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

Grading of evidence –

Evidence to recommendation tables

First issued 14 January 2021

(included in the background document)

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World Health Organization

Background

These are the annexes to the Interim recommendations for use of the Pfizer–BioNTech vaccine BNT162b2vaccine.

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 5 November 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) up to approx. 2 months following immunization.

[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:	One or 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)*[a]	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 the risk of serious adverse events following 1 or 2 doses of BNT162b2 vaccine in adults (aged 16–55 years) is low. A very rare, but significantly elevated risk of myocarditis/pericarditis has been reported after mRNA COVID-19 vaccine use. These cases occurred more often in younger men (16-24 years of age) and after the second dose of the vaccine, typically within few days after vaccination.

[a] Post-licensure data have identified a very rare but increased risk of myocarditis and pericarditis, mainly in male individuals who received COVID-19 mRNA vaccines.

[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 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	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 older adults (aged >55 years) up to approx. 2 months following immunization.

[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:	One or 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)* [b]	4
	Factors decreasing confidence	Limitation in study design[c]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Not serious[d]	0
		Imprecision	Serious[e]	-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**
	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).**
Summary of Findings	**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 up to approx. 2 months following immunization. Data suggests that individuals with moderately to severely compromised immune systems, such people living with organ or stem cell transplants, blood cancer, certain autoimmune disease and treatment with specific immunosuppressive medications, may not mount the same level of immunity following a regular 2-dose vaccination schedule compared to people who are not immunocompromised.

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

[b] Observational data has been generated on vaccine effectiveness in specific subpopulations.

[c] 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.

[d] 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.

[e] 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:	One or 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) up to approx. 2 months following immunization.

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

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

Population:	Children (aged 12–15 years)
Intervention:	One or 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	Not serious[c]	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 the estimate of the effect on the health outcome (level 2).**
	Conclusion			We have a moderate level of 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 very rare, but significantly elevated risk of myocarditis/pericarditis has been reported recently after mRNA COVID-19 vaccine use. These cases occurred more often in male than in female adolescents and after the second dose of the vaccine, typically within few days after vaccination.

[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] Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated.

[c] The clinical trials had limited estimates around safety outcomes as 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. Post-licensure surveillance and observational safety data support the very low risk of serious adverse events following immunization.

Annex 9. GRADE table: Efficacy of BNT162b2 vaccine in children (5–11 years)

Population:	Children (aged 5–11 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 5–11 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating[a]		1/ RCT *(9)*	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 5–11 years) up to approx. 2 months following immunization.

[a] Vaccine efficacy against any COVID-19 disease severity 7 days after dose 2 was 91% (95% CI: 68-98%).

[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 10. GRADE table: Safety of BNT162b2 vaccine in children (5–11 years)

Population:	Children (aged 5–11 years)
Intervention:	One or 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 5–11 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(9)*	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 5–11 years) 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] 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 1/1518 (0.1%) in the vaccinated group and 1/750 (0.1%) in the comparison group.

Annex 11. GRADE table: Efficacy of BNT162b2 vaccine in children (6 months–4 years)

Population:	Children (aged 6 months– 4 years)
Intervention:	Three doses of BNT162b2 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of three doses of BNT162b2 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in children (aged 6 month–4 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(10)*	4
	Factors decreasing confidence	Limitation in study design	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[a]	-1
		Imprecision	Serious[b]	-2
		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			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence in the quality of evidence that 3 doses of BNT162b2 vaccine are efficacious in preventing PCR-confirmed COVID-19 in children (aged 6 months–4 years).

[a] These descriptive efficacy data are preliminary, as the protocol specified 21 cases have not yet been achieved. Further, there was a short duration of follow-up of 1.3 months and highly variable dosing intervals between doses 2 and 3. These points were considered as limitations that led to downgrading of the evidence.

[b] Vaccine efficacy post Dose 3 cannot be precisely estimated due to the limited number of cases accrued during blinded follow-up, as reflected in the wide confidence intervals associated with the estimates. This was considered as limitation that led to downgrading of the evidence

Annex 12. GRADE table: Safety of BNT162b2 vaccine in children (6 months–4 years)

Population:	Children (aged 6 months– 4 years)
Intervention:	One, two or three 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 6 months– 4 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(10)*	4
	Factors decreasing confidence	Limitation in study design	Serious[a]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious[b]	-2
		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			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence in the quality of evidence that the risk of serious adverse events in children (aged 6 months–4 years) following 1, 2 or 3 doses of BNT162b2 vaccine is low.

