World Health Organization

mRNA vaccines against COVID-19: Pfizer-BioNTech COVID-19 vaccine BNT162b2

Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines

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Contents:

General considerations on mRNA vaccines

The advantage of RNA-based vaccines is their potential for rapid development and reduced side effects. 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, therefore allowing protein to be made within the cell. . Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows the delivery of precise genetic information 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, thus speeding up its commercial production. The fast and highly scalable mRNA manufacturing and LNP formulation processes enable rapid production of many vaccine doses, making it suitable for rapid vaccine development and pandemic vaccine supply.

COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) vaccine characteristics

The Pfizer-BioNTech COVID-19 vaccine, named BNT162b2, encodes a P2 mutant spike protein (PS 2) and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA). BNT162b2 elicits a blunted innate immune sensor activating capacity and thus augments antigen expression. Encapsulation into LNPs enables transfection of the mRNA into host cells after 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. In the cytosol, the RNA is translated into the encoded viral protein. RNA-expressed S is being degraded intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific humoral T cell mediated immune response with activity against the virus.

Development process, contents, formulation

BNT162b2 is a messenger ribonucleic acid (mRNA) vaccine produced as a highly It is a highliy purified single-stranded, 5`-capped mRNA that has been generated through in vitro transcription in cell-free conditions from the corresponding DNA. The mRNA encodes the viral spike (S) from SARS-CoV-2.
The following excipients are included: ALC-0315, ALC-0159 (polyethylene glycole), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, and water for injections.

Pre-clinical Studies

The BNT162b2 mRNA vaccine against SARS-CoV-2 elicited high neutralizing antibody titers in mice after a single injection. Vaccination of mice also resulted in a 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 diseases. In addition, the induction of a T_{FH} response lends support that the vaccine may confers durable immunity. Translation of this immunogenicity profile into protection against viral infection subsequently was tested in a non-human primate (NHP) study.

The immunogenicity of BNT162b2 in rhesus macaques paralleled that observed in the murine model.[1] Seven days after a second dose of two-dose series (at 0 and 21 days) of 100 µg of this mRNA vaccine, 50% virus neutralization titre of antibodies reached 18-times that of a human SARS-CoV-2 convalescent serum panel and remained 3.3-times higher than this benchmark at five weeks after the last immunisation, though the absolute titer had decayed from 1,689 to 310. The T_H1-biased $CD4^+$ T-

cell response and IFNγ^{+} CD8^{+} T-cell response mirrored that of the cellular immunogenicity profile reported in mice. A two-dose series 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 at 55 days after the second vaccination. Viral RNA, as measured by RT-qPCR, in the bronchoalveolar lavage fluid (BAL) and nasopharyngeal (NP) and oropharyngeal (OP) swabs was significantly reduced in the vaccinated animals as compared to the unvaccinated controls. Absence of virus was seen at Day 3 and Day 6 after challenge. Earlier or later time points were not measured. Histopathologic outcomes are not presented in any detail in the context of this NHP study; protective efficacy is limited to virologic outcomes. Overall, thes preclinical data indicate an immunogenic and efficacious vaccine with respect to protection from viral infection in the lower and upper airways of rhesus macaques three days after challenge.

Clinical Studies: phases 1/2

Phase 1/2 trial – Safety

Two candidates of the mRNA vaccine were tested in Phase 1 trials: BNT162b1 and BNT162b2. The latter was ultimately advanced to Phase 3 trials due to greater tolerability and greather breadth of T-cell epitopes represented.[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 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, though the trial was ongoing at the time of publication.

