the study before having met the primary efficacy endpoint with a follow-up time of less than 15 days after the second vaccination. • Prior receipt of any vaccines (licensed or investigational) ≤30 days before enrolment • Planned receipt of any vaccine other than the study intervention within 30 days before and after each study vaccination with the exception of the licensed seasonal influenza vaccination and the licensed pneumococcal vaccine. Participants will be encouraged to receive these vaccinations at least 7 days before or after their study vaccine. • Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines) • Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate. • Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting <14 days) . • Any autoimmune conditions, except mild psoriasis, well-controlled autoimmune thyroid disease, vitiligo or stable coeliac disease not requiring immunosuppressive or immunomodulatory therapy. • History of allergic disease or reactions likely to be exacerbated by any component of the ChAdOx1 nCoV-19 or MenACWY vaccines. • Any history of angioedema. • Any history of anaphylaxis. • Pregnancy, lactation or willingness/intention to become pregnant during the study. • History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ). • History of serious psychiatric condition likely to affect participation in the study (e.g. ongoing severe depression, history of admission to an in-patient psychiatric facility, recent suicidal ideation, history of suicide attempt, bipolar disorder, personality disorder, alcohol and drug dependency, severe eating disorder, psychosis, use of mood stabilizers or antipsychotic medication). • Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture. • Any other serious chronic illness requiring hospital specialist supervision. • Chronic respiratory diseases, including mild asthma (resolved childhood asthma is allowed) • Chronic cardiovascular disease (including hypertension), gastrointestinal disease, liver disease (except Gilberts Syndrome), renal disease, endocrine disorder (including diabetes) and neurological illness (excluding migraine) • Seriously overweight (BMI≥40 Kg/m2) or underweight (BMI≤18 Kg/m2) • Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week. • Suspected or known injecting drug abuse in the 5 years preceding enrolment. • Any clinically significant abnormal finding on screening biochemistry, hematology blood tests or urinalysis. • Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data. • History of laboratory confirmed COVID-19. • New onset of fever or a cough or shortness of breath or anosmia/ageusia since February 2020. Should a reliable test become available, this exclusion criteria will be replaced with seropositivity for SARSCoV-2 before enrolment. • Those who have been at high risk of exposure before enrolment, including but not limited to: close contacts of confirmed COVID-19 cases, anyone who had to self-isolate as a result of a symptomatic household member, frontline healthcare professionals working in A&E, ICU and other higher risk

