World Health Organization

Strategic Advisory Group of Experts (SAGE) on Immunization Guidance: Pfizer mRNA-BNT162b2 vaccine

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Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcomes?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

"The vaccine" or "The intervention" = Pfizer-BioNTech COVID-19 vaccine
"The problem" = COVID-19 disease

Vaccine efficacy - overview

Table 13. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

At risk = having ≥ of the Charlson Comorbidity Index (CMI) category or BMI ≥30 kg/m..- predicts 10 year survival in persons with one or more comorbidities

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

Vaccine efficacy – severe disease

Table 18. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N*=21669)		Placebo (N*=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First severe COVID-19 occurrence after Dose 1	1	4.021 (21314)	9	4.006 (21259)	88.9	(20.1, 99.7)
After Dose 1 to before Dose 2	0		4		100.0	(-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0		1		100.0	(-3800.0, 100.0)
≥7 Days after Dose 2	1		4		75.0	(-152.6, 99.5)

Vaccine efficacy – one dose

Figure 13 Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

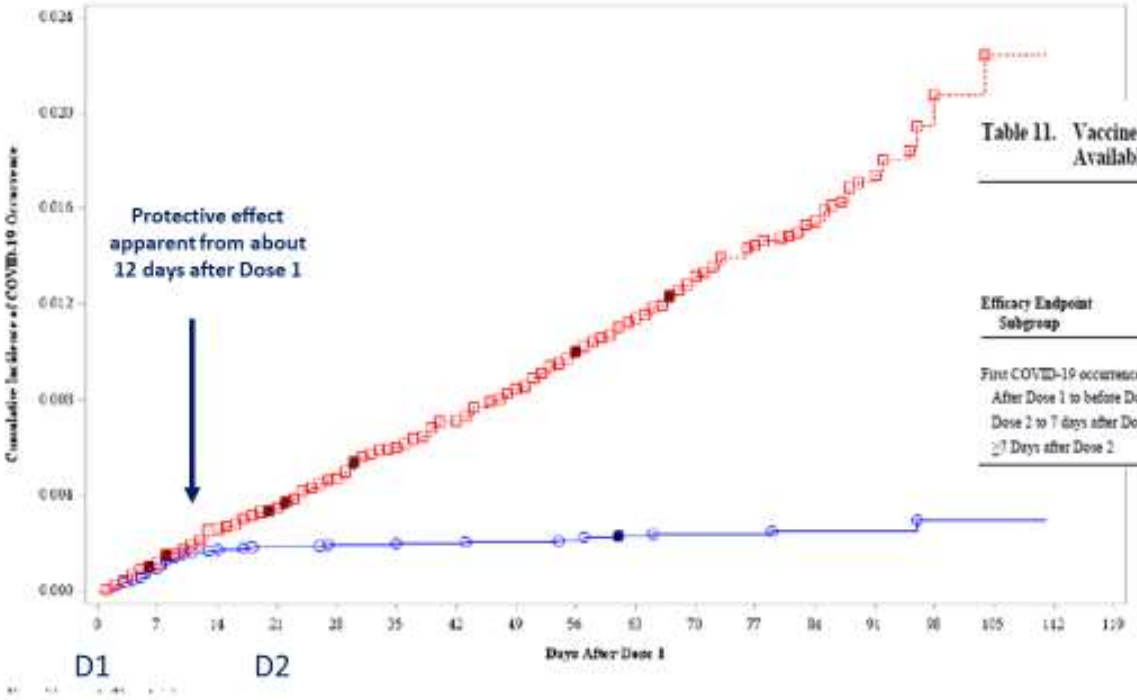


Table 11. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N=21669)		Placebo (N=21686)			
Efficacy Endpoint Subgroup	n[b]	Surveillance Time[c] (n[b])	n[b]	Surveillance Time[c] (n[b])	VE (%)	(95% CI[d])
First COVID-19 occurrence after Dose 1	50	4 015 (21314)	275	3 982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Safety - reactogenicity, lymphadenopathy, Bell's palsy and severe allergic reactions

Safety endpoint	Data
Reactogenicity and adverse events	Frequent, mostly mild to moderate Less frequency and severity in adults (≥55 years of age) than in younger adults (18-55 years of age) Generally higher after 2nd dose compared to first (all ages)
Lymphadenopathy	Vaccine n=64, placebo n=6 Occurred in the arm and neck region within 2 to 4 days after vaccination Plausible relation to vaccination
Bell`s palsy	Vaccine n=4, placebo n=0 Observed frequency consistent with background rate in general population No clear basis upon which to conclude a causal relationship at this time, further surveillance
Severe allergic reactions	0 reported anaphylactic reactions in the clinical trials Exclusion criteria- significant allergic reaction to any vaccine or component of BNT162b 137 [0.63%] hypersensitivity-related AEs in the vaccine group vs 111 [0.51%] in the placebo group

Safety – Special Considerations: PEGylation (or pegylation)

- The BNT162b2 vaccine contains four lipids. The lipids encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry, ensure stability and an adjuvant effect.

