Annexes to the recommendations for use of the Pfizer–BioNTech vaccine BNT162b2 against COVID-19

Grading of evidence –

Evidence to recommendation tables

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(included in the background document)

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World Health Organization

Background

Annexes 1–8 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 9–12 contain the SAGE evidence-to-recommendation framework tables (ETR tables). 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 27 May 2021).

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Annex 1. GRADE table: Efficacy of BNT162b2 vaccine in adults

Population:	Adults (aged 16–55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (aged 16–55 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating[a]		1/ RCT *(1, 2)*	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are very confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in adults (aged 16–55 years).

[a] High vaccine effectiveness of BNT162b2 has been confirmed in post-introduction observational studies.

[b] 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.

Annex 2. GRADE table: Safety of BNT162b2 vaccine in adults

Population:	Adults (aged 16–55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo/active control in adults (aged 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]	Not serious	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are confident that the risk of serious adverse events following 1 or 2 doses of BNT162b2 vaccine in adults (aged 16–55 years) is low.

[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.

Annex 3. GRADE table: Efficacy of BNT162b2 vaccine in older adults

Population:	Older adults (aged >55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (aged >55 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating[a]		*1/ RCT (1, 2)*	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in older adults (aged >55 years).

[a] High vaccine effectiveness of BNT162b2 has been confirmed in post-introduction observational studies.

[b] 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.

Annex 4. GRADE table: Safety of BNT162b2 vaccine in older adults

Population:	Older adults (aged >55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo/active control in older adults (aged >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]	Not serious	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are confident that the risk of serious adverse events following 1 or 2 doses of BNT162b2 vaccine in older adults (aged >55 years) is low.

[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.

Annex 5. GRADE table: Efficacy of BNT162b2 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/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo/active control 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[a]		1/ RCT *(1, 2, 4)*	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[c]	0
		Imprecision	Serious[d]	-1
		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 the estimate of the effect on the health outcome (level 3).**
	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.

[a] High vaccine effectiveness of BNT162b2 has been confirmed in post-introduction observational studies.

[b] 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.

[c] The phase 3 trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Around 46% of the trial population were either obese or affected by comorbidities. Additional studies in pregnant and lactating women with regard to the COVID-19 mRNA vaccines (BNT162b2 or mRNA-1273) were conducted and data generated demonstrating immunogenicity in these populations.

[d] Missing effect estimates in certain subpopulations and data in immunocompromised individuals were considered as limitations that led to downgrading of the evidence.

Annex 6. GRADE table: Safety of BNT162b2 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/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo/active control 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, 5)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[b]	0
		Imprecision	Serious[c]	-1
		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 the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that the risk of serious adverse events in individuals with comorbidities or health states that increase risk for severe COVID-19 following 1 or 2 doses of BNT162b2 vaccine is low.

[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] The phase 3 trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. Around 46% of the trial population were either obese or affected by comorbidities. Additional studies in pregnant and lactating women with regard to the COVID-19 mRNA vaccines (BNT162b2 or mRNA-1273) were conducted and data generated demonstrating a good safety profile in these populations.

[c] Missing safety data in certain subpopulations and data in immunocompromised individuals were considered as limitations that led to downgrading of the evidence.

Annex 7. GRADE table: Efficacy of BNT162b2 vaccine in children (12–15 years)

Population:	Children (aged 12–15 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of BNT162b2 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in children (aged 12–15 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating[a]		1/ RCT *(6-8)*	4
	Factors decreasing confidence	Limitation in study design[b]	Not serious	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 the estimate of the effect on the health outcome (level 4).**
	Conclusion			We are confident that 2 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in children (aged 12–15 years).

[a] Vaccine efficacy against any COVID-19 disease severity 7 days after dose 2 was 100% (95%CI: 75.3–100%).

[b] Pfizer–BioNTech presented the data to SAGE (unpublished data) before the data were published. 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.

Annex 8. GRADE table: Safety of BNT162b2 vaccine in children (12–15 years)

Population:	Children (aged 12–15 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following BNT162b2 vaccination compared with placebo/active control in children (aged 12–15 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(6-8)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Serious[c]	-1
		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 low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2).**
	Conclusion			We have low confidence in the quality of evidence that the risk of serious adverse events in children (aged 12–15 years) following 1 or 2 doses of BNT162b2 vaccine is low.