[a] Not adequately powered to detect rare adverse events. These may emerge only when large populations have been vaccinated. This was considered as limitation that led to downgrading of the evidence

[b] Downgraded for limitations in follow-up time of clinical trial. The median blinded follow-up time post Dose 3 in the analyses was only 35 days for participants 6-23 months of age and 40 days for participants 2-4 years of age. This was considered as limitation that led to downgrading of the evidence

Annex 13. 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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. 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)*. Based on data identified through a living systematic review of COVID-19 vaccine effectiveness studies, high vaccine effectiveness (VE) against symptomatic disease up to 4 months following receipt of 2 doses has been demonstrated following large-scale roll-out of BNT162b2, including in the context of variants *(12)*. In the period of 4-6 months after vaccination with 2 doses of BNT162b2, immunity wanes and VE against symptomatic infection declines*(13)*, while VE against severe disease was largely maintained 6 months and more following vaccination*(14)*. A third dose during a period when Delta was the prevalent variant resulted in a vaccine efficacy of 96% (95% CI: 89-99), which reflects the reduction in disease occurrence in the boosted group versus the non-boosted group in those without evidence of prior SARS-CoV-2 infection (relative efficacy)*(15)*. In the context of the Omicron variant, early data from 4 countries (United Kingdom, Denmark, Canada, South Africa) suggest that the VE after 2 doses is significantly lower against infection and symptomatic disease compared to	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 *(16)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2-neutralizing geometric mean titres, as did candidate BTNT162b1 *(17)*. A third dose of BNT162b2 induced strong anamnestic responses (5 to 1 Boost: 2-fold higher than peak titers post-primary series), with a 25 to 50-fold increase from titers 8-9 months after primary series, including for variants of concern studied (Beta and Delta)*(18)*. Various heterologous primary and prime-boost

						Delta *(13)*. Based on a currently limited number of studies, VE against hospitalization appears to be substantially higher than that against symptomatic disease, but nonetheless lower than against Delta*(14)*. Mitigating effects of a third dose were observed in settings were Omicron was circulating. Preliminary data from the UK and Denmark suggest a decrease in risk of symptomatic infection as well as hospital admission following the receipt of a third dose of BNT162b2*(12)*.	schedules using BNT162b2 as booster dose have demonstrated to be safe, immunogenic and effective. WHO has summarized the available evidence and issued interim recommendations for heterologous COVID-19 vaccine schedules*(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. In phase 3 clinical trial with more than 10,000 participants 16 years of age and older, safety of BNT162b2 booster doses were	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 *(17)*.

							consistent with other clinical safety data for the vaccine and no safety concerns were identified*(15)*.	
	Balance between benefits and harms	*Favours intervention* ☒	*Favours comparison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Two doses of BNT162b2 confer high vaccine efficacy. Observational data confirm the beneficial effects of two doses of BNT162b2, in particular in the context of non-Omicron variants and in the <6 months following primary immunization. VE against hospitalization and severe disease is maintained following 6 months post primary immunization. An additional third dose of BNT162b2 decreases the risk of symptomatic infection and hospitalization, in particular in the context of Omicron. Safety data suggest minimal harms. Further data are 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	*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	

	undesirable outcomes?	☐ ☒ ☐ ☐ ☐	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 are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge resources in many settings 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.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(20)*. In January 2022, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient

							countries, and cover essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 compared with other vaccines have been conducted in some settings. 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.	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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*.
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 *(29)*, which offers guidance on the fair allocation of COVID-19 vaccines	Vaccine nationalism is seen as a threat to reducing health inequity, particularly since high-income countries have

							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.	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 *(30)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% *(31)*. 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 *(32, 33)*.	
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 feasibility concerns, 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. 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 14. 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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.	
BENEFITS & HARMS OF THE	<u>Benefits of the intervention</u> Are the desirable	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	Primary efficacy analysis shows that BNT162b2 is 93.7% efficacious (95%CI: 80.6–98.8%) in individuals aged >55 years; 94.7% (95%CI: 66.7–99.9%) in those aged ≥65 years; and 100.0%	Phase 1/2 trial data *(3)* show immunogenicity of the BTNT162b1 vaccine, receptor-binding domain (RBD)-binding IgG concentrations and