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

- ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate))
- ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide)
- ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid).

- The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the lipid nanoparticle, which contributes to storage stability and reduces nonspecific binding to proteins.

COVID-19 and anaphylaxis

MMWR January 6, 2021

- 21 cases 1,893,360 first doses (11.1 per million)
  - Brighton Collaboration
    - Level 1 – 10/21 – rash and swollen lip in 2 cases
    - Level 2 - 11/21

- Same period 83 “non-anaphylaxis” 0-1 day risk window
  - 72/83 – non-serious, rash and mild respiratory symptoms

- Possible risk factors
    - 17/21 (81%) documented allergies or allergic reactions
    - 7/21 (33%) history of anaphylaxis (vaccines-2, drug-2, nut-1, idiopathic-1,JF-1)
    - 19/21 (90%) female

    - Note
      - Insect venom, drug and ? vaccine allergy not more common in those with atopic disease
      - Food and drug allergy not considered a risk factor for vaccine allergy

E2R	Question	SAGE WG Judgement
Public health problem	Is the COVID-19 pandemic of public health importance?	**Yes**
Benefits and Harms	How substantial are the desirable benefits of the intervention?	**Substantial**
	How substantial are the undesirable harms of the intervention?	**Small**
	Do the benefits outweigh the risk/harm?	**Yes**
	What is the overall certainty of the evidence for the outcomes?	**High for prevention of symptomatic SARS-CoV-2** **Low for hospitalizations and death** **Moderate for safety** **Absent for impact on transmission**
Value	Do the target populations value the desirable benefit as large relative to the undesirable risks/harms?	**Will vary within and between countries**
Acceptability	Is BNT162b2 acceptable to key stakeholders?	**Probably yes**
Feasibility	Is BNT162b2 feasible to implement?	**Very difficult but not impossible in many LMICs**
Resource use	Is BNT162b2 a reasonable and efficient use of resources?	**Will vary within and between countries**
Equity	What would be the impact of the intervention on health equity within and between countries?	**Risk of increasing inequity**

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

Interim guidance

7 January 2021

World Health Organization

WHO recommendation for the use of mRNA BNT162b2 (Pfizer-BioNTech)

- BNT162b2 has been shown to have an efficacy of 95% against symptomatic SARS-CoV-2 infection
- No data on impact on transmission or viral shedding
- Vaccination is recommended for persons aged 16 years and above.
- The recommended schedule is two doses given intramuscularly with an interval of 21–28 days between the doses.
- The same product should be used for both doses. There are no studies on interchangeability with other vaccines against COVID-19

Vaccination of specific populations

- BNT162b2 is not a live vaccine, the mRNA does not enter the nucleus and is rapidly degraded. Animal studies show no toxicity to the fetus, but no data on safety in pregnant women exist.
- SAGE recommends not to use BNT162b2 in pregnancy until more data are available, except in circumstances where the benefit of vaccinating a pregnant woman outweighs the risks, such as in health workers at high risk of exposure or women with significant comorbidities.
- Vaccination can be offered to breastfeeding women if part of risk group, and WHO does not recommend discontinuation of breastfeeding after vaccination.
- Lack of data for immune compromised, autoimmune disease, HIV

Vaccination logistics

- The BNT162b2 vaccine currently requires **ultra-cold-chain distribution and storage conditions**

- **Appropriate medical treatment to manage** anaphylaxis must be immediately available, as the incidence of anaphylaxis within 30 minutes after vaccination is 11.1 cases per 1 million vaccinees.
- Persons with a history of severe allergic reactions must be observed for 30 minutes post-administration.
- As anaphylaxis has also been reported in a small number of persons without a history of severe allergies, all vaccinees should be observed for at least 15 minutes post-administration.