[a] Pfizer–BioNTech presented the data to SAGE (unpublished data) before the data were published. 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] Downgraded for limited estimates around safety outcomes. The number of serious adverse events occurring during the observation period were 0.4% (5/1131) in the vaccinated group and 0.2% (2/1129) in the comparison group.

Annex 9. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in adults

Question:	Should BNT162b2 vaccine be administered to adults to prevent COVID-19?
Population:	Adults (aged 16–55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison(s):	Placebo/active control
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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (9).

	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 157 897 763, with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 2021). 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 &		*No*	*Uncertain*	*Yes*	*Varies*	Primary efficacy analysis shows that BNT162b2 is 95.6% efficacious (95%CI: 89.4–98.6%) in	Phase 1/2 trial data *(3)* show immunogenicity of the BTNT162b1 vaccine,

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	individuals aged 16–55 years against COVID-19 beginning 7 days after the second dose (*1, 2)*. 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, 2 doses of 1–50 µg of BNT162b1 elicited robust CD4+ and CD8+ T-cell responses *(10)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2-neutralizing geometric mean titres, as did candidate BTNT162b1 *(11)*. High vaccine effectiveness of BNT162b2 has been demonstrated in post-introduction observational studies. *(12-15)*. Vaccine effectiveness for 1 dose of BNT162b2 was estimated at 54% (95% CI 50-58%) and 90% (95%CI 82-95%) after two doses in the presence of B1.1.7*(16)*.

						The estimated effectiveness of the vaccine against any documented infection with the B.1.1.7 variant was 89.5% (95%CI: 85.9–92.3%), and 75.0% (95%CI: 70.5–78.9%) with the B.1.351 variant *(17)*. Heterologous prime-boost schedules with ChAdOx1-nCoV19 and BNT162b2 have demonstrated safety and immunogenicity*(18, 19)*.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*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 (aged 16–55 years) than by older vaccine recipients (aged >55 years), 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 (shoulder injury related to vaccine administration; right axillary lymphadenopathy; paroxysmal ventricular arrhythmia; and right leg paresthesia) were reported among BNT162b2 recipients across all age groups.	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 *(11)*.

	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest benefit; safety data suggest minimal harms. Further ongoing 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* ☒	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*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 on the relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. the currently reported safety signals), varies. Different population groups may have different opinions regarding the weights assigned 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 assigns more weight to the desirable effects than to the undesirable effects related to COVID-19 vaccination.	

						Targeted studies 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 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, 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, in order 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 *(20)*. 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 *(21)*.
	Cost–effectiveness	*No* ☐	*Uncertain* ☐	*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 costs of COVID-19 vaccination in general at global level. No formal cost–effectiveness analyses of BNT162b2 compared	The global economy is estimated to be losing US$ 375 billion per month because of the coronavirus pandemic. G20 countries have invested approximately US$ 10 trillion in domestic economic stimulus to mitigate the economic consequences of reduced business

						with other vaccines have been conducted. The ability to use BNT162b2 in existing cold-chain infrastructure in all country settings may allow higher population-level coverage. 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.	activity and unemployment due to the pandemic. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(20, 22-27)*.
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(28)*, 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 temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally. The required cold 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	Vaccine nationalism is seen as a threat to reducing health inequity, particularly since 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 *(29)*.

							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.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	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.	The fact that 190 economies are participating in COVAX suggests a very high acceptability of COVID-19 vaccination in general.
		☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	COVID-19 vaccine acceptability in general 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% *(30)*. Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have	
		☒	☐	☐	☐	☐		

							already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time *(31, 32)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*	The temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally, although BNT162b2 can now be distributed and stored at 2–8°C for 1 month (31 days). The required cold 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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	
		☐	☐	☐	☐	☐	☒		
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)	Please see the interim recommendations.			
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.			
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.			

Annex 10. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in older adults

Question:	Should BNT162b2 vaccine be administered to older adults to prevent COVID-19?
Population:	Older adults (aged >55 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison(s):	Active control/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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (9).