	anticipated effects large?			(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. Based on data identified through a living systematic review of COVID-19 vaccine effectiveness studies, high vaccine effectiveness (VE) against symptomatic disease up to 4 months following receipt of 2 doses has been demonstrated following large-scale roll-out of BNT162b2, including in the context of variants *(12)*. In the period of 4-6 months after vaccination with 2 doses of BNT162b2, immunity wanes and VE against symptomatic infection declines*(13)*, while VE against severe disease was largely maintained 6 months and more following vaccination*(14)*. A third dose during a period when Delta was the prevalent variant resulted in a vaccine efficacy of 96% (95% CI: 89-99), which reflects the reduction in disease occurrence in the boosted group versus the non-boosted group in those without evidence of prior SARS-CoV-2 infection (relative efficacy)*(15)*. In the context of the Omicron variant, early data from 4 countries (United Kingdom, Denmark, Canada, South Africa) suggest that the VE after 2 doses is significantly lower against infection 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 *(16)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2-neutralizing geometric mean titres as did candidate BTNT162b1 *(17)*. High vaccine effectiveness of BNT162b2 has been demonstrated in post-introduction observational studies *(35-38)*.

					symptomatic disease compared to Delta *(13)*. Based on a currently limited number of studies, VE against hospitalization appears to be substantially higher than that against symptomatic disease, but nonetheless lower than against Delta *(14)*. Mitigating effects of a third dose were observed in settings were Omicron was circulating. Preliminary data from the UK and Denmark suggest a decrease in risk of symptomatic infection as well as hospital admission following the receipt of a third dose of BNT162b2 *(12)*. Data on VE of a third dose in older adults are very limited. Use of BNT162b2 booster doses in Denmark among individuals >60 years indicate that VE is re-established (after rapidly waning vaccine effectiveness from day 30-150 following primary immunization) upon revaccination (54.6% (30.4 to 70.4%)) *(34)*.	
	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	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 *(17)*.

							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)*	
	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* ☐ **Safety of the intervention** *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐					Please see the related GRADE tables.	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☒	*Probably no important uncertainty or variability* ☐	*No important uncertainty or variability* ☐	*No known undesirable outcomes* ☐	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. 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.	Targeted studies should assess this aspect.
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge resources in many settings 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.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(20)*. In January 20222, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution,

							provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted in some settings. 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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide economic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*.
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 *(29)*, which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles that should guide distribution. If	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral contracts with

							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.	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 *(30)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% *(31)*. 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 *(32, 33)*.	
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 feasibility concerns, 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. 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 15. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in individuals with underlying conditions

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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. 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.

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. Recent data suggest that vaccine effectiveness and immunogenicity are lower in immunocompromised persons (ICPs) compared to persons without immunocompromising conditions *(39)*. The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in some ICPs*(40)*. Data from small studies have demonstrated that COVID-19 mRNA vaccines are immunogenic in pregnant women and that vaccine-elicited antibodies are transported to infant cord blood and breast milk, suggesting possible neonatal as well as maternal protection *(4, 41).* Based on data identified through a living systematic review of COVID-19 vaccine effectiveness studies,	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 *(16)*. Vaccine candidate BTNT162b2 elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titres as did candidate BTNT162b1 *(17)*. High vaccine effectiveness of BNT162b2 is has been demonstrated in post-introduction observational studies *(35-38)*.

				high vaccine effectiveness (VE) against symptomatic disease up to 4 months following receipt of 2 doses has been demonstrated following large-scale roll-out of BNT162b2, including in the context of variants *(12)*. In the period of 4-6 months after vaccination with 2 doses of BNT162b2, immunity wanes and VE against symptomatic infection declines*(13)*, while VE against severe disease was largely maintained 6 months and more following vaccination*(14)*. A third dose during a period when Delta was the prevalent variant resulted in a vaccine efficacy of 96% (95% CI: 89-99), which reflects the reduction in disease occurrence in the boosted group versus the non-boosted group in those without evidence of prior SARS-CoV-2 infection (relative efficacy)*(15)*. In the context of the Omicron variant, early data from 4 countries (United Kingdom, Denmark, Canada, South Africa) suggest that the VE after 2 doses is significantly lower against infection and symptomatic disease compared to Delta *(13)*. Based on a currently limited number of studies, VE against hospitalization appears to be substantially higher than that against symptomatic disease, but nonetheless lower than against Delta*(14)*.	