Phase 1/2 trial – Immunogenicity

Neutralizing antibody titers (50% neutralizing geometric mean titers (GMT)) elicited by BNT162b2 peaked at one week after the second vaccination and began decaying one week after that. There was a trend toward higher titers among individuals who had received the highest vacine dose of 30 μg. Vaccination with this dose elicited titers that were relatively lower than those seen in animal studies with titers in the 18 to 55 year olds that were 1.7 to 4.6 times than that seen in a convalescent serum panel and 1.1 to 2.2 times the convalescents among the 65 to 85 year olds. Safety and immunogenicity outputs were among an adult population that was stratified by age but relatively skewed toward a Caucasian background (85%). The make-up of the Phase III 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 6 countries (US, Brazil, Argentina, Turkey, South Africa, and Germany) and involved in total about 43,000 participants aged 16 to 85 years, who were healthy or had stable medical conditions, randomised 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 2 doses separated by 21 days. Most participants were white (83%) and from US sites (77%). Similar numbers of males and females were included and 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 comorbid condition that would likely increase their risk of severe Covid-19 and 35% of participants were obese. The primary analysis

of the trial results was conducted when participants had been followed for an average of 2 months after the second vaccine dose and 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 before 7 days after the second vaccine dose. The primary assessment of efficacy was based on the total of 178 cases of symptomatic laboratory-confirmed SARS-CoV-2 infection occurring 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 with the estimate of vaccine efficacy (VE) being 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 cases numbers were 8 in the vaccine group and 162 in the placebo group with the estimate of VE being 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 to 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.

In the period 7 or more days after the second vaccine dose, 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 or obesity alone. In particular, among those aged 65 years or older, without evidence of prior infection prior 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% to 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% to 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 and, importantly, in subgroups of participants likely to be at higher risk of severe Covid-19, including those 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 measured 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.

Clinical studies: Phase 2-3 trials: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 favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the 7 days after vaccination, were frequent and mostly mild to moderate. Reactogenicity and adverse events (AEs) were generally milder and less frequent in participants in the older group (≥55 years of age) compared with 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 after dosing for both adult 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 of serious adverse events (SAEs), deaths, and discontinuations due to AEs were low and comparable for both the vaccine and placebo groups. There were no specific safety concerns 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), for redness 2.6 days (range 1 to 34 days), and for 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) vs. the placebo group (6). In the vaccine group, 54 (0.5%) occurred in the younger (16- 55 years) age group and 10 (0.1%) in the older (>55 years) age group. Lymphadenopathy occurred in the arm and neck region, and was reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff.

Bell's Palsy

Bell's palsy was reported by four vaccine participants 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 after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The usual incidence of Bell`s palsy is 15-30/100,000/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 and 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 FDA 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, neurologic, 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 the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials. Any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer BioNTech vaccine.

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

Serious Adverse Events

Two of the SAE's considered as possibly related to vaccine included shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. The lymphadenopathy was temporally associated and biologically plausible.

Special populations

Comorbidities in the Clinical Trial

Across both treatment groups, 20.5% had any comorbidity (per the Charlson Comorbidity Index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and 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 did not have safety data available to contribute to the safety analyses at the time of the data cutoff.

Pregnancies in the Clinical Trial

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination. A positive test resulted in their exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occurred after vaccination, or before vaccination and were not detected by pre-vaccination screening tests. Twenty-three inadvertent pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo).

Pregnancy outcomes are currently not known. Available data on the BNT162b2 vaccine administered to pregnant women are insufficient to inform 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.

Two of the lipids are used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)) and two have not been commonly used in an authorised medicinal product

- ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate))
- ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

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

From the excipients officially declared, ALC-0159 has the ability to cause allergic reactions since it contains polyethylene glycol (PEG) or macrogol.

Summary of vaccine safety aspects

Reactogenicity and adverse events (AEs) associated with the vaccine were generally milder and less frequent in participants in the older group (≥55 years of age) compared with 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 after dosing 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 inform vaccine-associated risks in pregnancy. Adverse events of special interest (that would potentially require longer follow up) include lymphadenopathy, Bell's Palsy and Allergic reactions.

