Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19

Background document to the WHO Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing

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Contents

Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 5 January 2021 extraordinary meeting [1], which resulted in the issuance of the 8 January 2021 WHO Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1, accessed 11 January 2021).

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

General considerations on mRNA vaccines

The advantages of RNA-based vaccines are that they can be developed rapidly. mRNA-based vaccines avoid the risk of integration with the host cell genome and are able to produce pure viral protein. mRNA is transiently expressed, allowing protein to be made within the cell. Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows precise genetic information to be delivered, together with an adjuvant effect, to antigen-presenting cells. It is molecularly well defined, free from materials of animal origin, and synthesized by an efficient, cell-free in vitro transcription process from DNA templates. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, allowing speedy commercial production. The fast and highly scalable mRNA manufacturing and LNP formulation processes allow rapid production of many vaccine doses, which is particularly important during a pandemic.

Characteristics of COVID-19 vaccine BNT162b2 (Pfizer–BioNTech)

The Pfizer–BioNTech COVID-19 vaccine, BNT162b2, is an mRNA vaccine encoding a P2 mutant spike protein (PS 2) and formulated as an RNA–lipid nanoparticle of nucleoside-modified mRNA (modRNA). BNT162b2 elicits a blunted innate immune sensor activating capacity and thus augments antigen expression. Encapsulation into LNPs allows transfection of the mRNA into host cells after intramuscular (IM) injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol, where it is translated into the encoded viral protein. The mRNA is rapidly degraded intracellularly, while the resulting peptides are presented at the cell surface, triggering a specific humoral T-cell-mediated immune response with activity against the spike protein.

Development process, contents, formulation

BNT162b2 is produced as a highly purified single-stranded, 5`-capped mRNA; the mRNA encodes the viral spike from SARS-CoV-2. The following excipients are included: ALC-0315, ALC-0159 (polyethylene glycol), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, and water for injection.

Preclinical studies

A single injection of BNT162b2 elicited high neutralizing antibody titres in mice. Vaccination of mice also resulted in robust T helper 1 (T_H1) and T follicular helper (T_{FH}) type $CD4^+$ responses as well as a robust $IFN\gamma^+IL\text{-}2^+$ $CD8^+$ T-cell response. This pattern of cell-mediated immunity suggests a low likelihood that the vaccine will induce a hypersensitivity response and resulting vaccine-associated enhanced respiratory disease. In addition, the induction of a T_{FH} response supports the hypothesis that the vaccine may confer durable immunity. Translation of this immunogenicity profile into protection against subsequent viral infection was tested in a non-human primate (NHP) study.

The immunogenicity of BNT162b2 in rhesus macaques paralleled that observed in the murine model (1). Two doses of 100 µg of this mRNA vaccine were given at 0 and 21 days. Seven days after the second dose, the 50% virus neutralization titre of antibodies reached 18 times that of a human SARS-CoV-2 convalescent serum panel; it remained 3.3 times higher than this benchmark five weeks after the second immunization, although the

absolute titre decayed from 1689 to 310. The T_H1-based $CD4^+$ response and the $IFN\gamma^+$ $CD8^+$ T-cell response mirrored the cellular immunogenicity profile reported in mice. Two doses of 100 µg of BNT162b2, separated by a three-week interval, protected 2–4-year-old rhesus macaques against viral infection when challenged, intranasally and intratracheally, with $1x10^6$ plaque-forming units (pfu) of SARS-CoV-2 55 days after the second vaccination. Viral RNA, as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR), in the bronchoalveolar lavage fluid (BAL) and nasopharyngeal (NP) and oropharyngeal (OP) swabs, was significantly lower in the vaccinated animals than in the unvaccinated controls. The virus was absent on day 3 and day 6 after challenge. No measurements were made at other times. Histopathological outcomes were not presented in any detail in this NHP study; protective efficacy was limited to virological outcomes. Overall, these preclinical data indicate that BNT162b2 is an immunogenic vaccine that is efficacious in protecting against viral infection in the lower and upper airways of rhesus macaques three days after challenge.

Clinical studies: phases 1 and 2

Safety

Two candidate mRNA vaccines were tested in phase 1 trials: BNT162b1 and BNT162b2. The latter was ultimately advanced to phase 3 trials because it was better tolerated and represented a greater breadth of T-cell epitopes (2). Overall, the vaccine, given as a two-dose regimen at one of three doses (10 µg, 20 µg, 30 µg) was tolerated well in two age groups: 18–55 years and 65–85 years. Local and systemic adverse events were generally mild and were more frequent in the two higher dose groups. Systemic adverse events were generally milder in the older age group. Perturbations in laboratory values that were deemed related to vaccine administration were also milder in older individuals. No serious adverse events were reported, and no stopping rules met.

Immunogenicity

Neutralizing antibody titres (50% neutralizing geometric mean titres (GMTs)) elicited by BNT162b2 peaked one week after the second vaccination and began decaying one week after that. There was a trend towards higher titres in individuals who had received the highest vaccine dose of 30 µg. Vaccination with this dose elicited titres that were lower than those seen in animal studies; titres were 1.7–4.6 times higher than that seen in a convalescent serum panel among the 18–55-year-olds and 1.1–2.2 times higher among the 65–85-year-olds. The adult population studied for safety and immunogenicity was stratified by age but skewed towards a Caucasian background (85%). The population in the phase 3 trial assessing efficacy of BNT162b2 was more diversified.

Clinical studies: phase 2/3 trials (3)

Efficacy

Trial population

The phase 2/3 pivotal registration trial of the vaccine was conducted at sites in six countries (Argentina, Brazil, Germany, South Africa, Turkey and the USA) and involved about 43 000 participants aged 16 to 85 years, who were healthy or had stable medical conditions, randomized equally between vaccine and placebo groups. About 6% of participants had serological evidence of a past SARS-CoV-2 infection at entry to the trial. The vaccine was administered in two doses separated by 21 days, with a range of 19 to 42 days. Most participants were white (83%) and from sites in the USA (77%). Similar numbers of males and females were included; 42% of the trial population was aged over 55 years, and 22% over 64 years, with a median age at vaccination of 52 years. About 46% of participants were obese or had a co-morbid condition that was likely to increase their risk of severe COVID-19. The primary analysis of the trial results was conducted when participants had been followed for an average of two months after the second vaccine dose; 92% had been followed for at least one month after the second dose.