						Mitigating effects of a third dose were observed in settings were Omicron was circulating. Preliminary data from the UK and Denmark suggest a decrease in risk of symptomatic infection as well as hospital admission following the receipt of a third dose of BNT162b2*(12)*. Currently no data are available in this target population on the use of BNT162b2 in the context of Omicron.	
	<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. 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. Reactogenicity data of an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered	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 *(17)*. Developmental and reproductive toxicology (DART) studies of BNT162b2 have not shown harmful effects in pregnant animals and their offspring.

							Clinical trial data on safety and immunogenicity in pregnancy are limited. However, a growing body of post-introduction vaccine pharmacovigilance data has not identified any acute safety problems, with obstetric outcomes including spontaneous abortion and neonatal outcomes similar to reported background rates*(5, 42, 43)*	
	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. An extended primary series including an additional (third) dose (100 µg) for ICPs may be required. Further studies will need to be undertaken as part of post-marketing surveillance.	
	What is the overall quality of this evidence for the critical outcomes?	**Effectiveness of the intervention** *No included studies* ☐	*Very low* ☐	*Low* ☐	*Moderate* ☒	*High* ☐	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	*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	

	undesirable outcomes?	☐	☒	☐	☐	☐			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 *studies* should assess this aspect.
RESOURCE USE	Are the resources required small?	*No* ☒	*Uncertain* ☐	*Yes* ☐	*Varies* ☐				Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge resources in many settings 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.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(20)*. In January 20222, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover

							essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted in some settings. 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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*.
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 *(29)*, which offers guidance on the fair allocation of COVID-19 vaccines based on six core ethical principles	Vaccine nationalism is seen as a threat to reducing health inequity, in particular as high-income countries have arranged bilateral

							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.	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 *(30)*.
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☒	*Comparison* ☐	*Both* ☐	*Neither* ☐	*Unclear* ☐	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% *(31)*. 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 *(32, 33)*.	
		☒	☐	☐		☐	☐			
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 feasibility concerns, 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. 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 16. 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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	By 1 August 2022, data from 115 countries included in the UNICEF database suggest that children and adolescents under 20 years of age accounted for 21% (57.8 million) of the reported COVID-19 cases *(44)*. The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.	
		☐	☐	☐	☒		

					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 *(45)*. 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 *(46)*. 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 *(47)*. Evidence suggests that case fatality rate (CFR) may be higher in children in low- and middle-income countries than in high-income countries *(46)*.	
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)*.	

						Estimated effectiveness of 2 doses of BNT162b2 in persons aged 12–18 years against MIS-C was 91% (95% CI: 78–97%)*(48)*. No data are currently available on the duration of continued protection against severe disease in adolescents	
	<u>Harms of the intervention</u> 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 and pericarditis have been reported after mRNA COVID-19 vaccination. 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 the two COVID-19 mRNA vaccines than after the first dose and typically within several days after COVID-19 vaccination. GACVS	

							notes that myocarditis can occur following SARS-CoV-2 infection (COVID-19 disease) and that mRNA vaccines have clear benefit in preventing hospitalization and death from COVID-19. *(49)*.	
	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 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 WHO SAGE Roadmap For Prioritizing Use Of COVID-19 Vaccines.
	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 & PREFER	How certain is the relative importance of the desirable	*Important uncertainty or variability*	*Possibly important uncertainty or variability*	*Probably no important uncertainty*	*No important uncertainty*	*No known undesirable outcomes*	There is possibly important uncertainty regarding how the target population weighs the desirable and undesirable effects	

	and undesirable outcomes?			*or variability*	*or variability*				(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. 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 *(50)*.	Targeted studies should assess this aspect.
		☐	☐	☐	☒	☐	☐			
RESOURCE USE	Are the resources required small?	*No*		*Uncertain*		*Yes*	*Varies*		Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge resources in many settings to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(20)*. In January 20222, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market
		☒		☐		☐	☐			

						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.	Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted in some settings. 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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*.

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 *(29)*, 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-reach or otherwise already disadvantaged communities. If other vaccines with less demanding storage requirements	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 *(30)*.

							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* ☐	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% *(31)*. 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 *(50)*. 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 *(32, 33)*.	
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 feasibility concerns, 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. 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.				