Vaccine storage

This vaccine requires ultra-low temperature freezer for storage up to 6 months. Temperature-controlled thermal shippers utilizing dry ice to maintain recommended temperature conditions of **-70°C±10°C for up to 10 days** will be needed for transportation. Each thermal shipper should have a reusable GPS temperature monitoring device. The intent is to utilize Pfizer-strategic transportation partners to ship by air to major hubs within a country/region and by ground transport to dosing locations.
GPS-enabled thermal sensors with a control tower that will track the location and temperature of each vaccine shipment across their pre-set routes will be used. These GPS-enabled devices will allow to proactively prevent unwanted deviations. Shipment it 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 that are commonly available in hospitals. The vaccine can be stored for five days at refrigerated **2-8°C conditions**.
- - The Pfizer thermal shippers, in which doses will arrive, that can be used as temporary storage units by refilling with dry ice for **up to 15 days of storage**.

After storage for 15 days in the Pfizer thermal shipper, vaccination centers can transfer the vials to 2-8°C storage conditions for an additional five days, for a total of 20 days. Once thawed and stored under 2-8°C conditions, the vials cannot be re-frozen or stored under frozen condition
The various storage options at the POU allow for equitable access to the Pfizer vaccine to areas with differing infrastructure.

Manufacturer's recommended dosage and schedules including boosters

The Pfizer-BioNTech COVID-19 vaccine BNT162b2 (30 microgram) is administered intramuscularly as a series of two 30 microg doses of the diluted vaccine solution (0.3ml 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 included 19 to 45 days. Studies to determine the need for, and timing of, boosters have been initiated. For the current timing, the schedule determines 2 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. https://www.fda.gov/media/144245/download (accessed 20 December 2020.

Appendices:

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 to placebo to prevent 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[1]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[2]	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).

(1) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (www.fda.gov/media/144246/download, accessed 10 December 2020). 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 Dec 10.

[1] 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.

[2] Of the trial participants, approximately 40% were aged 55 years and older Data on long-term protection emerging from the ongoing Phase II/III clinical trial remains limited, as trial data are currently only reported for a follow-up of approx. 2 months. This was considered as not constitute a limitation that leads to down-grading of the evidence. SAGE will continue to revise any emerging data and adjust its quality assessment as required.

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 to 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[3]	Serious[4]	-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 COVID-19 in adults (≥16-55 years) is low.

(1) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (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 Oct;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 Dec 10.

[3] 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.

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

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 to placebo to prevent 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[5]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[6]	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).

(1) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (www.fda.gov/media/144246/download, accessed 10 December 2020). 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 Dec 10.

[5] 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.

[6] Of the trial participants, approximately 40% were aged 55 years and older. Data on long-term protection emerging from the ongoing Phase II/III clinical trial remains limited, as trial data are currently only reported for a follow-up of approx. 2 months. This was considered as not constitute a limitation that leads to down-grading of the evidence. SAGE will continue to revise any emerging data and adjust its quality assessment as required.

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 to placebo in 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[7]	Serious[8]	-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 COVID-19 in older adults (≥55 years) is low.

[7] 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.
[8] Downgraded for limitations in follow-up time of clinical trial which may not allow for detection of adverse events occurring only several months after vaccination. Not adequately powered to detect rare adverse events. These may only emerge when large populations have been vaccinated.

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 to placebo to prevent 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[9]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[10,11]	-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, and persons who were immunocompromised.

(1) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (www.fda.gov/media/144246/download, accessed 10 December 2020). 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 Dec 10.

[9] 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.
[10] Around 55% of the trial population were either obese and/or affected by co-morbidities. Data on long-term protection emerging from the ongoing Phase II/III clinical trial remains limited, as trial data are currently only reported for a follow-up of approx. 2 months. This was considered as not constitute a limitation that leads to down-grading of the evidence. SAGE will continue to revise any emerging data and adjust its quality assessment as required.
[11] Trial excluded pregnant or breastfeeding women, and persons who were immunocompromised.

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

Population : In 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 to 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[12]	Serious[13]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[14]	-1
		Imprecision	None serious	0
		Publication bias	None 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 are 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.

(1) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (www.fda.gov/media/144246/download, accessed 10 December 2020). 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 Dec 10.

[12] 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.