	areas. Should a reliable test become available, this exclusion criteria will be replaced with seropositivity for SARS-CoV-2 before enrolment. • Living in the same household as any vulnerable groups at risk of severe COVID-19 disease (as per PHE guidance) Additional exclusion criteria (subset of participants receiving Paracetamol in group 4 only)
Participants (study groups)	Between April 23 and Nov 4, 2020, 23 848 participants were recruited and vaccinated across the four studies: 1077 in COV001 (UK), 10 673 in COV002 (UK), 10 002 in COV003 (Brazil), and 2096 in COV005 (South Africa). 11 636 participants in COV002 and COV003 met the inclusion criteria for the primary analysis, 5807 of whom received two doses of ChAdOx1 nCoV-19 and 5829 of whom received two doses of control product.
Sample size calculation	First interim analysis was planned to be triggered when at least 53 cases in participants who had received two standard-dose vaccines (SD/SD) had accrued that met the primary outcome definition more than 14 days after the second dose. This analysis provides 77% power for the 20% threshold to assume a true vaccine efficacy of 70%.
Age at enrollment	Participants in COV002 and COV003 included in efficacy analyses: 18–55 years (6542 [86.7%] of 7548 in the UK and 3676 [89.9%] of 4088 in Brazil). Those aged >=56 years were recruited later and contributed 12.2% of the total cohort in the current analysis (1006 [13.3%] in the UK and 412 [10.1%] in Brazil). Safety: COV001 (UK) N=1067 18-55 years: 99.8%; COV002 (UK) N=10663 age: 18-55 years: 76-79%; COV003 (Brazil) N=10002 age: 18-55 years: 83%; COV005 (South Africa) N=2013 age: 18-55 years: 95% 9% of participants were ≥ 65 years of age
Ethinicity	76% of participants were White: 6902 (91.4%) participants in the UK and 2723 (66.6%) participants in Brazil were white.
Comorbidity	BMI ≥ 30 kg/m2 at baseline, Cardiovascular Disorder (chronic heart failure, ischaemic heart disease (including angina), atrial fibrillation, peripheral vascular disease, valvular heart disease, hypertension, myocardial infarction), Respiratory disease (Chronic obstructive pulmonary disease, Bronchiectasis, Asthma) or Diabetes (Type 1 diabetes, Type 2 diabetes not using insulin, Type 2 diabetes using insulin) 36% of participants had a significant comorbidity at baseline
Sex (% male)	7045 (60.5%) participants were female. Safety: COV001 (UK) N=1067 Females: 49-50%; COV002 (UK) N=10663 Females: 59-60%; COV003 (Brazil) N=10002 Females: 54-55%; COV005 (South Africa) N=2013 Females: 43-44% Females: 259 (48.5%)
Duration of follow-up after vaccination	Safety data on 74 341 person-months of follow-up after 1stdose (median 3·4 months, IQR 1.3–4.8) and 29 060 person-months of follow-up after two doses (median 2.0, 1.3–2.3).
Type of follow-up after vaccination	Participants were asked to contact the study site if they experienced specific symptoms associated with COVID-19. Those who met symptomatic criteria had a clinical assessment, a swab taken for a nucleic acid amplification test (NAAT), and blood samples taken for safety and immunogenicity. Weekly telephone/email/text contacts -
Initial no. of participants included	Between April 23 and Nov 4, 2020, 23 848 participants were included.
Final no. of participants analyzed for each endpoint	Between April 23 and Nov 4, 2020, 23 848 participants were recruited and vaccinated across the four studies: 1077 in COV001 (UK), 10 673 in COV002 (UK), 10 002 in COV003 (Brazil), and 2096 in COV005 (South Africa). 11 636 participants in COV002 and COV003 met the inclusion criteria for the primary analysis, 5807 of whom received two doses of ChAdOx1 nCoV-19 and 5829 of whom received two doses of control product. All participants randomized AZD1222: 12018 Placebo: 11735 Total: 23753 Any dose safety: AZD1222: 12 021 Placebo:11 724 Total: 23 745 Dose 1 SD for safety: AZD1222: 10069 Placebo: 9902 Total: 19971 Dose 1 LD for safety: AZD1222: 1947 Placebo: 1822 Total: 3769 Any dose efficacy: AZD1222 10014 Placebo: 10000 Total: 20014 SDSD + LDSD seronegative for efficacy: AZD1222: 5807 Placebo: 5829 Total: 11636 SDSD seronegative for efficacy: AZD1222: 4440 Placebo: 4455 Total: 8895 LDSD seronegative for efficacy: AZD1222: 1367 Placebo: 1374 Total: 2741 Randomized participants who received at least one dose in all studies are included in the safety analysis.
Safety -- definitions	All local and systemic AEs within 28 days after each vaccination observed by the Investigator or reported by the participant, will be recorded in the Diary of Symptoms and by the Investigators in the study CRF. For COV001, diary cards for the second vaccines will not be filled out for participants in groups 2f, 2g, 4c and 4d. For COV002, solicited and unsolicited AEs will be reported for 7 days only for group 1-3, 5, 7, 8, 11 and 12 and a subset of up to 3000 participants for groups 4, 6, 9, and 10. In

