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Evidence Assessment: Pfizer-BioNTech COVID-19 vaccine

FOR SAGE RECOMMENDATION

Prepared by the SAGE Working Group on COVID-19 vaccines

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

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Is the problem of public health importance?

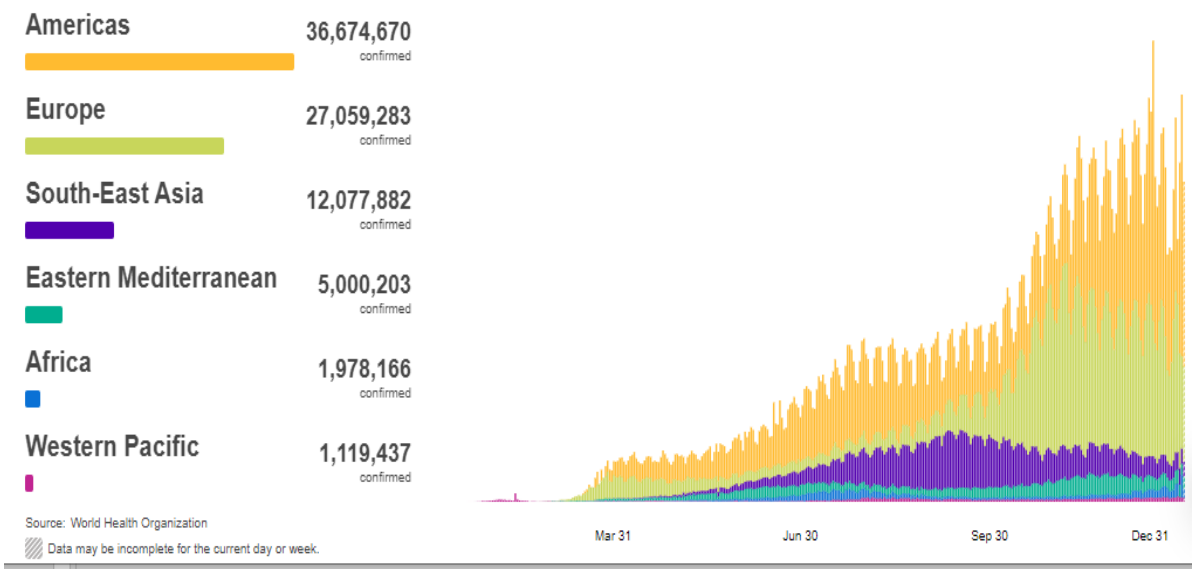
Global Situation: Weekly Overview

(as of 4 January 17H CET)

Cumulative:

- 83,910,386 confirmed cases.
- 1,839,660 deaths.

Situation by WHO Region



Countries with the highest number of cases

Name	Cases - cumulative total	Cases - newly reported in last 24 hours	Deaths - cumulative total	Deaths - newly reported in last 24 hours
Global	**83,910,386**	**583,907**	**1,839,660**	**7,957**
United States o...	20,258,725	284,312	347,555	2,302
India	10,340,469	16,504	149,649	214
Brazil	7,716,405	15,827	195,725	314
Russian Feder...	3,260,138	23,351	58,988	482
The United Kin...	2,654,783	54,990	75,024	454
France	2,611,616	12,489	64,659	116
Italy	2,155,446	14,245	75,332	347

COVID-19 deaths reported in the last 7 days per 1 million population

(From 14 December 2020, 10:00AM to 20 December 2020, 10:00AM (CET))