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

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

SAGE Evidence to recommendation framework[i]: BNT162b2 mRNA vaccine use in adults

Question: Should BNT162b2 mRNA vaccine[15] 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 of China. The origin 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 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 worldwide across 190 different countries or territories (Status 13 Dec 2020). There has been collateral damage to other public health programs.	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	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Primary efficacy analysis demonstrates BNT162b2 to be 95.6% (95%CI: 89.4–98.6) efficacious in individuals	Phase I/II trial data (3) show immunogenicity of the BTNT162b1 vaccine, receptor-binding domain

[15] Pfizer/BioNTech COVID-19 mRNA vaccine, referred to as BNT162b2.

	Are the desirable anticipated effects large?	☐	☐	☒	☐	aged 16-55 years against COVID-19 beginning 28 days after the first dose.(1;2)	(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 compared to 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 titers as did candidate BTNT162b1.(5)
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Data demonstrate BNT162b2 vaccine was well tolerated across all populations with over 43,000 participants enrolled. Systemic events were reported more often by younger vaccine recipients (16 to 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 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). Nevertheless, there are no long-term safety data available yet and follow-up time remains limited. After country implementation of vaccination in the US and UK, 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 II/III clinical trials (5)

	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggests benefit and short-term safety data suggests minimal harms. Further ongoing study will need to be undertaken as a 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* ☐ | *Mod-erate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☒ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Importa nt uncertai nty or variabilit y* ☐ | *Possibly importa nt uncertai nty or variabilit y* ☒ | *Probably no importa nt uncertai nty or variabilit y* ☐ | *No importa nt uncertai nty or variabilit y* ☐ | *No known undesira ble outcome s* ☐	Available scientific evidence on the relative importance related to the intervention as well as the comparison 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, varies. There may also be variability around novel product platforms as for mRNA vaccines, that may represent a source of uncertainty/variability. Different population groups may consider differently regarding the weighing of desirable relative to 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 target population probably values the desirable effects more 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 programs in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate vaccination 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, during which period 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)
	Cost-effectiveness	*No* ☐ / *Un-certain* ☐ / *Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but given the emerging evidence, the benefits, including the impact on recovery of 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.(7;9-14)

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☒	*Un-certain* ☐	*Reduced* ☐	*Varies* ☐		Equity and ethical considerations are critical. SAGE issued a Values Framework (15) which offers guidance globally on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. Granted fair distribution, 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 vaccines pillar, the COVAX facility which aims to ensure equitable access to vaccines to its participating member states.(16)
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-venti on* ☒	*Com paris on* ☐	*Both* ☐	*Neit her* ☐	*Un-clear* ☐		No scientific evidence available. As vaccination is an eagerly awaited tool in combatting COVID-19, therefore it is assumed that key stakeholders, in particular Ministries of Health and Immunization Mangers are strongly in favor of COVID-19 vaccination. But they have to make an additional effort to convince other partners or stakeholders to support COVID 19 immunization.	The 190 economies participating in COVAX suggest a very high acceptability of COVID-19 vaccination in general, though not of this vaccine in particular.

	Which option is acceptable to target group?	*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. A global survey (19 countries) on acceptance rates in the general population (any COVID-19 vaccine product), revealed that 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Differences in acceptance rates ranged from almost 55-87%.(17)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☒	BNT162b2 is an ultra-low temperature formulation and required storage is at -70°C. Ultracold chain is not 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 available and procured by national programmes.	The combination of the product's logistical features coupled with its reactogenicity makes mass workplace vaccination, which will be intended for this vaccine in many settings, more difficult. In particular in health workers are vaccinated at once, several may be out the next day with 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 ☒		