Efficacy against COVID-19

Two primary endpoints were specified: efficacy among all participants and efficacy among participants who had no evidence of a previous SARS-CoV-2 infection 7 days after the second vaccine dose. The primary assessment of efficacy was based on the 178 cases of symptomatic laboratory-confirmed SARS-CoV-2 infection that

occurred between 7 days after the second vaccine dose and the end of the follow-up period. Of these cases, 9 were in the vaccinated group and 169 in the placebo group, giving an estimated vaccine efficacy (VE) of 94.6% (95% credibility interval (CI) 89.9–97.3%). When analysis was confined to participants without evidence of a previous SARS-CoV-2 infection, the case numbers were 8 in the vaccine group and 162 in the placebo group, with an estimated VE of 95.0% (95% CI 90.3–97.6%).

Analyses were also conducted including all cases from the time of the first dose. There was evidence of protection both between the first and second doses (VE 52.4%, 95% CI 29.5–68.4%) and between the second dose and 7 days after the second dose (VE 90.5%, 95% CI 61.05–98.9%). More detailed analyses indicated that there was no evidence of protection until about 12 days after the first dose, but subsequently the incidence of COVID-19 was lower among vaccinated participants.

For the period starting 7 days after the second vaccination, no significant variations in the estimates of vaccine efficacy were apparent when the primary analyses were stratified according to sex, age, race, ethnicity, country, comorbid conditions or obesity, and obesity alone. In particular, among those aged 65 years or older, without evidence of prior infection up to 7 days after the second dose, there was 1 case in the vaccinated group and 19 cases in the placebo group (VE 94.7%, 95% CI 66.7–99.9%).

Efficacy against severe COVID-19

A total of 10 cases of severe COVID-19 occurred in trial participants, 1 in the vaccinated group and 9 in the placebo group (VE 88.9%, 95% CI 20.1–99.7%). Of these cases, 5 occurred 7 or more days after the second vaccine dose, 1 in the vaccine group and 4 in the placebo group (VE 75%, 95% CI –152.6–99.5%).

Summary of efficacy evidence in phase 2/3 trials

The vaccine was highly efficacious against laboratory-confirmed COVID-19 from 7 days after the second vaccine dose until the end of the follow-up period, which was, on average, 2 months. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variations in efficacy were found in the various subgroups that were analyzed. Importantly, in subgroups likely to be at higher risk of severe COVID-19, including those aged over 65 years and those with comorbid conditions or obesity, the estimates of efficacy were very high. Few participants in the trial developed severe COVID-19, so efficacy against this endpoint is less certain, but from the time of the first dose, there was only 1 severe case in the vaccinated group and 9 in the placebo group, consistent with high efficacy.

Vaccine safety

Safety data from 37 586 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose suggested a favourable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the seven days after vaccination, were frequent and mostly mild to moderate. Reactogenicity and adverse events (AEs) were generally milder and less frequent in the older group (≥55 years of age) than the younger group (18–55 years of age) and tended to be more frequent and severe after the second dose. Reactogenicity was mostly mild to moderate and short-lived for both age groups (median onset was 0–2 days after either dose for a median duration of 1–2 days). The vaccine's AE profile did not suggest any specific safety concerns. The median onset of systemic AEs was 1–2 days after either dose for a median duration of 1 day. Severe adverse reactions occurred in 0.0–4.6% of participants. The incidence rates of serious adverse events (SAEs), deaths, and discontinuation due to AEs were low and comparable for the vaccine and placebo groups. No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

Adverse events

The most common solicited adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%). The mean duration of pain at the injection site after dose 2 was 2.5 days (range 1 to 36 days), redness 2.6 days (range 1 to 34 days), and swelling 2.3 days (range 1 to 34 days).

Adverse events of special interest, that would potentially require longer follow up

Lymphadenopathy

Lymphadenopathy was reported in 64 participants (0.3%). There were more cases in the vaccine group (64) than the placebo group (6). In the vaccine group, 54 (0.5%) occurred in the younger age group (16–55 years) and 10 (0.1%) in the older age group (>55 years). Lymphadenopathy occurred in the arm and neck region, and was reported within 2–4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off.

Bell's palsy

Bell's palsy was reported by four participants in the vaccine group and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days post-vaccination) was reported as resolved with sequelae within three days of onset, and the other three were reported as continuing or resolving as of the 14 November 2020 data cut-off, with ongoing durations of 10, 15, and 21 days, respectively. The usual incidence of Bell`s palsy is 15–30 per 100 000 per year (4). The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population. An association between COVID-19 and Bell's palsy has been reported. At this point in time, there is no clear basis upon which to conclude a causal relationship, but surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations is an absolute requirement. Bell`s palsy has been addressed in the risk management plan.

Allergic reactions

The Food and Drug Administration of the USA independently conducted standard MedDRA queries (SMQs) on the phase 2/3 all-enrolled safety population using FDA-developed software. This was to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including allergic, neurological, inflammatory, and autoimmune conditions. The SMQs revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137, 0.63%) compared with the placebo group (111, 0.51%). No imbalances between treatment groups were evident for any of the other SMQs evaluated (5).

Severe allergic reactions have been reported following administration of the Pfizer–BioNTech COVID-19 vaccine during mass vaccination outside of clinical trials. Severe allergic reactions to any ingredient of this vaccine, or a previous dose of this vaccine, are a contraindication.

Additional adverse reactions may become apparent with more widespread use of the Pfizer–BioNTech COVID-19 vaccine.

Serious adverse events

Two of the SAEs considered as possibly related to the vaccine were shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla ipsilateral to the vaccine injection site. The lymphadenopathy was temporally associated and biologically plausible.

Special populations

Comorbidities

Across both treatment groups, 20.5% of participants had a comorbidity (as per the Charlson Comorbidity Index). The most frequently reported comorbidities were diabetes, with or without chronic complications (8.4%) and pulmonary disease (7.8%), which were reported at similar frequencies in each group. More participants had comorbidities in the older population (31.1%) than the younger population (12.8%), including diabetes (14.6% and 3.8%), malignancy (7.4% and 1.0%), and pulmonary disease (8.8% and 7%).

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. The HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition, but their safety data were not available to contribute to the safety analyses at the time of the data cut-off.