Annex 17. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in children (5–11 years)

Question:	Should BNT162b2 vaccine be administered to children (aged 5–11 years) to prevent COVID-19?
Population:	Children (aged 5–11 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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	By 1 August 2022, data from 115 countries included in the UNICEF database suggest that children and adolescents under 20 years of age accounted for 21% (57.8 million) of the reported COVID-19 cases *(44)*. The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.Althou	
		☐	☐	☐	☒		

					gh 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 *(45)*. 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 *(46)*. 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 *(47)*. Evidence suggests that case fatality rate (CFR) may be higher in children in low- and middle-income countries than in high-income countries *(46)*.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	A phase 2-3 trial assessed neutralizing antibody titers elicited by BNT162b2 in 5 to 11 year-olds and compared with antibody titers elicited by BNT162b2 in 16 to 25 year-olds. In the 5 to 11 year age-group, 485 participants were enrolled (322 in the BNT162b2 group and 163 in the placebo group. The geometric mean ratio of neutralizing GMTs for 10 µg of BNT162b2 in 5 to 11-year-olds to that for 30 µg of BNT162b2 in 16 to 25 year-olds 1 month after the second dose was 1 (95% confidence interval [CI], 0.9 to 1.2).	

						The observed vaccine efficacy was 91% (95% CI, 68-98%) No data are currently available on the duration of continued protection against severe disease in children aged 5 to 11 years.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	BNT162b2 was well tolerated in children aged 5 to 11 years and showed a similar pattern to that seen in those aged 16 to 25 years. Pain at the injection site, fatigue, headaches, chills, joint pain and muscle pain were the most predominant effects, as well as fever. Injection-site pain was the most common local reaction, occurring in 71 to 74% of BNT162b2 recipients. Severe injection-site pain after the first or second dose was reported in 0.6% of BNT162b2 recipients and in no placebo recipients. One serious adverse event in a BNT162b2 recipient participant occurred and it was considered to be unrelated to the vaccine. No deaths or adverse events leading to withdrawal were reported. Post-introduction data, after administration of 8.7 million doses to children ages 5–11-years suggest that the vaccine was well tolerated. As of 18 December 2021, 12 cases of myocarditis were observed with a male dominance, mostly after the second dose. Reporting rates for males ages 5–	

							11-years were substantially lower than for males ages 12–15 and 16–17-years.*(51)*	
	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 public health and social measures due to high vaccination coverage in children 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 WHO SAGE Roadmap For Prioritizing Use Of COVID-19 Vaccines.
	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	*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	

	undesirable outcomes?	☐ *No* ☒ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies*	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. 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 *(50)*.	Targeted studies should assess this aspect.
RESOURCE USE	Are the resources required small?	☒ *No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies*	Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge resources in many settings to accelerate implementation with adequate infection prevention and control procedures in the context of COVID-19.	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion doses to 144 countries and territories*(20)*. In January 20222, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine

						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.	Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted in some settings. 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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*. 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 *(52)*.
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 *(29)*, 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	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 *(30)*.

							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.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention*	*Comparison*	*Both*	*Neither*	*Unclear*	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% 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% *(31)*. 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 *(50)*. 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 *(32, 33)*.	
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 feasibility concerns, 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. 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.				

Annex 18. SAGE evidence-to-recommendation framework: BNT162b2 vaccine use in children (6 months– 4 years)

Question:	Should BNT162b2 vaccine be administered to children (aged 6 months– 4 years) to prevent COVID-19?
Population:	Children (aged 6 months– 4 years)
Intervention:	Three 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 *(11)*.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Uncertain*	*Yes*	*Varies by setting*	By 1 August 2022, data from 115 countries included in the UNICEF database suggest that children and adolescents under 20 years of age accounted for 21% (57.8 million) of the reported COVID-19 cases *(44)*. The COVID-19 situation is evolving rapidly. The cumulative number of COVID-19 deaths globally has surpassed 6 million. The most recent epidemiological situation can be found on the following website: https://covid19.who.int/table.Althou	
		☐	☐	☐	☒		

					gh 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 *(45)*. 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 *(46)*. 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 *(47)*. Evidence suggests that case fatality rate (CFR) may be higher in children in low- and middle-income countries than in high-income countries *(46)*.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	In Phase 2/3, a total of 4,526 participants 6 months through 4 years of age were randomized 2:1 to receive two doses of 3 µg BNT162b2 or placebo, 3 weeks apart. Based on analyses of post-Dose 2 safety and effectiveness data, the protocol was amended to add a third primary series dose at least 8 weeks after Dose 2. A secondary analysis to evaluate vaccine efficacy was planned once 21 confirmed cases had accrued in the total study population. Preliminary descriptive efficacy analyses of COVID-19 cases	In the immune-bridging analysis, the measure of immune response to 3 doses (3 µg each) of the Pfizer-BioNTech COVID-19 vaccine in children aged 6 months–4 years without evidence of previous SARS-CoV-2 infection was at least as high as the response observed in persons aged 16–25 years who had received 2 doses (30 µg each) of the Pfizer-BioNTech COVID-19