<table>
<tr><td>Type of recommendation</td><td colspan="4">
<table>
<tr><td>We recommend the intervention
☐</td><td colspan="2">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</td><td>We recommend the comparison
☐</td><td>We recommend against the intervention and the comparison
☐</td></tr>
</table>
</td></tr>
<tr><td>Recommendation (text)</td><td colspan="4">Vaccination with BNT162b2 is recommended in persons aged 16 and above. The recommended schedule is two doses given intramuscularly (IM) into the deltoid muscle. Both doses are necessary for optimal protection.</td></tr>
<tr><td>Implementation considerations</td><td colspan="4">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 an open discussion will be required before the deployment.</td></tr>
<tr><td>Monitoring and evaluation</td><td colspan="4">Across diverse country settings, the following vaccination program implementation monitoring and evaluation should be conducted:
• Immunization safety surveillance;
• Vaccine supply and cold chain monitoring;
• Vaccine effectiveness studies;
• Cost and cost-effectiveness studies;
• Intra action reviews and post-introduction evaluations;
• Behavioral assessments (e.g., determinants of vaccine uptake; adherence to other preventive measures post-vaccination);
• Vaccination impact evaluations (e.g., on non-COVID-19 health outcomes, health systems, schooling, essential services, economic activity);
• Ongoing COVID-19 disease surveillance should continue.</td></tr>
</table>

Research priorities	Research gaps exist around: • Developmental & Reproductive Toxicology; • Vaccination during pregnancy and lactation; • Studies in immune compromised individuals; • Efficacy and safety in children below the age of 16; • Studies on efficacy against asymptomatic infection and transmission; • Co-administration with other vaccines; • Long-term efficacy and safety data; • Immune correlates or surrogates for clinical protection; • Stability of vaccine at higher temperatures for cold chain distribution and storage; • Also to consider post passive exposition to the vaccine as way to monitor the safety data.

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(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 Dec 10.

(2) PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048) VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT MEETING DATE: 10 December 2020. FDA. (www.fda.gov/media/144246/download, accessed 10 December 2020).

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(8) World Bank (2020) COVID-19 Strategic Preparedness and Response Program (SPRP) using the Multiphase Programmatic Approach (MPA) Project : Additional Financing (English).Washington, D.C. : World Bank Group. (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).

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(15) WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination. 11-23-2020.

(16) ACT Accelarator and COVAX facility. www.who.int/initiatives/act-accelerator. 11-23-2020.

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SAGE Evidence to recommendation framework[i]: BNT162b2 mRNA vaccine use older adults

Question: Should BNT162b2 mRNA vaccine[16] 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 of China. The origin 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 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 worldwide across 190 different countries or territories (Status 13 Dec 2020). There has been collateral damage to other public health programs. Older adults are particularly affected by COVID-19 and they bear an exponentially 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	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Primary efficacy analysis demonstrates BNT162b2 to be 93.7 %(95%CI: 80.6–98.8) efficacious in individuals aged >55 years, 94.7% (95%CI: 66.7–99.9) in those	Phase I/II trial data (3), show immunogenicity of the BNT162b1 vaccine, receptor-binding domain

[16] Pfizer/BioNTech COVID-19 mRNA vaccine, referred to as BNT162b2.

	Are the desirable anticipated effects large?	☐	☐	☒	☐	≥65 years and 100.0% (95%CI: −13.1–100.0) in those over ≥75 years against COVID-19 beginning 28 days after the first dose.(1;2) Of the trial participants, approximately 40% were aged 55 years and older.	(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 to 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 titers as did candidate BNT162b1.(5)
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Data demonstrate the BNT162b2 vaccine was well tolerated across all populations with over 43,000 participants enrolled. Systemic events were reported more often by younger vaccine recipients (16 to 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 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). Nevertheless, there are no long-term safety data available yet and the follow-up time remains limited. After country implementation of vaccination in the US and UK, 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 II/III clinical trials (5)

	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Efficacy data suggests benefit and short term safety data suggests minimal harms. Further ongoing study will need to be undertaken as a 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* ☐ | *Mod-erate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☒ | *High* ☐	Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Importa nt uncertai nty or variabilit y* ☐ | *Possibly importa nt uncertai nty or variabilit y* ☒ | *Probably no importa nt uncertai nty or variabilit y* ☐ | *No importa nt uncertai nty or variabilit y* ☐ | *No known undesira ble outcome s* ☐	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, large to the undesirable effects, i.e. the currently reported safety signals, related to COVID-19 vaccination. There may also be variability around novel product platforms as for mRNA vaccines, that may represent a source of uncertainty/variability. Different population groups may consider differently regarding the weighing of desirable relative to 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 target population probably values the desirable effects more than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect.	
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *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 programs in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge resources to accelerate vaccination 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, during which period 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)
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☐	*Varies* ☒	Formal global cost-effectiveness analyses have not been conducted, but given the emerging evidence, the benefits, including the impact on recovery of 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	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.(7;9-14)