Pregnancies

Female study participants with childbearing potential were screened for pregnancy prior to each vaccination. Anyone who tested positive was excluded or discontinued from the study. The study is collecting data on outcomes of all reported pregnancies that occurred either after vaccination or before vaccination but without being detected by prevaccination screening tests. Twenty-three such pregnancies were reported up to the data cut-off date of 14 November 2020 (12 in the vaccine group, 11 in the placebo group). Pregnancy outcomes are currently not known. Available data on the BNT162b2 vaccine administered to pregnant women are insufficient to allow assessment of vaccine-associated risks in pregnancy.

Special considerations

PEGylation (or pegylation)

The Pfizer BioNTech BNT162b2 vaccine contains four lipids. The lipids encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles. The four lipids are:

- cholesterol
- 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
- ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate))
- ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

Two of the lipids are commonly used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)). ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid). The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the lipid nanoparticle, which contributes to storage stability and reduces nonspecific binding to proteins.

Severe allergies

Of the excipients, ALC-0159 has the ability to cause allergic reactions, since it contains polyethylene glycol or macrogol.

First published data on anaphylaxis following mass roll-out in the United States after emergency use authorization

During December 14–23, 2020, monitoring by the Vaccine Adverse Event Reporting System detected 21 cases of anaphylaxis after administration of a reported 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million doses); 71% of these occurred within 15 minutes of vaccination (6).

Summary of vaccine safety aspects

Reactogenicity and adverse events associated with the vaccine were generally milder and less frequent in the older group (≥55 years of age) than the younger group (18–55 years of age) and tended to increase after the second dose. Reactogenicity was mostly mild to moderate and short-lived for both adult age groups (median onset was 0–2 days after either dose for a median duration of 1–2 days). Available data on the vaccine administered to pregnant women are insufficient to allow assessment of vaccine-associated risks in pregnancy. Adverse events of special interest (that would require longer follow up) include lymphadenopathy, Bell's palsy and allergic reactions.

Vaccine storage

This vaccine requires an ultra-low-temperature freezer for storage up to 6 months. Temperature-controlled thermal shippers using dry ice to maintain the recommended temperature of –70 °C ± 10 °C for up to 10 days will be needed for transportation. Each thermal shipper should have a reusable global positioning system (GPS) temperature-monitoring device.

The intent is to use Pfizer strategic transportation partners to ship by air to major hubs within a country or region and by ground transport to dosing locations. GPS-enabled thermal sensors will be used and a control tower will track the location and temperature of each vaccine shipment along their pre-set routes. These GPS-

enabled devices will allow detection of unwanted deviations. Shipment and transfer of vaccines is directed to "points of use" (POU).

Once a POU receives a thermal shipper with the vaccine, there are three options for storage.

- Ultra-low-temperature freezers, which are commercially available and can extend shelf-life for up to six months.
- Refrigeration units, which are commonly available in hospitals: the vaccine can be stored for five days in such refrigerators at 2–8 °C.
- The Pfizer thermal shippers in which doses arrive can be refilled with dry ice and used as temporary storage units for up to 15 days. After the 15 days, the vials may be transferred to refrigerated storage at 2–8 °C for an additional five days, giving a total storage time of 20 days.

Once thawed and stored at 2–8 °C, the vials may not be refrozen or stored in frozen condition.

The various storage options at the POU allow equitable access to the Pfizer vaccine for areas with differing infrastructure.

Manufacturer's recommended dosage and schedules including boosters

The Pfizer–BioNTech COVID-19 vaccine BNT162b2 (30 µg) is administered intramuscularly as a series of two 30-µg doses of the diluted vaccine solution (0.3 ml each) according to the following schedule: a single dose followed by a second dose 21 days later. The interval between the two doses in the trial ranged from 19 to 45 days. Studies to determine the need for, and timing of, boosters have been initiated. For the current timing, the schedule determines two doses only.

References

1. Lambert PH, Ambrosino DM, Andersen SR et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine 2020; 38(31): 4783-91.
2. Walsh EE, Frenck R, Falsey AR et al. RNA-based COVID-19 vaccine BNT162b2 selected for a pivotal efficacy study. medRxiv 2020.
3. Polack FP, Thomas SJ, Kitchin N et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020.
4. Morris AM, Deeks SL, Hill MD et al. Annualized incidence and spectrum of illness from an outbreak investigation of Bell's palsy. Neuroepidemiology 2002; 21(5): 255-61.
5. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. FDA Briefing Document Pfizer-BioNTech COVID-19 Vaccine. Food and Drug Administration; 2020 (https://www.fda.gov/media/144245/download; accessed 20 December 2020).
6. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. MMWR, January 6, 2021, early release https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm?s_cid=mm7002e1_w; accessed 12 January 2021)

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WHO: Annelies Wilder-Smith, Joachim Hombach, Melanie Marti, Susan Wang, Katherine O'Brien.

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

Annexes

Note:

The annexes contain the grading of recommendations, assessment, development and evaluations – *GRADE tables* (Annex 1 to 6) and the SAGE evidence-to-recommendation framework tables – *ETR tables* (Annex 7-9). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).

Annex 1: GRADE table: Efficacy of BNT162b2 COVID-19 vaccine in adults

Population: Adults (16–55 years)

Intervention: Two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo in preventing PCR-confirmed COVID-19 in adults (≥16–55 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious[b]	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4, or ⨁⨁⨁⨁).
	Conclusion			We are very confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (16–55 years).

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(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: 383:2603-2615.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 2: GRADE table: Safety of BNT162b2 COVID-19 vaccine in adults

Population: Adults (16–55 years)

Intervention: One or two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo in adults (16–55 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT(1–3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⨁⨁⨁).
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of BNT162b2 vaccine in adults (16–55 years) is low.

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(2) Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586(7830):589-93.

(3) 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: 383:2603-2615..

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 3:GRADE table: Efficacy of BNT162b2 COVID-19 vaccine in older adults

Population: Older adults (>55 years)

Intervention: Two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo in preventing PCR-confirmed COVID-19 in older adults (>55years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[b]	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4, or ⨁⨁⨁⨁).
	Conclusion			We are confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (>55 years).

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(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: 383:2603-2615..

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Of the trial participants, approximately 40% were aged over 55 years. Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

Annex 4:GRADE table: Safety of BNT162b2 COVID-19 vaccine in older adults

Population: Older adults (>55 years)

Intervention: One or two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo in older adults (>55 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT(1–3)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⨁⨁⨁).
	Conclusion			We are moderately confident that the risk of serious adverse events following one or two doses of BNT162b2 vaccine in older adults (>55 years) is low.