	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 157 897 763 with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 2021). 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 &		*No*	*Uncertain*	*Yes*	*Varies*	Primary efficacy analysis shows that BNT162b2 is 93.7% efficacious (95%CI: 80.6–98.8%) in	Phase 1/2 trial data *(3)* show immunogenicity of the BTNT162b1 vaccine,

	Benefits of the intervention Are the desirable anticipated effects large?	☐	☐	☒	☐	individuals aged >55 years; 94.7% (95%CI: 66.7–99.9%) in those aged ≥65 years; and 100.0% (95%CI: −13.1–100.0%) in those aged ≥75 years, beginning 7 days after the second dose *(1, 2)*. Of the trial participants, approximately 40% were over the age of 55 years.	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, 2 doses of 1–50 µg of BNT162b1 elicited robust CD4+ and CD8+ T-cell responses *(10)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2-neutralizing geometric mean titres as did candidate BTNT162b1 *(11)*. High vaccine effectiveness of BNT162b2 has been demonstrated in post-introduction observational studies *(12-15)*.
	Harms of the intervention Are the undesirable	*No* ☐	*Uncertain* ☐	*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 (aged 16–55 years) than by older vaccine recipients	Local reactions and systemic events reported after administration of the BNT162b1 vaccine were dose-dependent *(3)*. BNT162b2 was

	anticipated effects small?						(aged >55 years) 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 (shoulder injury related to vaccine administration; right axillary lymphadenopathy; paroxysmal ventricular arrhythmia; and right leg paresthesia) were reported among BNT162b2 recipients across all age-groups. 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)*.	associated with a lower incidence and severity of systemic reactions than BNT162b1, hence chosen for evaluation in phase 2/3 clinical trials *(11)*.
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Efficacy data suggest some, but not significant, benefit of the intervention; short-term safety data suggest limited harms. Further studies will be needed 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* ☐	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☒	*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* ☐				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 potential protection conferred by the vaccine, more important than the undesirable effects, i.e. the currently reported safety signals related to COVID-19 vaccination. Different population groups may have different opinions regarding the weights assigned 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 assigns more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted studies should assess this aspect. As more data on vaccine efficacy in older adults are generated, the uncertainty around the importance of the desirable effects of the intervention will probably be reduced.	
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	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, in order to deliver 2 billion

					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, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	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 *(20)*. 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 *(21)*.
	Cost–effectiveness	*No*	*Uncertain*	*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 in general at global level. No formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted. 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 because of 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. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic
		☐	☐	☐	☒	

							product (GDP) *(20, 22-27)*.
EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(28)*, 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 temperature storage requirements of the current formulation of the Pfizer–BioNTech 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 *(29)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders	*Intervention*	*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	The fact that 190 economies are participating in COVAX suggests a very high

	(e.g. ministries of health, immunization managers)?	☒	☐	☐	☐	☐	stakeholders, in particular ministries of health and immunization managers are strongly in favour of COVID-19 vaccination.	acceptability of COVID-19 vaccination in general.
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	COVID-19 vaccine acceptability in general 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% *(30)*.	
		☒	☐	☐	☐	☐	Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time *(31, 32)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*	The temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally although BNT162b2 can now be distributed and stored at 2–8°C for 1 month (31 days). The required	
		☐	☐	☐	☐	☐	☒		

				cold 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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	
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)	Please see the interim recommendations.
IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

Annex 11. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in individuals with comorbidities

Question:	Should BNT162b2 vaccine be administered to individuals with comorbidities[a] or health states that increase risk for severe COVID-19 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):	Active control/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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (9).

	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 157 897 763, with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 2021). 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.
		☐	☐	☒	☐		

[a] Comorbidities included were cardiovascular disease, hypertension, obesity and type 2 diabetes. Comorbidities for which there were too few data to evaluate were asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), HIV infection, immunocompromised, liver disease, and neurological conditions.

					There has been collateral damage to other public health programmes.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*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 comorbidities. 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. Vaccination of pregnant women with COVID-19 mRNA vaccine (BNT162b2 or mRNA-1273) suggests immunogenicity in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk *(4)*. No data are available on vaccination of severely immunosuppressed persons *(2, 3)*.	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 *(10)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titres as did candidate BTNT162b1 *(11)*. High vaccine effectiveness of BNT162b2 is has been demonstrated in post-introduction observational studies *(12-15)*.