	COV003, solicited AEswill be reported for a subset of 200 participants. SAEs and Adverse Events of Special Interest will be collected throughout the study period. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23 or higher.
Safety assessment	a) Incidence of AEs for 28 days post each dose of study intervention b Incidence of SAEs, MAAEs (Medically Attended Adverse Events), and AESIs (Adverse Events of Special Interest) ((Neurologic: Generalized convulsion, Guillain-Barre syndrome, Acute disseminated encephalomyelitis) (Immunologic: Vasculitides, Anaphylaxia, Vaccine-associated enhanced respiratory disease) (Hematologic: Thrombocytopenia)) from Day 1 post treatment through Day 730 c) only in substudy: Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention
local reactions (pain, swelling, redness, …)	Pain at the site of injection, erythema/redness at the site of injection, tenderness, induration/swelling at the site of the injection
local reactions	
local reactions: pain	Grade 1: Does not interfere with activity Grade 2: Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity Grade 3: Any use of narcotic pain reliever or prevents daily activity Grade 4: Emergency room visit or hospitalization
local reactions: tenderness	Grade 1: Mild discomfort to touch Grade 2: Discomfort with movement Grade 3: Significant discomfort at rest Grade 4: Emergency room visit or hospitalization
local reactions: Erythema/redness	Grade 1: 1-2 inches (2.5–5 cm) Grade 2: >2-4 inches (5.1–10 cm) Grade 3: > 4 inches (> 10 cm) Grade 4: Necrosis or exfoliative dermatitis
local reactions: Induration/swelling	Grade 1: 1-2 inches (2.5–5 cm) Grade 2: >2-4 inches (5.1–10 cm) Grade 3: > 4 inches (> 10 cm) Grade 4: Necrosis
systemic reactions (myalgia, nausea, fatigue, …)	Fever (> 100 °F [> 37.8 °C]), chills, muscle pains, fatigue, headache, malaise, arthralgia,
Fever	Grade 1: 37.9-38.6 °C Grade 2: 38.6-39.3 °C Grade 3: 39.3-40°C Grade 4: > 40°C
Arthralgia	Grade 1 (mild): no or minimal interference with usual social & functional activities Grade 2 (moderate): greater than minimal interference with usual social & functional activities Grade 3 (severe): inability to perform usual social & functional activities Grade 4 (potentially life threatening): inability to perform basic selfcare functions
Chills	Grade 1 (mild): no or minimal interference with usual social & functional activities Grade 2 (moderate): greater than minimal interference with usual social & functional activities Grade 3 (severe): inability to perform usual social & functional activities Grade 4 NA
Headache	Grade 1 (mild): no or minimal interference with usual social & functional activities Grade 2 (moderate): greater than minimal interference with usual social & functional activities Grade 3 (severe): inability to perform usual social & functional activities Grade 4 (potentially life threatening): inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant alertness or other neurologic function
Fatigue/ tiredness	Grade 1 (mild): no or minimal interference with usual social & functional activities Grade 2 (moderate): greater than minimal interference with usual social & functional activities Grade 3 (severe): inability to perform usual social & functional activities Grade 4 (potentially life threatening): inability to perform basic selfcare functions OR hospitalization