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(2) Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586(7830):589-93.

(3) 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: 383:2603-2615..

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

Annex 5: GRADE table: Efficacy of BNT162b2 COVID-19 vaccine in individuals with underlying conditions

Population: Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: Two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b,c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).
	Conclusion			We are moderately confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19 as included in the clinical trial. No data were obtained on vaccination of pregnant or breastfeeding women, or persons who were immunocompromised.

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(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: 383:2603-2615..

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Around 46% of the trial population were either obese or affected by co-morbidities. Data on long-term protection emerging from the ongoing phase 2/3 clinical trial remain limited, as trial data have so far been reported only for a follow-up of approximately 2 months. This was considered as not constituting a limitation that would lead to downgrading of the evidence. SAGE will continue to review any emerging data and adjust its quality assessment as required.

[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised.

Annex 6: GRADE table: Safety of BNT162b2 COVID-19 vaccine in individuals with underlying conditions

Population: Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: One or two doses of BNT162b2 vaccine

Comparison: Placebo/ no vaccination

Outcome: Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo in individuals with comorbidities or health states that increase risk for severe COVID-19?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT(1, 2)	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-1
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following one or two doses of BNT162b2 vaccine COVID-19 is low.

References:

(1) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(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: 383:2603-2615..

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for limitations in follow-up time of clinical trial, which may not allow detection of adverse events occurring several months after vaccination. Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

[c] Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised.

Annex 7: SAGE evidence-to-recommendation framework: BNT162b2 mRNA vaccine use in adults

Question: Should BNT162b2 mRNA vaccine be administered to adults to prevent COVID-19?

Population: Adults (16–55 years)

Intervention: Two doses of BNT162b2 vaccine

Comparison(s): No vaccination/placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM		No	Un-certain	Yes	Varies by setting	The cumulative number of COVID-19 cases globally has surpassed 70 228 447, with more than 1 595 000 deaths. Cases have been found in 190 different countries or territories throughout the world (status 13 Dec 2020). There has been collateral damage to other public health programmes.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		
BENEFITS & HARMS OF THE OPTIONS		No	Un-certain	Yes	Varies	Primary efficacy analysis shows that BNT162b2 is 95.6% efficacious (95%CI: 89.4–98.6%) in individuals aged 16–55 years against COVID-19 beginning 7 days after the second dose.(1, 2)	Phase 1/2 trial data (3) show immunogenicity of the BTNT162b1 vaccine, receptor-binding domain (RBD)-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (10, 30 and 100 µg) and after a second dose. Geometric mean
		☐	☐	☒	☐		

						neutralizing titres reached 1.9-4.6-fold that of a panel of COVID-19 convalescent human sera. Further, two doses of 1–50 µg of BNT162b1 elicited robust CD4+ and CD8+ T-cell responses (4). Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titres as did candidate BTNT162b1 (5).
		No ☐	Un-certain ☒	Yes ☐	Varies ☐	Data from over 37 586 participants demonstrate that BNT162b2 vaccine was well tolerated across all populations. Systemic events were reported more often by younger vaccine recipients (16–55 years of age) than by older vaccine recipients (>55 years of age) and more often after dose 2 than dose 1. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). There are no long-term safety data available yet and follow-up time remains limited. After country implementation of vaccination in the United Kingdom and the USA, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of severe allergic reactions to other antigens (6).	Local reactions and systemic events reported after administration of the BNT162b1 vaccine were dose-dependent (3). BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, hence chosen for evaluation in phase 2/3 clinical trials (5).

		Favours inter-vention ☒ / Favours com-parison ☐ / Favours both ☐ / Favours neither ☐ / Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harms. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
		Effectiveness of the intervention No included studies ☐ / Very low ☐ / Low ☐ / Mod-erate ☐ / High ☒ Safety of the intervention No included studies ☐ / Very low ☐ / Low ☐ / Mod-erate ☒ / High ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES		Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐ / No known undesirable outcomes ☐	Available scientific evidence on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), vary. There may also be variability around novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	

		No ☐	Probably No ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐	Available scientific evidence suggests that target population probably assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE		No ☒		Un-certain ☐	Yes ☐		Varies ☐	Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to, human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (7). The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (8).
		No		Un-certain	Yes		Varies	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to

		☐	☐	☐	☒	vaccination. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	mitigate the economic consequences of reduced business activity and unemployment due to the pandemic (7, 9–14).
EQUITY		Increa-sed ☒	Un-certain ☐	Reduced ☐	Varie s ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (15), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. The ultra-low-temperature storage requirements of the current formulation of the Pfizer vaccine raise equity concerns, both within countries and globally. Ultracold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (16).
ACCEPTABILITY		Inter-vention	Com parison	Both	Neither	Un-clear	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers, are strongly in favour of it. But they may need to convince other	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.

		☒ ☐ ☐ ☐ ☐	partners or stakeholders to support COVID-19 immunization.	
		Inter-vention ☒ / Com parison ☐ / Both ☐ / Neither ☐ / Un-clear ☐	Vaccine acceptability varies between (sub-) population groups and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (17).	
FEASIBILITY		No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / *Varies* ☒	BNT162b2 is an ultra-low-temperature formulation and needs to be stored at –70 °C. Ultracold chain may not be available, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish. BNT162b2 vaccine is not provided with a diluent, which needs to be procured separately by national programmes.	The combination of the product's logistic features and its reactogenicity makes mass workplace vaccination, which will be intended for this vaccine in many settings, more difficult. In particular, if many health workers are vaccinated at the same time, several may be unable to work the next day because of mild post-vaccination immune responses.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings

	☐	☐	☐	☐	☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Vaccination with BNT162b2 is recommended in persons aged 16 and above. The recommended schedule is two doses (30 µg, 0.3 ml each) given intramuscularly into the deltoid muscle. An interval of 21–28 days between the doses is recommended. If the second dose is inadvertently administered less than 21 days after the first, the dose does not need to be repeated. If administration of the second dose is inadvertently delayed it should be given as soon as possible thereafter, according to the manufacturer's instructions. It is currently recommended that individuals receive no more than two doses in total.				
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and ultracold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In countries where various immunization stakeholders have a crucial role in vaccine distribution, information and open discussion will be required before the vaccine is deployed.				

Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of BNT162b2 in pregnant women; • impact on infants of vaccination of breastfeeding mothers; • safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease; • impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • clinical trials on the efficacy and safety of vaccination of children below the age of 16 years; • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to determine how protection changes with time since vaccination and whether protection can be prolonged by booster doses; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • stability of vaccine under alternative cold-chain distribution and storage conditions; • effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions; • interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

References

(1) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020: 383:2603-2615.

(2) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(3) Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-93.

(4) Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586(7830):594-9.

(5) Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A et al. Safety and Immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020: 383:2439-2450.

(6) Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine. London: Medicines and Healthcare Products Regulatory Agency; 2020(www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine; accessed 14 December 2020).

(7) ACT accelerator: an economic inverstment case & financing requirements. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/an-economic-investment-case-financing-requirements; accessed 13 December 2020).

(8) COVID-19 strategic preparedness and response program (SPRP) using the multiphase programmatic approach (MPA) project: additional financing. Washington, DC: World Bank Group; 2020 (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing; accessed 21 December 2020).

(9) Cutler DM, Summers LH. The COVID-19 pandemic and the $16 trillion virus. JAMA. 2020;324(15):1495-6.

(10) Sandmann FG, White PJ, Ramsay M, Jit M. Optimising benefits of testing key workers for infection with SARS-CoV-2: a mathematical modelling analysis. Clin Infect Dis. 2020 Jul 8.

(11) Ending the COVID-19 pandemic: the need for a global approach. New York: Eurasia Group; 2020 (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).

(12) Hafner M, Yerushalmi E, Fays C, Dufresne E, Van Stolk C. COVID-19 and the cost of vaccine nationalism. Cambridge: RAND Europe; 2020 (www.rand.org/t/RRA769-1; accessed 13 December 2020).

(13) World economic outlook: a long and difficult ascent. Washington, DC: International Monetary Fund; 2020 (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary; accessed 13 November 2020) .

(14) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U et al. Vaccine efficacy needed for a COVID-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. Am J Prev Med. 2020;59(4):493-503.

(15) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination; accessed 23 November 2020).

(16) ACT Accelarator and COVAX facility. Geneva: World Health Organization; 2020 (www.who.int/initiatives/act-accelerator; accessed 23 November 2020).

(17) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med (2020). https://doi.org/10.1038/s41591-020-1124-9

Annex 8: SAGE evidence-to-recommendation framework: BNT162b2 mRNA vaccine use in older adults

Question: Should BNT162b2 mRNA vaccine be administered to older adults to prevent COVID-19?

Population: Older adults (>55 years)

Intervention: Two doses of BNT162b2 vaccine

Comparison(s): No vaccination/Placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM		No	Un-certain	Yes	Varies by setting	The cumulative number of COVID-19 cases globally has surpassed 70 228 447 with more than 1 595 000 deaths. Cases have been found in 190 different countries or territories throughout the world (status 13 December 2020). There has been collateral damage to other public health programmes. Older adults are particularly affected by COVID-19 and bear a significantly higher risk of severe COVID-19 outcomes and death.	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		
BENEFITS & HARMS OF THE OPTIONS		No	Un-certain	Yes	Varies	Primary efficacy analysis shows that BNT162b2 is 93.7% efficacious (95%CI: 80.6–98.8%) in individuals aged >55 years, 94.7% (95%CI: 66.7–99.9%) in those ≥65 years and 100.0% (95%CI: −13.1–100.0%) in those ≥75 years beginning 7 days after the second dose.(1;2) Of the trial participants, approximately 40% were aged 55 years or older.	Phase 1/2 trial data (3) show immunogenicity of the BNT162b1 vaccine, receptor-binding domain (RBD)-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (10, 30 and 100 µg) and after a second dose using the same
		☐	☐	☒	☐		

						concentration. Geometric mean neutralizing titres reached 1.9-4.6-fold compared with that of a panel of COVID-19 convalescent human sera. Further, two doses of 1-50 µg of BNT162b1 elicited robust CD4+ and CD8+ T cell responses (4). Vaccine candidate BNT162b2 elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titres as did candidate BNT162b1 (5).
		No ☐	Un-certain ☒	Yes ☐	Varies ☐	Data from over 37 586 participants demonstrate that BNT162b2 vaccine was well tolerated. Systemic events were reported more often by younger vaccine recipients (16–55 years of age) than by older vaccine recipients (>55 years of age) and more often after dose 2 than dose 1. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). There are no long-term safety data available yet and the follow-up time remains limited. After country implementation of vaccination in the United Kingdom and the USA, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of severe allergic reactions to other antigens (6).	Local reactions and systemic events reported after administration of the BNT162b1 vaccine were dose-dependent (3). BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, and was chosen for evaluation in phase 2/3 clinical trials (5).

	Favours inter-vention ☒	Favours com-parison ☐	Favours both ☐	Favours neither ☐	Unclear ☐	Efficacy data suggest benefit, and short-term safety data suggest minimal harm. Further ongoing studies will need to be undertaken as part of post-marketing surveillance.	
	Effectiveness of the intervention No included studies ☐ / Very low ☐ / Low ☐ / Mod-erate ☐ / High ☒ Safety of the intervention No included studies ☐ / Very low ☐ / Low ☐ / Mod-erate ☒ / High ☐					Please see the related GRADE tables.	
VALUES & PREFERENCES							
	Important uncertainty or variability	Possibly important uncertainty or	Probably no important uncertainty or	No important uncertainty or variability	No known undesirable outcomes	The majority of severe disease occurs in older individuals. Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination.	

		varia bility ☐	varia bility ☒ ☐ ☐	☐	There may also be variability around novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
		No ☐	Pro babl y No ☐	Unc ertai n ☐	Pro babl y Yes ☒	Ye s ☐	Varie s ☐	Available scientific evidence suggests that the target population probably assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE		No ☒	Un-certain ☐	Yes ☐	Varie s ☐	Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not restricted to human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (7). The World Bank has approved a financing window of up to US $12 billion to support low- and middle-income countries in purchasing and distributing vaccine (8).
		No	Un-certain	Yes	Varie s	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence	The global economy is estimated to be losing US$375 billion per month

		☐	☐	☐	☒	indicates that the benefits, including the impact on recovery of the global economy are likely to outweigh the cost of COVID-19 vaccination. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic (7, 9–14).
EQUITY		Increa-sed ☒	Un-certain ☐	Reduced ☐	Varie s ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework (15), which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If they are distributed fairly. COVID-19 vaccines may have considerable impact on reducing health inequities. The ultra-low-temperature storage requirements of the current formulation of the Pfizer vaccine raise equity concerns, both within countries and globally. Ultracold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard to reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (16).