						assessed, analysis perspective, and local cost-effectiveness thresholds used.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☒	*Un-certain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE issued a Values Framework (15) which offers guidance globally on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. Granted fair distribution, 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 vaccines pillar, the COVAX facility which aims to ensure equitable access to vaccines to its participating member states.(16)
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Inter-venti on*	*Com paris on*	*Both*	*Neit her*	*Un-clear*	No scientific evidence available. As vaccination is an eagerly awaited tool in combatting COVID-19, therefore it is assumed that key stakeholders, in particular Ministries of Health and Immunization Mangers are strongly in favor of COVID-19 vaccination.	The 190 economies participating in COVAX suggest a very high acceptability of COVID-19 vaccination in general, though not of this vaccine in particular.

	Immunization Managers)?	☒	☐	☐	☐	☐	But they have to make an additional effort to convince other partners or stakeholders to support COVID 19 immunization.	
	Which option is acceptable to target group?	*Inter-vention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	Vaccine acceptability varies between (sub-) population groups, and may be correlated with the perceived risk posed by the disease. A global survey (19 countries) on acceptance rates in the general population (any COVID-19 vaccine product), revealed that 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Differences in acceptance rates ranged from almost 55-87%.(17)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☐	*Varies* ☒	BNT162b2 is an ultra-low temperature formulation and required storage is at -70°C. Ultracold chain is not 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 available and procured 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 comparable efficacy and safety in older persons as in younger persons. Very frail elderly persons as well as persons above the age of 85 years were not included in the trial; however, the safety and immunogenicity data obtained in a large subset of older persons with and without comorbidities suggest that the benefits of vaccination outweigh potentials risks in these particular groups.				
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 an open discussion will be required before the deployment.				
Monitoring and evaluation	Across diverse country settings, the following vaccination program implementation, monitoring and evaluation should be conducted: • Immunization safety surveillance; • Vaccine supply and cold chain monitoring; • Vaccine effectiveness studies; • Cost and cost-effectiveness studies; • Intra action reviews and post-introduction evaluations; • Behavioral assessments (e.g., determinants of vaccine uptake; adherence to other preventive measures post-vaccination);				

	• Vaccination impact evaluations (e.g., on non-COVID-19 health outcomes, health systems, schooling, essential services, economic activity); • Ongoing COVID-19 disease surveillance should continue.
Research priorities	Research gaps exist around: • Developmental & Reproductive Toxicology; • Vaccination during pregnancy and lactation; • Studies in immune compromised individuals; • Efficacy and safety in children below the age of 16; • Studies on efficacy against asymptomatic infection and transmission; • Co-administration with other vaccines; • Long-term efficacy and safety data; • Immune correlates or surrogates for clinical protection; • Stability of vaccine at higher temperatures for cold chain distribution and storage; • Also to consider post passive exposition to the vaccine as way to monitor the safety data.

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SAGE Evidence to recommendation framework[i]: BNT162b2 mRNA vaccine use in individuals with comorbidities

Question: Should BNT162b2 mRNA vaccine[17] be administered to individuals with comorbidities or health states that increase risk for severe COVID-19[18] 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 of China. The origin 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 economy across the globe.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*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 worldwide across 190 different countries or territories (Status 13 Dec 2020).	The COVID-19 situation is evolving rapidly, the most recent epidemiological situation can be found on the following website:

[17] Pfizer/BioNTech COVID-19 mRNA vaccine, referred to as BNT162b2.
[18] Medical and health conditions such as: Individuals of any age, including the following conditions and health states: obesity, chronic conditions (e.g. hypertension, diabetes, asthma, pulmonary, liver, or kidney disease), chronic HIV, HCV, or HBV infection that is stable and controlled any immunosuppression, pregnancy, organ transplant and cancer.