Myalgia	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Prevents daily activity Grade 4: ER visit or hospitalization
severe adverse events	Serious adverse events were recorded throughout the study and reviewed at each study visit, with causality assigned by the site investigator.
adverse events of special interest (AESI) according to CEPI criteria (e.g. enhanced COVID-19, Guillain-Barrée Syndrom)	Generalized Convulsion, Guillain-Barré Syndrome and Other Immune-mediated Reactions, Hypersensitivity Including Anaphylaxis/Anaphylactic Reactions, Vaccine-associated Enhanced Respiratory Disease, Thrombocytopenia
Effectiveness -- definitions	Symptoms for swabbing included any one of the following: fever of at least 37·8°C, cough, shortness of breath, and anosmia or ageusia. In South Africa, the list of qualifying symptoms for swabbing was broader, and additionally included myalgia, chills, sore throat, headache, nasal congestion, diarrhoea, runny nose, fatigue, nausea, vomiting, and loss of appetite. Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms Test for asymptomatic infections, participants in COV002 in the UK were asked to provide a weekly selfadministered nose and throat swab for NAAT testing from 1 week after first vaccination Nasal swab for SARS-CoV-2 RT-PCR (local laboratory) (predose 1) Serum sample for SARS-CoV-2 serology testing (predose 1&2) and 5-times in different time intervals after 2nd dose
Efficacy assessment	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case. Each study had to meet prespecified criteria of having at least five cases eligible for inclusion in the primary outcome before a study was included in efficacy analyses. Neither COV001 or COV005 met these criteria and so are not included in the efficacy assessment for this interim analysis. It is expected that they will be included in efficacy assessments in future analyses once more cases have accrued. Additionally, only efficacy groups for COV002 (ie, groups 4, 6, 9, and 10) were included.
COVID-19 Qualifying Symptoms	The primary outcome was virologically confirmed, symptomatic COVID-19, defined as a NAATpositive swab combined with at least one qualifying symptom (fever ≥37·8°C, cough, shortness of breath, or anosmia or ageusia). Criteria without minimum duration: fever, shortness of breath, difficulty breathing Criteria present for ≥ 2 days: chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste, new loss of smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea. The digital health device will continuously track biophysical parameters, including but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity. If a participant presents with a COVID-19 qualifying symptom(s) on Days 1-3, the nasal and nasopharyngeal swabs collected on Day 1 will be tested locally for SARS-CoV-2. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio < 300 mm Hg) -Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation) -Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors) -Significant acute renal, hepatic, or neurologic dysfunction - Admission to an intensive care unit -Death
VE calculating	Vaccine efficacy was calculated as 1 – adjusted relative risk (ChAdOx1 nCoV-19 vs control groups)
SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection
COVID-19	COVID-19 (Primary): Virologically-confirmeda symptomatic cases of COVID-19 PCR-confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.
COVID-19 (severe)	COVID-19a severe disease WHO ≥ Grade 6 (Hospitalised; oxygen by NIV or high flow)
COVID-19 hospitalization	COVID-19a hospital admission WHO ≥ Grade ≥ 4 (Hospitalised; no oxygen therapy)

COVID-19 hospitalization on intensive care	COVID-19a requiring ICU WHO ≥ Grade ≥ 7 (Intubation and mechanical ventilation, pO2/FiO2 ≥ 150 or SpO2/FiO2 ≥ 200)
COVID-19 related death	COVID-19a death WHO Grade = 10 (Dead)
Safety -- results	Safety of the vaccine is being assessed using data from all four studies. Safety data on 74 341 person-months of follow-up after first dose (median 3·4 months, IQR 1·3–4·8) and 9 060 person-months of follow-up after two doses (median 2·0, 1·3–2·3). Most of the solicited* (local and systemic) AEs were mild to moderate in severity. Individual Grade 3 solicited AEs were reported in ≤ 5% of participant the first dose Most frequently reported local solicited AEs in the AZD1222 group were tenderness (63.7%, Dose 1 SD) and pain (54.2% Dose 1 SD); other local solicited AEs were reported in < 20% of participants Most frequently reported systemic solicited AEs in the AZD1222 group were fatigue (53.1% Dose 1 SD) and headache (52.6%, Dose 1 SD); other frequently reported systemic solicited AEs were malaise (44.2%, Dose 1 SD) and muscle pain (44.0%, Dose 1 SD) Fever was reported in 7.9% of participants (Dose 1 SD); Grade 3 fever was reported in 0.7% of participants Solicited AEs were generally milder and reported less frequently after the second dose of AZD1222 than after first dose of AZD1222.
Number (%) with local reactions: vaccine vs. comparator	Local injection site AEs were reported by 74.7% in the vaccine group and by 50.4% control group within the first 7 days following any dose of AZD1222
Number (%) with pain: vaccine vs. comparator	Pain (54.2% vs 36.7% in control) ≥ GRADE 3: 0,5 vs. 0,2
Number (%) with tenderness: vaccine vs. comparator	Tenderness (63.7% vs 39.5% in control) ≥ GRADE 3: 1,2 vs. 0,3
Number (%) with Erythema/redness: vaccine vs. comparator	warmth (17.7% vs 14.5% in control), ≥ GRADE 3: 0,0 vs. 0,0 redness (14.0% vs 8.8% in control), ≥ GRADE 3: 4,8 vs. 2,4
Number (%) with lymphadenpathy: vaccine vs. comparator	Swelling (10.0% vs 5.8% in control) ≥ GRADE 3: 5.3 vs. 2.7
Number (%) with systemic reactions (myalgia, nausea, fatigue, …)	Systemic AEs were reported by 73.0% in the vaccine group and by 59.6% in the control group owithin the first 7 days following any dose of AZD1222.
Number (%) with fever: vaccine vs. comparator	Fever (7.9% vs 1.2% in control) ≥ GRADE 3: 0.7 vs. 0.3
Number (%) with nausea/Vomiting: vaccine vs. comparator	nausea (21.9% vs 13.1% in control) ≥ GRADE 3: 0.9 vs. 0.1
Number (%) with chills: vaccine vs. comparator	feverishness (33.6% vs 10.7% in control), chills (31.9% vs 8.3% in control)
Number (%) with headache: vaccine vs. comparator	Headache (52.6% vs 39.0% in control ≥ GRADE 3: 2.7 vs. 0.9
Number (%) with fatigue/ tiredness: vaccine vs. comparator	Fatigue (53.1% vs 38.2% in control) ≥ GRADE 3: 3.2 vs. 1.1
Number (%) with myalgia: vaccine vs. comparator	Muscle pain (44.0% vs 21.6% in control) ≥ GRADE 3: 1.9 vs. 0.4