ACCEPTABILITY		Inter-vention ☒ Comparison ☐ Both ☐ Neither ☐ Unclear ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination. But they may need to convince other partners or stakeholders to support COVID-19 immunization.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
		Inter-vention ☒ Comparison ☐ Both ☐ Neither ☐ Unclear ☐	Vaccine acceptability varies between (sub-) population groups, and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) of acceptance rates in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (17).	
FEASIBILITY		No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☒	BNT162b2 is an ultra-low temperature formulation and needs to be stored at –70 °C. Ultracold chain may not be available, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish. BNT162b2 vaccine is not provided with a diluent: this needs to be procured separately by national programmes.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	The risk of severe COVID-19 and death increases steeply with age. Data from the phase 3 trial indicate that the efficacy and safety of the vaccine are comparable across all age groups (above the age of 16). Vaccination is recommended for older persons. Persons above the age of 85 years and very frail older persons were not included in the clinical trials. However, the safety and immunogenicity data obtained in a large subset of older people with and without comorbidities suggest that the benefits of vaccination outweigh the potential risks. Vaccination is recommended for older persons without an upper age limit.				
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and ultracold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In the countries where various immunization stakeholders have a crucial role in vaccine distribution, information and open discussion will be required before the vaccine is deployed.				

Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of BNT162b2 in pregnant women; • impact on infants of vaccination of breastfeeding mothers; • safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease; • impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • clinical trials on the efficacy and safety of vaccination of children below the age of 16 years; • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to determine how protection changes with time since vaccination and whether protection can be prolonged by booster doses; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • stability of vaccine under alternative cold-chain distribution and storage conditions; • effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions; • interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

References

(1) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020: 383:2603-2615.

(2) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).

(3) Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-93.

(4) Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586(7830):594-9.

(5) Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A et al. Safety and Immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020 Oct 14.

(6) Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine. London: Medicines and Healthcare Products Regulatory Agency; 2020(www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine; accessed 14 December 2020).

(7) ACT accelerator: an economic inverstment case & financing requirements. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/an-economic-investment-case-financing-requirements; accessed 13 December 2020).

(8) COVID-19 strategic preparedness and response program (SPRP) using the multiphase programmatic approach (MPA) project: additional financing. Washington, DC: World Bank Group; 2020 (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing; accessed 21 December 2020).

(9) Cutler DM, Summers LH. The COVID-19 pandemic and the $16 trillion virus. JAMA. 2020;324(15):1495-6.

(10) Sandmann FG, White PJ, Ramsay M, Jit M. Optimising benefits of testing key workers for infection with SARS-CoV-2: a mathematical modelling analysis. Clin Infect Dis. 2020 Jul 8.

(11) Ending the COVID-19 pandemic: the need for a global approach. New York: Eurasia Group; 2020 (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).

(12) Hafner M, Yerushalmi E, Fays C, Dufresne E, Van Stolk C. COVID-19 and the cost of vaccine nationalism. Cambridge: RAND Europe; 2020 (www.rand.org/t/RRA769-1; accessed 13 December 2020).

(13) World economic outlook: a long and difficult ascent. Washington, DC: International Monetary Fund; 2020 (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary; accessed 13 November 2020) .

(14) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U et al. Vaccine efficacy needed for a COVID-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. Am J Prev Med. 2020;59(4):493-503.

(15) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination; accessed 23 November 2020).

(16) ACT Accelarator and COVAX facility. Geneva: World Health Organization; 2020 (www.who.int/initiatives/act-accelerator; accessed 23 November 2020).

(17) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med (2020). https://doi.org/10.1038/s41591-020-1124-9.

Annex 9: SAGE evidence-to-recommendation framework: BNT162b2 mRNA vaccine use in individuals with comorbidities

Question: Should BNT162b2 mRNA vaccine be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[15] to prevent COVID-19?

Population: Individuals with comorbidities or health states that increase risk for severe COVID-19

Intervention: Two doses of BNT162b2 vaccine

Comparison(s): No vaccination/Placebo

Outcome: COVID-19 (PCR-confirmed)

Background: On 31 December 2019, WHO was alerted to several cases of pneumonia of unknown origin in Wuhan City, Hubei Province, China. The cause was found to be a novel coronavirus, SARS-CoV-2. The disease caused by this novel virus has been named COVID-19. The outbreak of COVID-19 was declared a public health emergency of international concern in January 2020. The disease has since spread, with an enormous impact on the health and well-being of individuals and populations worldwide. It has further caused major disruptions to various sectors of society and the economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No	Un-certain	Yes	Varies by setting	The cumulative number of COVID-19 cases globally has surpassed 70 228 447 with more than 1 595 000 deaths. Cases have been found in 190 countries or territories throughout the world (Status 13 Dec 2020). There has been collateral damage to other public health programmes. Individuals with certain comorbidities are particularly affected by COVID-19 and bear a higher risk of severe COVID-19 outcomes and death. Identified risk factors include comorbidities such as hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity (particularly a body mass index (BMI) >40). People with multiple	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table
		☐	☐	☒	☐		

[15] Medical and health conditions in individuals of any age, including the following: obesity, chronic conditions (e.g. hypertension, diabetes, asthma, pulmonary, liver, or kidney disease), chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) that is stable and controlled, any immunosuppression, pregnancy, organ transplant and cancer.