	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*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 (aged 16–55 years) than by older vaccine recipients (aged >55 years) 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 (shoulder injury related to vaccine administration; right axillary lymphadenopathy; paroxysmal ventricular arrhythmia; and right leg paresthesia) were reported among BNT162b2 recipients across all age groups. Preliminary findings from the US Vaccine Adverse Event Reporting System (VAERS) did not show obvious safety signals among pregnant women who received mRNA Covid-19 vaccines *(5)*. No data are available on vaccination of severely immunosuppressed persons.	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 *(11)*.
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*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	**Effectiveness of the intervention** *No included studies*	*Very low*	*Low*	*Moderate*	*High*	Please see the related GRADE tables.	

	evidence for the critical outcomes?	☐	☐	☐	☒	☐		
		Safety of the intervention						
		No included studies ☐	*Very low* ☐	*Low* ☐	*Moderate* ☒	*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* ☐	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported safety signals), related to COVID-19 vaccination. 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 attaches 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* ☒	*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 programmes in many settings; and	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, in order to deliver 2 billion doses. This does not include all delivery costs in all countries

						(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, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	participating in COVAX, bilateral procurement deals, or research and development investments outside of COVAX *(20)*. 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 *(21)*.
	Cost–effectiveness	*No* ☐	*Uncertain* ☐	*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 in general at global level. No formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted. 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 because of 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. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(20, 22-27)*.

EQUITY	What would be the impact on health inequities?	*Increased* ☒	*Uncertain* ☐	*Reduced* ☐	*Varies* ☐	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(28)*, 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 temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally. The required cold 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 *(29)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders	*Intervention*	*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	The fact that 190 economies are participating in COVAX suggests a very high

	(e.g. ministries of health, immunization managers)?	☒	☐	☐	☐	☐		stakeholders, in particular ministries of health and immunization managers, are strongly in favour of COVID-19 vaccination.	acceptability of COVID-19 vaccination in general.
	Which option is acceptable to target group?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*		COVID-19 vaccine acceptability in general 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% *(30)*.	
		☒	☐	☐	☐	☐		Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time *(31, 32)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably* No	*Uncertain*	*Probably* Yes	*Yes*	*Varies*	The temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally, although BNT162b2 can now be distributed and stored at 2–8°C for 1 month (31 days). The required cold 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. Administration of the vaccine to novel target groups currently not reached by national immunization programmes may pose a challenge in certain settings.	

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)	Please see the interim recommendations.

IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

Annex 12. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in children (12–15 years)

Question:	Should BNT162b2 vaccine be administered to children (aged 12–15 years) to prevent COVID-19?
Population:	Children (aged 12–15 years)
Intervention:	Two doses of BNT162b2 vaccine
Comparison(s):	Active control/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.

Vaccines are a critical tool in combating the pandemic. In the rapidly evolving field of COVID-19 vaccines, WHO has issued to date interim recommendations on the use of a number of COVID-19 vaccines (9).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	By 31 May 2021, data from 100 countries included in the UNICEF database suggest that children and adolescents under 20 years of age accounted for 13% (10.7 million) of the reported COVID-19 cases (33). The cumulative number of COVID-19 cases across all age groups globally has surpassed 157 897 763, with more than 3 287 082 deaths. Cases have been found in 190 different countries or territories throughout the world (status 10 May 2021).	The COVID-19 situation is evolving rapidly; the most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.
		☐	☐	☐	☒		

						There has been collateral damage to other public health programmes. Although children are less affected by direct morbidity and mortality impacts of infection from SARS-CoV-2 when compared to other age groups, children are still at risk of developing severe illness and complications from COVID-19 *(34)*. Current evidence suggests that children with certain underlying medical conditions, and infants (aged <1 year) may be at increased risk for severe illness from SARS-CoV-2 infection *(35)*. Children infected with SARS-CoV-2 are also at risk for developing Multisystem Inflammatory Syndrome in Children (MIS-C), a severe, potentially fatal, rare multiorgan inflammatory condition with persistent fever *(36)*. Evidence suggests that case fatality rate (CFR) may be higher in children in low- and middle-income countries than in high-income countries *(35)*.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	A recent trial assessed safety, immunogenicity, and efficacy of BNT162b2 in children aged 12–15 years (n=2260). Non-inferiority in Geometric Mean Ratio (GMR) in neutralization titers between the 12–15 year group and the 16–25 year group was met. Vaccine efficacy against COVID-19 in those aged 12–15 years was	

					100% (95%CI: 75.3–100%), 7 days after dose 2 *(7, 8)*.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	BNT162b2 was well tolerated in children aged 12–15 years and showed a similar pattern to that seen in those aged 16–25 years. Pain at the injection site, fatigue, headaches, chills, joint pain and muscle pain were the most predominant effects, as well as fever. Increased systemic events after dose 2 were similar to that seen with children aged 16–25 years. In total, 0.4% (5/1131) of the vaccine group participants, and 0.2% (2/1129) of the comparison group participants reported serious adverse events. None of the serious adverse events were assessed by the investigator as related to study intervention. Myocarditis signals which have been reported in the United States after mRNA COVID-19 vaccination are currently being investigated. Reported cases have occurred mostly in male adolescents and young adults age 16 years or older, more often after getting the second dose of one of these two COVID-19 vaccines than after the first dose and typically within several days after COVID-19 vaccination *(37)*.	