Number (%) with joint pain: vaccine vs. comparator	Joint pain (26.4% vs 12.4% in control) ≥ GRADE 3: 1.1 vs. 0.5
Number (%) with serious adverse events: vaccine vs. comparator	Across all four studies, the vaccine had a good safety profile with serious adverse events and adverse events of special interest balanced across the study arms. Serious adverse events occurred in 168 participants, 79 of whom received ChAdOx1 nCoV-19 and 89 of whom received MenACWY or saline control. There were 175 events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), three of which were considered possibly related to either the experimental or a control vaccine. A case of haemolytic anaemia in the control group in the UK phase 1/2 study occurring 10 days after MenACWY vaccine was considered possibly related to the intervention and has been previously described. A case of transverse myelitis was reported 14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, with the independent neurological committee considering the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination. A potentially vaccine-related serious adverse event was reported 2 days after vaccination in South Africa in an individual who recorded fever higher than 40°C, but who recovered rapidly without an alternative diagnosis and was not admitted to hospital. There were two additional cases of transverse myelitis that were originally reported as potentially related but later determined to be unlikely to be related to vaccination by an independent committee of neurological experts. One case that occurred 10 days after a first vaccination with ChAdOx1 nCoV-19 was initially assessed as possibly related, but later considered unlikely to be related by the site investigator when further investigation revealed preexisting, but previously unrecognised, multiple sclerosis. The second case was reported 68 days after MenACWY vaccination. While considered possibly related by the site investigator at the time of reporting, an independent panel of neurological experts considered this to be unlikely. All trial participants have recovered, or are in a stable or improving condition. There were four non-COVID-19 deaths reported across the studies (three in the control arm and one in the ChAdOx1 nCoV-19 arm) that were all considered unrelated to the vaccine, with cause of death assessed as road traffic accident, blunt force trauma, homicide, and fungal pneumonia.
Number (%) with adverse events of special interest (AESI) according to CEPI criteria (e.g. enhanced COVID-19, Guillain-Barrée Syndrom)	AESI were grouped under neurological, vascular, haematological and immunological (including anaphylaxis and vaccine associated enhanced disease). There were no clinically meaningful imbalances in AESI incidence for any subgroup (country, age, serostatus or comorbidity). 95 (0.8%) vs. 126 (1.1%; control group)
Pregnancies	Pregnancy was reported for 21 subjects; 12 in the AZD1222 group and 9 in the control group. Of these pregnancies, 5 ended in spontaneous abortion – 2 in the AZD1222 group and 3 in the control group. Due to the limited duration of follow-up, the outcome of the remaining pregnancies is awaited.
Effectiveness -- results	Efficacy is being assessed by a prespecified global pooled analysis combining data from COV002 and COV003. Cases were eligible for inclusion in efficacy if the first symptom or first NAAT-positive result was on or before the data cutoff date
Number (%) with SARS-CoV-2 infection: vaccine vs. comparator	VE asymptomatic infections (UK): SD/SD: 3.8% (−72.4 to 46.3) ; LD/SD: 58.9% (95% CI 1.0 to 82.9), COOV2 only: AZD1222(N=3744)/ Control (N=3804) Number of participants with Observed Events n (%) 11 (0.29) 20 (0.53) VE (%) 44.97 95% CI (%) (-14.75, 73.61) P-value 0.111
Number (%) with COVID-19: vaccine vs. comparator (COVID-19 in seronegative participants at baseline who received SDSD or LDSD and had a case ≥ 15 days post second dose)	UK and Brazil: There were 30 (0.5%) cases among 5807 participants in the vaccine arm and 101 (1.7%) cases among 5829 participants in the control group, resulting in vaccine efficacy of 70.4% (95·8% CI 54.8–80.6). VE SD/SD: 62.1% (95% CI 41.0–75.7), LD/SD: 90.0% (67.4–97.0) >65: 6,3% (95% CI: -1404 - 94.2)
Number (%) with COVID-19 hospitalization: vaccine vs. comparator	not reported