						occurring at least 7 days post Dose 3 included 376 BNT162b2 recipients and 179 placebo recipients 6-23 months of age and 589 BNT162 recipients and 271 placebo recipients 2-4 years of age. In these analyses, three COVID-19 cases occurred in participants 6-23 months of age, with 1 COVID-19 case in the BNT162b2 group compared to 2 in the placebo group, corresponding to an estimated VE of 75.6% (95% CI: −369.1%, 99.6%), and 7 COVID-19 cases occurred in participants 2-4 years of age, with 2 cases in the BNT162b2 group and 5 in the placebo group, corresponding to an estimated VE of 82.4% (95% CI: −7.6%, 98.3%). In a combined analysis of both age groups, VE was 80.4% (95% CI: 14.1%, 96.7%) with 3 cases in the BNT162b2 group and 7 cases in the placebo group. Cases were accrued during February 2022 through April 2022, when the Omicron variant was prevalent in the United States. Among all COVID-19 cases accrued from Dose 1 through the data cutoff of April 29, 2022, 1 placebo recipient 6-23 months of age and 7 participants 2-4 years of age (6 BNT162b2 recipients and 1 placebo recipient) met the protocol specified criteria for severe COVID-19 during both blinded and open-label follow-up.	vaccine, with a geometric mean ratio (GMR) for 50% neutralizing antibody titre of 1.19 (95% CI = 1.00–1.43) for children aged 6–23 months and 1.30 (95% CI = 1.13–1.50) for children aged 2–4 years, satisfying the non-inferiority criteria.
		No	*Uncertain*	*Yes*	*Varies*	Solicited local adverse reactions (ARs) generally occurred at similar frequencies after any dose and	

	Harms of the intervention Are the undesirable anticipated effects small?	☐	☐	☒		☐	solicited systemic ARs occurred at slightly decreasing frequencies with each successive dose. From the combined safety database of 3,013 BNT162b2 recipients 6 months through 4 years of age, 1% of participants (N=29) reported serious adverse events (SAEs), as compared to 1.5% of participants (N=22) in the combined safety database of 1,513 placebo recipients 6 months through 4 years of age.	
	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 public health and social measures due to high vaccination coverage in children 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 WHO SAGE Roadmap For Prioritizing Use Of COVID-19 Vaccines.
	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. 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 *(50)*.	Targeted studies should assess this aspect.
RESOURCE USE	Are the resources required small?	*No* ☒	*Uncertain* ☐	*Yes* ☐	*Varies* ☐		Considerable resources are needed to ensure the implementation of a COVID-19 vaccination programme, especially given the urgency of vaccination roll-out worldwide, which necessitates additional surge	COVAX, the vaccine pillar of the Access to COVID-19 Tools Accelerator (ACT-Accelerator), has now shipped over 1 billion

						resources in many settings 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 to 144 countries and territories*(20)*. In January 20222, an additional funding of at least US$ 5.2 billion is required for the Gavi COVAX Advance Market Commitment to establish a Pandemic Vaccine Pool of a minimum of 600 million additional doses to address uncertainties and risks in the virus' evolution, provide bundled finance to strengthen delivery systems in recipient countries, and cover essential ancillary costs*(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. Formal cost–effectiveness analyses of BNT162b2 vaccine compared with other vaccines have been conducted in some settings. 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,	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 e.g. reduced business activity and unemployment due to the pandemic, which is expected to amount up to US$13.8 trillion through 2024 *(22)*. Initial estimates suggest that timely rolled out COVID-19 vaccination will provide nomic value in

					and local cost–effectiveness thresholds used.	terms of averted morbidity and mortality costs and averted losses in gross domestic product (GDP) *(23-28)*. 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 *(52).*
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 *(29)*, 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	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 *(30)*.

							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-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* ☐	Vaccination is an important tool to combat COVID-19 and key stakeholders, in particular ministries of health and immunization managers, are generally strongly in favour of COVID-19 vaccination.	190 economies are participating in COVAX suggesting 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% 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% *(31)*. 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 *(50)*. 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 *(32, 33)*.	
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 feasibility concerns, 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. 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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