						comorbidities are at a higher risk of COVID-19-related adverse outcomes (1). Although the relative risk may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than for healthy older adults (>75 years).	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	No ☐	Un-certain ☐	Yes ☒	Varies ☐	Primary efficacy analysis demonstrates that BNT162b2 is 95.6% efficacious (95%CI: 89.4–98.6%) in individuals aged 16–55 years beginning 7 days after the second dose. Around 46% of the trial population were either obese or affected by co-morbidities. Consistent vaccine efficacy was observed in subjects with a Charlson Comorbidity Index score of at least 1 or obesity. In those with any comorbidity or obesity, efficacy was 95.3% compared with 94.7% in those with no comorbidity, although these analyses were not adequately powered. Limited or no data are available on vaccination of pregnant or severely immunosuppressed persons (2, 3)	Phase 1/2 trial data (4) show immunogenicity of the BNT162b1 vaccine, receptor-binding domain (RBD)-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level (10, 30 and 100 µg) and after a second dose. Geometric mean neutralizing titres reached 1.9–4.6-fold that of a panel of COVID-19 convalescent human sera. Further, two doses of 1–50 µg of BNT162b1 elicited robust CD4+ and CD8+ T cell responses (5). Vaccine candidate BNT162b2 elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titres as did candidate BNT162b1 (6).
	Harms of the intervention Are the undesirable anticipated effects small?	No ☐	Un-certain ☒	Yes ☐	Varies ☐	Data from over 37 586 participants demonstrate that BNT162b2 vaccine was well tolerated Systemic events were reported more often by younger vaccine recipients (16–55 years of age) than by older vaccine recipients (more than 55 years of age) and more often after dose 2 than dose 1. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the	Local reactions and systemic events reported after administration of the BNT162b1 vaccine were dose-dependent.(4) BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, hence chosen for evaluation in Phase II/III clinical trials (6)

			trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Limited or no data are available on vaccination of pregnant or severely immunosuppressed persons. After implementation of vaccination in the United Kingdom and the USA, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of severe allergic reactions to other antigens (7).	
	Balance between benefits and harms	Favours inter-vention ☒ / Favours com-parison ☐ / Favours both ☐ / Favours neither ☐ / Unclear ☐	Efficacy data suggest benefit, and the short-term safety data suggest minimal harms. Further studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: No included studies ☐ / Very low ☐ / Low ☐ / Moderate ☒ / High ☐ Safety of the intervention: No included studies ☐ / Very low ☐ / Low ☒ / Moderate ☐ / High ☐	Please see the related GRADE tables.	

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐	No known undesirable outcomes ☐	There is possibly important uncertainty related to the target population weighing of desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals, related to COVID-19 vaccination. There may also be variability around novel product platforms for mRNA vaccines, which may represent a source of uncertainty/variability. Different population groups may have different opinions regarding the relative weights attributed to desirable and undesirable outcomes	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐	Varies ☐	Available scientific evidence suggests that the target population probably attached more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	No ☒ / Un-certain ☐ / Yes ☐	Varies ☐	Considerable resources will be needed to ensure the implementation of a COVID-19 vaccination programme, especially given: (i) that COVID-19 vaccination is likely to be prioritized for populations (e.g. health care workers, older adults) without pre-existing robust immunization programmes in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19. Resources required include, but are not	An estimated US$15.9 billion is needed for the vaccines pillar (COVAX) of the Access to COVID-19 Tools Accelerator (ACT-A) for 2020–21, when the initiative aims to deliver 2 billion vaccine doses. This does not include all delivery costs in all countries participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX (8).

						restricted to: human resources, vaccine costs, logistics, cold-chain capacity, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	The World Bank has approved a financing window of up to US$12 billion to support low- and middle-income countries in purchasing and distributing vaccine (9).
	Cost-effectiveness	No ☐	Un-certain ☐	Yes ☐	Varies ☒	Formal global cost-effectiveness analyses have not been conducted, but the emerging evidence indicates that the benefits, including the impact on recovery of the global economy, are likely to outweigh the cost of COVID-19 vaccination. Cost-effectiveness analyses should be conducted at country level; cost-effectiveness of COVID-19 vaccination may vary by country depending on COVID-19 burden, comparator interventions assessed, analysis perspective, and local cost-effectiveness thresholds used.	The global economy is estimated to be losing US$375 billion per month due to the coronavirus pandemic. G20 countries have invested approximately US$10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business activity and unemployment due to the pandemic (8, 10–15)
EQUITY	What would be the impact on	Increa-sed	Un-certain	Reduced	Varies	Equity and ethical considerations are critical. SAGE has produced a Values Framework (16)	Vaccine nationalism is seen as a threat to reducing health inequity, in

	health inequities?	☒	☐	☐		☐	which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If distributed fairly, COVID-19 vaccines may have considerable impact on reducing health inequities. The ultra-low-temperature storage requirements of the current formulation of the Pfizer vaccine raise equity concerns, both within countries and globally. Ultracold chain capacity is not currently available in many low- and middle-income-countries, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements are not made available, or if vaccines that are feasible and available to deliver are less efficacious or less safe, health inequities will result and existing health inequities may be exacerbated.	particular as high-income countries have arranged bilateral contracts with manufacturers. This has led to the establishment of the Access to COVID-19 Tools (ACT) Accelerator and, within this, the COVAX facility, which aims to ensure equitable access to vaccines for its participating member states (17).
ACCEPTABILITY		Inter-vention ☒	Com parison ☐	Both ☐	Neither ☐	Un-clear ☐	No scientific evidence is available. As vaccination is an eagerly awaited tool to combat COVID-19, it is assumed that key stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination. But they may need to convince other partners or stakeholders to support COVID-19 immunization.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general, though not necessarily of this vaccine in particular.
		Inter-vention	Com parison	Both	Neither	Un-clear	Vaccine acceptability varies between (sub-) population groups, and may be correlated with the perceived risk posed by the disease. In a global survey (19 countries) on acceptance rates	

		☒	☐	☐	☐	☐	in the general population of any COVID-19 vaccine product, 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Acceptance rates ranged from almost 55% to 87% (18).	
FEASIBILITY		No ☐	Probably No ☐	Uncertain ☐	Probably Yes ☐	Yes ☐	*Varies* ☒	BNT162b2 is an ultra-low-temperature formulation and needs to be stored at –70 °C. Ultracold chain may not be available, in particular in low- and middle-income-countries, and is expensive and time-consuming to establish. BNT162b2 vaccine is not provided with a diluent, which needs to be procured separately by national programmes.		