Number (%) with COVID-19 hospitalization on intensive care: vaccine vs. comparator	not reported
Number (%) with severe COVID-19:	Severe COVID-19: 87.6 (95% CI: 46.0 - 97.15)
Number (%) with COVID-19 related death: vaccine vs. comparator	not observed
Number (%) with COVID-19 after 1st and before 2nd dose: vaccine vs. comparator (Any Dose Efficacy regardless of serostatus, post first dose)	AZD1222 (N=10014)/ Control (N=10000) Number of participants with Observed Events n (%) 108 (1.08) 227 (2.27); after 1st dose and before 2nd dose: VE (%) 52.69 /95% CI (%) (40.52, 62.37) P-value <0.001; 14 days after 1st dose and before 2nd dose: VE (%)71,3 (95% CI 49 - 84)
Covid-19 occurance at least 7 days after 2. doses in participants with and without evidence of infeciotn	52.69% (95% CI: 40.52%, 62.37%)

6. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie des BNT162b2-Impfstoffs von BioNTech (2)

Tabelle 1: Risk of BIAS-Bewertung der Phase-3-Zulassungsstudie des BNT162b2-Impfstoffs von BioNTech (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
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 Evidenzprofil: Vaccination with BNT162b2 (BionTech/Pfizer) 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 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.

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

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.

9. GRADE Evidence Profile: Vaccination with mRNA-1273 (Moderna) against COVID-19(3)

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.

10. Risk of Bias-Bewertung der Phase 3-Zulassungsstudie des AZD1222-Impfstoffs (AstraZeneca/University of Oxford) (4)

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	some concerns[1]	some concerns[2]	low	low	some concerns
Hospitalisierung	low	some concerns[1]	some concerns[2]	low	low	some concerns
Asymptomatische Infektion	low	some concerns[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 der Studienpopulation erhielten eine abweichende Dosierung des Impfstoffs. Die Auswirkungen sind unklar.
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 (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.