		☐	☐	☒	☐	There has been collateral damage to other public health programs. Individuals with certain co-morbidities are particularly affected by COVID-19 and they 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 BMI >40) were associated with higher in-hospital mortality in hospital. Moreover, people with multiple comorbidities are at a higher risk for 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 healthy older adults (75+ years).	https://covid19.who.int/table
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Primary efficacy analysis demonstrates BNT162b2 to be 95.6% (95%CI: 89.4–98.6) efficacious in individuals aged 16-55 years against COVID-19 beginning 28 days after the first dose. Around 55% of the trial population were either obese and/or affected by co-morbidities. Consistent vaccine efficacy was observed in subjects with a Charlson Comorbidity Index score of at least one or obesity. In those with any comorbidity or obesity, efficacy was 95.3% compared to 94.7% in those with no comorbidity, though these analysis were not adequately powered. Limited or no data are available on vaccination of pregnant or severely immune-suppressed. (2;3)	Phase I/II 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 compared to 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 titers as did candidate BNT162b1.(6)

	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ / *Un-certain* ☒ / *Yes* ☐ / *Varies* ☐	Data demonstrate BNT162b2 vaccine was well tolerated across all populations with over 43,000 participants enrolled. Systemic events were reported more often by younger vaccine recipients (16 to 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 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 immune-suppressed. After country implementation of vaccination in the US and UK, cases of anaphylactic reactions to the vaccine were observed in people with and without a history of severe allergic reactions to other antigens. (7)	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)
	Balance between benefits and harms	*Favours inter-vention* ☒ / *Favours com-parison* ☐ / *Favours both* ☐ / *Favours neither* ☐ / Unclear ☐	Efficacy data suggests benefit and short term safety data suggests minimal harms. Further ongoing study will need to be undertaken as a 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* ☐ / *Mod-erate* ☒ / *High* ☐	Please see the related GRADE tables.	

		Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Mod-erate* ☐ | *High* ☐		
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* ☐	Available scientific evidence suggests that the target population probably considers the desirable effects, i.e. the protection conferred by the vaccine, large to the undesirable effects, i.e. the currently reported safety signals, related to COVID-19 vaccination. There may also be variability around novel product platforms as for mRNA vaccines, that may represent a source of uncertainty/variability. Different population groups may consider differently regarding the weighing of desirable relative to 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 target population probably values the desirable effects more 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 programs in many settings, and (ii) the urgency of vaccination roll-out worldwide, which may necessitate additional surge	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, during which period the initiative aims to deliver 2 billion doses. This does not include all delivery costs in all countries participating in COVAX, bilateral

						resources to accelerate vaccination 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.	procurement deals, or research and development investments outside of COVAX.(8) 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 given the emerging evidence, the benefits, including the impact on recovery of 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 health inequities?	*Increa-sed* ☒	*Un-certain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE issued a Values Framework (16) which offers guidance globally on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. Granted fair distribution, 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	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 vaccines pillar, the COVAX facility which aims to ensure equitable access to vaccines to its participating member states.(17)

			result and existing health inequities may be exacerbated.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ | *Comparison* ☐ | *Both* ☐ | *Neither* ☐ | *Unclear* ☐	On scientific evidence available. As vaccination is an eagerly awaited tool in combatting COVID-19, therefore it is assumed that key stakeholders, in particular Ministries of Health and Immunization Mangers are strongly favor of COVID-19 vaccination. But they have to make an additional effort to convince other partners or stakeholders to support COVID 19 immunization.	The 190 economies participating in COVAX suggest a very high acceptability of COVID-19 vaccination in general, though not of this vaccine in particular.
	Which option is acceptable to target group?	*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. A global survey (19 countries) on acceptance rates in the general population (any COVID-19 vaccine product), revealed that 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Differences in acceptance rates ranged from almost 55-87%.(18)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☒	BNT162b2 is an ultra-low temperature formulation and required storage is at -70°C. Ultracold chain is not 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 available and procured 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 independent of age. Phase 2/3 clinical trials demonstrate similar safety and efficacy profiles in persons with several 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, pulmonary, liver or kidney disease, as well as chronic HIV, HCV or HBV infection that are stable and controlled. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19. **Immune compromised persons**				