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

Recommendation (text)	Persons with comorbidities Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. Phase 2/3 clinical trials have demonstrated that the vaccine has similar safety and efficacy profiles in persons with various underlying medical conditions, including those that place them at increased risk for severe COVID-19. The comorbidities studied in phase 2/3 clinical trials include hypertension; diabetes; asthma; and pulmonary, liver and kidney disease; as well as chronic (stable and controlled) infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19. Immunocompromised persons Immunocompromised persons are at higher risk of severe COVID-19. Available data are currently insufficient to assess vaccine efficacy or vaccine-associated risks in severely immunocompromised persons. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, immunocompromised persons who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment. Pregnant women Pregnant women are at higher risk of severe COVID-19 compared to women of child-bearing age who are not pregnant, and COVID19 has been associated with an increased risk of preterm birth. The available data on BNT162b2 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. However, it should be noted that the BNT162b2 vaccine is not a live virus vaccine, the mRNA does not enter the nucleus of the cell and is degraded quickly. Developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects in pregnancy. Further studies are planned in pregnant women in the coming months. As data from these studies become available, recommendations on vaccination will be updated accordingly. In the interim, WHO recommends not to use BNT162b2 in pregnancy, unless the benefit of vaccinating a pregnant woman outweighs the potential vaccine risks, such as in health workers at high risk of exposure and Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing: Interim guidance -4- pregnant women with comorbidities placing them in a high-risk group for severe COVID-19. Information and, if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided. WHO does not recommend pregnancy testing prior to vaccination. Lactating women Breastfeeding offers substantial health benefits to lactating women and their breastfed children. Vaccine efficacy is expected to be similar in lactating women as in other adults. However, there are no data on the safety of COVID-19 vaccines in lactating women or

	on the effects of mRNA vaccines on breastfed children. As the BNT162b2 vaccine is not a live virus vaccine and the mRNA does not enter the nucleus of the cell and is degraded quickly, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. On the basis of these considerations, a lactating woman who is part of a group recommended for vaccination, e.g. health workers, should be offered vaccination on an equivalent basis. WHO does not recommend discontinuing breastfeeding after vaccination. Persons living with HIV Persons living with HIV may be at higher risk of severe COVID-19. Among the phase 2/3 clinical trial participants with well controlled HIV, there were no reported differences in safety signals. HIV-positive persons who are well controlled on highly active antiretroviral therapy and are part of a group recommended for vaccination can be vaccinated. Available data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy or safety for persons living with HIV who are not well controlled on therapy. It is possible that the immune response to the vaccine may be reduced, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus, persons living with HIV who are part of a group recommended for vaccination may be vaccinated. Information and, where possible, counselling about vaccine safety and efficacy profiles in immunocompromised persons should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration. Persons with autoimmune conditions No data are currently available on the safety and efficacy of BNT162b2 in persons with autoimmune conditions, although these persons were eligible for enrolment in the clinical trials. Persons with autoimmune conditions who have no contraindications to vaccination may be vaccinated.
Implementation considerations	Before implementation, countries should consider whether they have adequate logistic and ultracold-chain capacity in place to ensure vaccine distribution and administration under the mentioned requirements. In the countries where various immunization stakeholders have a crucial role in the vaccine distribution, information and open discussion will be required before the vaccine is deployed.

Monitoring and evaluation	WHO recommends the following post-authorization monitoring activities: • vaccine effectiveness over time; • ongoing collection of safety data in vaccine recipients; • surveillance for COVID-19 among vaccinated individuals, looking for vaccine-induced enhanced disease (possibly as vaccine-induced antibody levels decline); • safety data from inadvertently vaccinated pregnant women during trials and post-authorization; • safety data from pregnant women who receive vaccine because they are members of prioritized groups, e.g. health workers; • prospective studies on the safety of BNT162b2 in pregnant women; • impact on infants of vaccination of breastfeeding mothers; • safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease; • impact of delayed second dose as currently implemented by certain countries.
Research priorities	WHO recommends the following research activities: • clinical trials on the efficacy and safety of vaccination of children below the age of 16 years; • immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons; • studies to determine how protection changes with time since vaccination and whether protection can be prolonged by booster doses; • studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding; • stability of vaccine under alternative cold-chain distribution and storage conditions; • effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions; • interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms; • global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed; • head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

References

(1) Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
(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 Dec 10.
(3) Pfizer-BioNtech COVID-19 vaccine (Bnt162, Pf-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. Meeting date: 10 December 2020. Food and Drug Administration; 2020 (www.fda.gov/media/144246/download, accessed 10 December 2020).
(4) Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-93.
(5) Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586(7830):594-9.
(6) Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A et al. Safety and Immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020 Oct 14.
(7) Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine. London: Medicines and Healthcare Products Regulatory Agency; 2020(www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine; accessed 14 December 2020).
(8) ACT accelerator: an economic inverstment case & financing requirements. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/an-economic-investment-case-financing-requirements; accessed 13 December 2020).
(9) COVID-19 strategic preparedness and response program (SPRP) using the multiphase programmatic approach (MPA) project: additional financing. Washington, DC: World Bank Group; 2020 (http://documents.worldbank.org/curated/en/882781602861047266/World-COVID-19-Strategic-Preparedness-and-Response-Program-SPRP-using-the-Multiphase-Programmatic-Approach-MPA-Project-Additional-Financing; accessed 21 December 2020).
(10) Cutler DM, Summers LH. The COVID-19 pandemic and the $16 trillion virus. JAMA. 2020;324(15):1495-6.
(11) Sandmann FG, White PJ, Ramsay M, Jit M. Optimising benefits of testing key workers for infection with SARS-CoV-2: a mathematical modelling analysis. Clin Infect Dis. 2020 Jul 8.
(12) Ending the COVID-19 pandemic: the need for a global approach. New York: Eurasia Group; 2020 (www.who.int/publications/m/item/ending-the-covid-19-pandemic-the-need-for-a-global-approach, accessed 13 December 2020).
(13) Hafner M, Yerushalmi E, Fays C, Dufresne E, Van Stolk C. COVID-19 and the cost of vaccine nationalism. Cambridge: RAND Europe; 2020 (www.rand.org/t/RRA769-1; accessed 13 December 2020).
(14) World economic outlook: a long and difficult ascent. Washington, DC: International Monetary Fund; 2020 (www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020#Full%20Report%20and%20Executive%20Summary; accessed 13 November 2020) .
(15) Bartsch SM, O'Shea KJ, Ferguson MC, Bottazzi ME, Wedlock PT, Strych U et al. Vaccine efficacy needed for a COVID-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. Am J Prev Med. 2020;59(4):493-503.
(16) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. Geneva: World Health Organization; 2020 (www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination; accessed 23 November 2020).
(17) ACT Accelarator and COVAX facility. Geneva: World Health Organization; 2020 (www.who.int/initiatives/act-accelerator; accessed 23 November 2020).
(18) Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med (2020). https://doi.org/10.1038/s41591-020-1124-9

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