	Balance between benefits and harms	*Favours intervention* ☐	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	*Unclear* ☒	In general, children present with less severe disease than adults. To date there are limited follow-up data of the intervention. The possibility to reduce non-pharmaceutical public health measures due to high vaccination coverage in children such as school closures may affect the psychosocial well-being of children. Based on limited safety data, the balance of benefits and harms is highly context-specific and remains unclear to date. Further studies will need to be undertaken as part of post-marketing surveillance.	Should be considered in line with the prioritization roadmap.
	What is the overall quality of this evidence for the critical outcomes?	**Effectiveness of the intervention** *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☐	*High* ☒	Please see the related GRADE tables.	
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☒	*Moderate* ☐	*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* ☐	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects (i.e. the protection conferred by the vaccine weighed against the currently reported limited safety signals), related to COVID-19 vaccination.	

												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 attaches more weight to the desirable effects than the undesirable effects related to COVID-19 vaccination. Targeted information campaigns should assess this aspect. There was substantial geographic variation in the acceptance of COVID-19 vaccination among pregnant women and mothers of children aged ≤18 years. COVID-19 vaccine acceptance levels among mothers for their children was above 85% in Brazil, Colombia, India and Mexico; and below 52% for Australia, Russia and the USA *(38)*.	
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 children with pre-existing co-morbidities placing them at higher risk of severe COVID-19, and (ii) the urgency of vaccination roll-out worldwide to the prioritized groups beyond adolescents, which may necessitate additional surge resources to accelerate	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, in order 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

						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, planning and coordination, training, social mobilization and communications, and immunization safety surveillance.	investments outside of COVAX *(20)*. 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 *(21)*.
	Cost–effectiveness	*No* ☐	*Uncertain* ☐	*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 in general at global level. No formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted. 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 because of 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. Initial estimates suggest that COVID-19 vaccination will provide substantial economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(20, 22-27)*. Preliminary cost–effectiveness analysis results for low- and lower-middle-income countries suggest that

							the cost–effectiveness of COVID-19 vaccination (with products other than BNT162b2) in reducing mortality decreases as coverage expands to younger age cohorts in an age-descending strategy *(39)*.
EQUITY	What would be the impact on health inequities?	*Increased*	*Uncertain*	*Reduced*	*Varies*	Equity and ethical considerations are critical. SAGE has produced a Values Framework *(28)*, 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. As a matter of global equity, as long as many parts of the world are facing extreme vaccine shortage, WHO recommends that countries that have achieved high vaccine coverage in the high-risk populations consider global sharing of BNT162b2 vaccine before proceeding to vaccination of children and adolescents who are at low risk for severe disease. The temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally. The required cold 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-	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 *(29)*.
		☒	☐	☐	☐		

							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.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*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.	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.
	Which option is acceptable to target group?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	No representative data on vaccine acceptance in the target age-group are available. In the general population, COVID-19 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% *(30)*. There was substantial geographic variation in the acceptance of COVID-19 vaccination among pregnant women and mothers of children aged ≤18 years. COVID-19 vaccine acceptance levels among mothers for their children was above 85% in Brazil, Colombia, India and Mexico; and below 52% for Australia, Russia and the USA *(38)*. Additionally, representative multi-country surveys are carried out periodically to assess the percentage of those willing to receive (or of those who have already received) COVID-19 vaccination (non-product specific). While these polls are limited to selected countries, they provide a certain degree of insight into vaccine acceptance and trends over time *(31, 32)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably* No ☐	*Uncertain* ☐	*Probably* Yes ☐	*Yes* ☐	*Varies* ☒	The temperature storage requirements of the current formulation of the Pfizer–BioNTech vaccine raise equity concerns, both within countries and globally, although BNT162b2 can now be distributed and stored at 2–8° C for 1 month (31 days). The required cold 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. In certain settings, school-based programmes such as for HPV vaccines could be leveraged to administer COVID-19 vaccines to children.	

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)	Please see the interim recommendations.

IMPLEMENTATION CONSIDERATIONS	Please see the interim recommendations.
MONITORING, EVALUATION AND RESEARCH PRIORITIES	Please see the interim recommendations.

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