	Immune-compromised persons are at higher risk of severe COVID-19. Available data on the vaccine administered to immune-compromised persons are insufficient to assess vaccine efficacy or vaccine-associated risks in immune-compromised persons at this time. There is potential for reduced immune responses to the vaccine, which may alter its effectiveness. In the interim, given that the vaccine is not a live virus vaccine and the mRNA does not enter the nucleus of the cell and is degraded quickly, immune-compromised persons who are part of a group recommended for vaccination may be vaccinated. Information, and where possible counselling, about unknown 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, and COVID-19 has been associated with increasing the risk of pre-term birth. Available data from BNT162b2 vaccination of pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy at this time. However, it should be noted that the BNT162b2 vaccine is not a live virus vaccine. Furthermore, the vaccine mRNA does not enter the nucleus of the cell and is degraded quickly. Findings from developmental and reproductive toxicology (DART) studies in animals do not show harmful effects in pregnancy. Further studies are planned in pregnant women in the next months. As these data become available, recommendations will be updated accordingly. In the interim, SAGE recommends not to use BNT162b2 in pregnancy until more data are available, except for circumstances where the benefit of vaccinating a pregnant woman outweighs the risks, such as in health workers at high risk of exposure. Information, and if possible, counselling on the lack of safety and efficacy data for pregnant women should be provided to inform individual benefit-risk assessment. If a woman becomes pregnant after receiving the first dose of vaccine, the second dose can be provided after a benefit-risk assessment based on information, and if possible, counselling. WHO does not recommend a requirement for pregnancy screening or testing prior to vaccination for purposes of vaccination decision-making. **Lactating women** Breastfed children have not been shown to be at risk of transmission of SARS-CoV-2 through breastmilk. 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 the breastfed child. 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 there is a risk to the breastfeeding child. If a lactating woman is part of a group (e.g., health workers recommended for vaccination, vaccination can be offered. SAGE does not recommend discontinuing breastfeeding after vaccination. **Persons living with HIV** Persons living with HIV are 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 may be vaccinated. There are no data for persons living with HIV who are not well controlled on highly active antiretroviral therapy. Given that the BNT162b2 vaccine is not a live virus vaccine and the mRNA does not enter the nucleus of the cell and is degraded quickly, information, and where possible counselling, about the lack of evidence available on vaccine safety and efficacy in HIV-positive

	persons without well-controlled HIV should be provided to inform individual benefit-risk assessment. Testing for HIV infection prior to vaccine administration is not needed.
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 an open discussion will be required before the deployment.
Monitoring and evaluation	Across diverse country settings, the following vaccination program implementation monitoring and evaluation should be conducted: • Immunization safety surveillance; • Vaccine supply and cold chain monitoring; • Vaccine effectiveness studies; • Cost and cost-effectiveness studies; • Intra action reviews and post-introduction evaluations; • Behavioral assessments (e.g., determinants of vaccine uptake; adherence to other preventive measures post-vaccination); • Vaccination impact evaluations (e.g., on non-COVID-19 health outcomes, health systems, schooling, essential services, economic activity); • Ongoing COVID-19 disease surveillance should continue.
Research priorities	Research gaps exist around: • Developmental & Reproductive Toxicology; • Vaccination during pregnancy and lactation; • Studies in immune compromised individuals; • Efficacy and safety in children below the age of 16; • Studies on efficacy against asymptomatic infection and transmission; • Co-administration with other vaccines; • Long-term efficacy and safety data; • Immune correlates or surrogates for clinical protection; • Stability of vaccine at higher temperatures for cold chain distribution and storage; • Also to consider post passive exposition to the vaccine as way to monitor the safety data.

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[i]This Evidence to Recommendation table is 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). http://www.decide-collaboration.eu/WP5/Strategies/Framework