11. GRADE Evidence Profile: Vaccination with AZD1222 (AstraZeneca/University of Oxford) against COVID-19 (4)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccination with AZD1222	No vaccination	VE or 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	30/5807 (0.52%)	101/5829 (1.7%)	VE 70% (55 to 81%)	12 fewer per 1000 (from 10 fewer to 14 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	29/5466 (0.53%)	100/5510 (1.8%)	VE 71% (56 to 81%)	13 fewer per 1000 (from 10 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	serious[2]	none	1/341 (0.29%)	1/319 (0.31%)	VE 6% (-1400 to 94%)	0 fewer per 1000 (from 3 fewer to 44 more)	⊕⊕OO LOW	IMPORTANT
Hospitalisation due to COVID-19 (follow-up median 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/12021 (0%)	5/11724 (0.04%)	VE 100%[3]	(cannot be calculated)	⊕⊕OO LOW	CRITICAL
Death due to COVID-19 - not measured												
0	-	-	-	-	-	-			-	-	no data	CRITICAL
Local reaction (example: pain at injection site after dose 1) (follow-up median 2 months)												
1	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	941/1736 (54.2%)	586/1596 (36.7%)	RR 1.48 (1.33 to 1.64)	176 more per 1000 (from 121 more to 235 more)	⊕⊕OO LOW	IMPORTANT
Systemic reaction (example: fatique after dose 1) (follow-up median 2 months)												

1	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	1407/2648 (53.1%)	955/2497 (38.2%)	RR 1.39 (1.30 to 1.48)	149 more per 1000 (from 115 more to 184 more)	⊕⊕OO LOW	IMPORTANT
Any serious adverse event (follow-up median 2 months)												
1	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	79/12021 (0.66%)	89/11724 (0.76%)	RR 0.87 (0.64 to 1.17)	1 fewer per 1000 (from 3 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
ICU admission due to COVID-19 - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Intubation due to COVID-19 - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
Adverse events of special interest - not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL

[1] some participants received differing doses of the vaccine; consequences for VE are not completely clear

[2] Wide 95% confidence interval

[3] 95%CI cannot be calculated

[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.

[5] Part of control arm received MenACWY vaccine

12. 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 (2, 3)**?**

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.
Nutzen und Risiken	Sind die zu erwartenden erwünschten Effekte groß?	☐ Nein ☐ Eher Nein ☐ Unklar ☐ Eher Ja ☐ Ja ☐ Teils Nein / Teils Ja	• 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.	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.

<table>
<tr><th></th><th>Kriterien</th><th>Bewertung</th><th>Stand der Wissenschaft / Evidenz</th><th>zusätzliche Hinweise</th></tr>
<tr><td></td><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></td><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></td><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><tr><td>COVID-19</td><td>IMPORTANT</td><td>MODERAT</td></tr><tr><td>COVID-19-Hospitalisierung</td><td>CRITICAL</td><td>SEHR GERING</td></tr><tr><td>COVID-19-Hospitalisierung (ITS-pflichtig)</td><td>CRITICAL</td><td>Keine Daten</td></tr><tr><td>COVID-19-Hospitalisierung (beatmungspflichtig)</td><td>CRITICAL</td><td>Keine Daten</td></tr><tr><td>COVID-19-bedingter Tod</td><td>CRITICAL</td><td>BNT162b2: Keine Daten/ mRNA-1273: GERING</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 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.</td></tr>
<tr><td></td><td></td><td>Sicherheit der Intervention
☐ keine Studien
☐ sehr niedrig</td><td>Relative Bedeutung der wichtigsten Ergebnisse bzw. Endpunkte:<table><tr><th>Ergebnis</th><th>relative Bedeutung</th><th>GRADE</th></tr></table></td><td>Die Sicherheitsendpunkte wurden alle aufgrund des</td></tr>
</table>

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz			zusätzliche Hinweise
		☐ niedrig ☐ moderat ☐ hoch	**Sicherheit der Intervention**			Verzerrungsrisikos als moderate Evidenzqualität eingeschätzt.
			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				

13. Literatur zum Anhang

1. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
2. 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.
3. 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.
4. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet. 2020.
5. Medicines and Healthcare products Regulatory Agency. Public Assessment Report Authorisation for Temporary Supply; COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]). 2020.