Post-authorization surveillance and monitoring:

anaphylaxis and other serious allergic reactions,

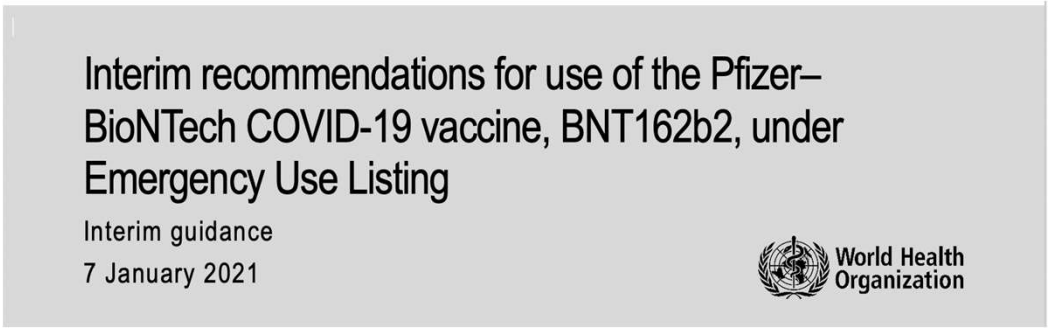
Bell`s palsy,

COVID-19 following vaccination that result in hospitalization or death (VAED)

cases of multisystem inflammatory syndrome,

Safety in pregnancy (inadvertent pregnancies, HCW)

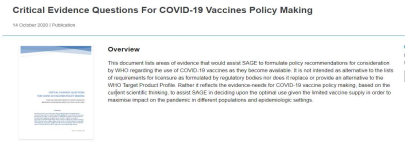
all vaccine administration errors, serious adverse events,



SAGE recommends the following research

- **Vaccine effectiveness:**
- studies to determine how protection changes with time since vaccination and whether protection can be prolonged by booster doses;
- studies to demonstrate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
- **Subpopulations:**
- prospective studies on the safety of BNT162b2 in pregnant women;
- Randomized controlled trial on efficacy and safety of vaccination in children below the age of 16 years;
- safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease;
- **Vaccination logistics:**
- immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
- impact of delayed second dose as currently implemented by certain countries;
- stability of vaccine under alternative cold-chain distribution and storage conditions;
- effectiveness of the proposed strategies for the prevention and management of anaphylactic reactions;
- interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms;
- **Other considerations:**
- global surveillance of virus evolution and the impact of virus mutants on vaccine effectiveness to support possible update of vaccines if needed;
- head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization assays and mucosal immunity assays.

Links to documentation

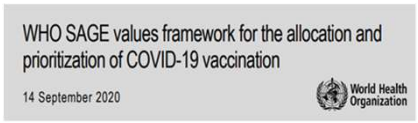

Critical Evidence Questions For COVID-19 Vaccines Policy Making

14 October 2020 / Publication

Overview

This document lists areas of evidence that would assist SAGE to formulate policy recommendations for consideration by WHO regarding the use of COVID-19 vaccines as they become available. It is not intended as alternative to the lists of requirements for licensure as formulated by regulatory bodies nor does it replace or provide an alternative to the WHO Target Product Profile. Rather it reflects the evidence needs for COVID-19 vaccine policy making, based on the current scientific thinking, to assist SAGE in deciding upon the optimal use given the limited vaccine supply in order to maximise impact on the pandemic in different populations and epidemiologic settings.

www.who.int/publications/m/item/critical-evidence-questions-for-covid-19-vaccines-policy-making


WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination

14 September 2020

World Health Organization

www.who.int/publications/i/item/who-sage-values-framework-for-the-allocation-and-prioritization-of-covid-19-vaccination


WHO SAGE ROADMAP FOR PRIORITIZING USES OF COVID-19 VACCINES IN THE CONTEXT OF LIMITED SUPPLY

An approach to inform planning and subsequent recommendations based upon epidemiologic setting and vaccine supply scenarios

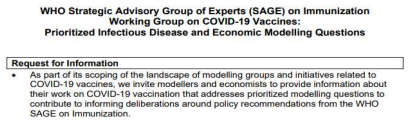
Version 1
20 October 2020

World Health Organization

www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply


EVIDENCE TO RECOMMENDATIONS: COVID-19 VACCINES

A framework to inform the assessment of evidence and formulation of subsequent COVID-19 vaccine recommendations


WHO Strategic Advisory Group of Experts (SAGE) on Immunization
Working Group on COVID-19 Vaccines:
Prioritized Infectious Disease and Economic Modelling Questions

Request for Information

- As part of its scoping of the landscape of modelling groups and initiatives related to COVID-19 vaccines, we invite modellers and economists to provide information about their work on COVID-19 vaccination that addresses prioritized modelling questions to contribute to informing deliberations around policy recommendations from the WHO SAGE on Immunization.

www.who.int/immunization/policy/sage/SAGE_WG_COVID19_Vaccines_Modelling_Questions_31July2020.pdf

October 2020 SAGE meeting Background Paper

www.who.int/immunization/sage/meetings/2020/october/SAGE_eYB_Oct2020final.pdf?ua=1

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MANY THANKS