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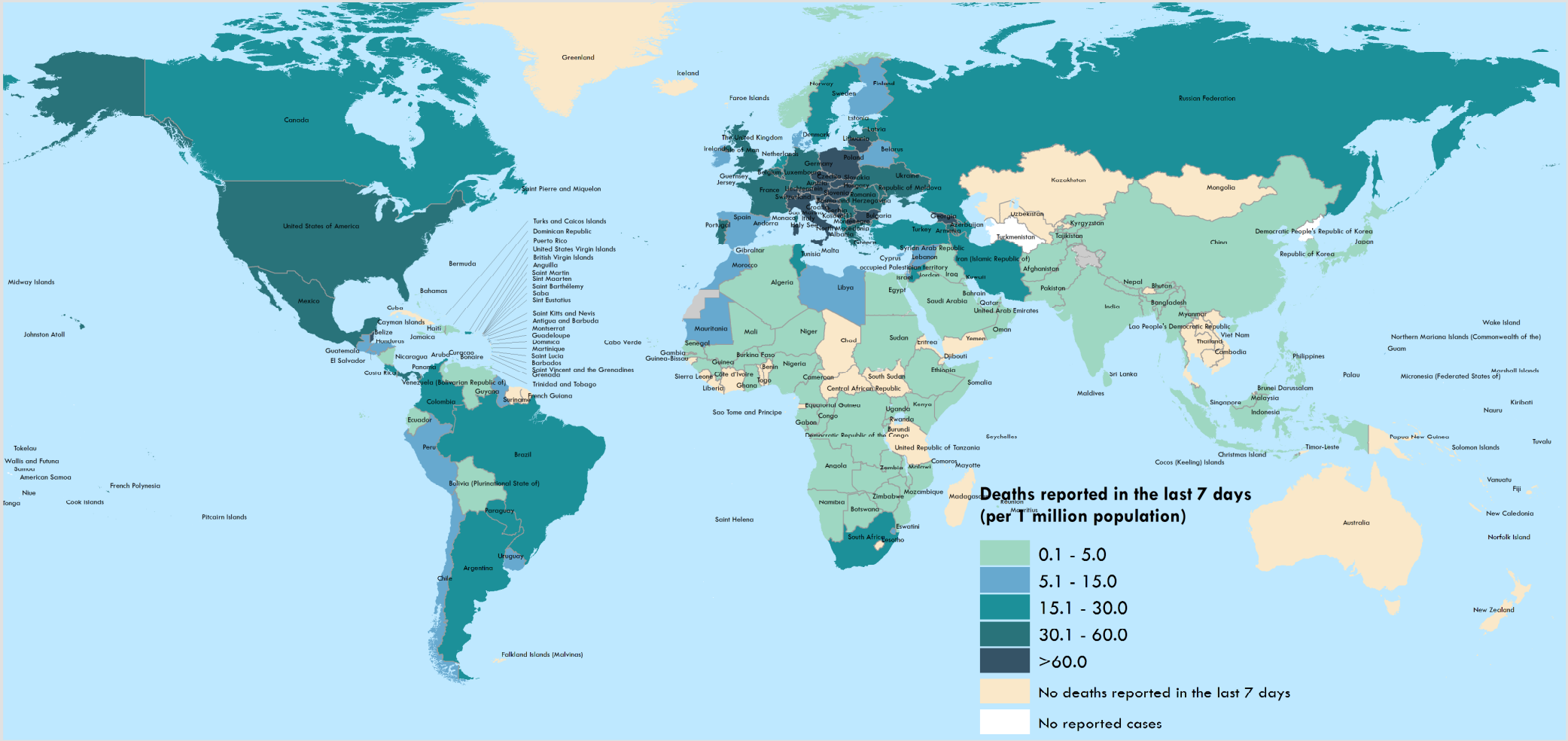

Data Source: *World Health Organization, United Nations Population Division (population prospect 2020)*

Map Production: *WHO Health Emergencies Programme*

Not applicable

0 2,500 5,000 km

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. [1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999). Number of cases of Serbia and Kosovo (UNSCR 1244, 1999) have been aggregated for visualization purposes. Data for Bonaire, Sint Eustatius and Saba have been disaggregated and displayed at the subnational level.

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What is the level of evidence of benefit of the intervention?

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

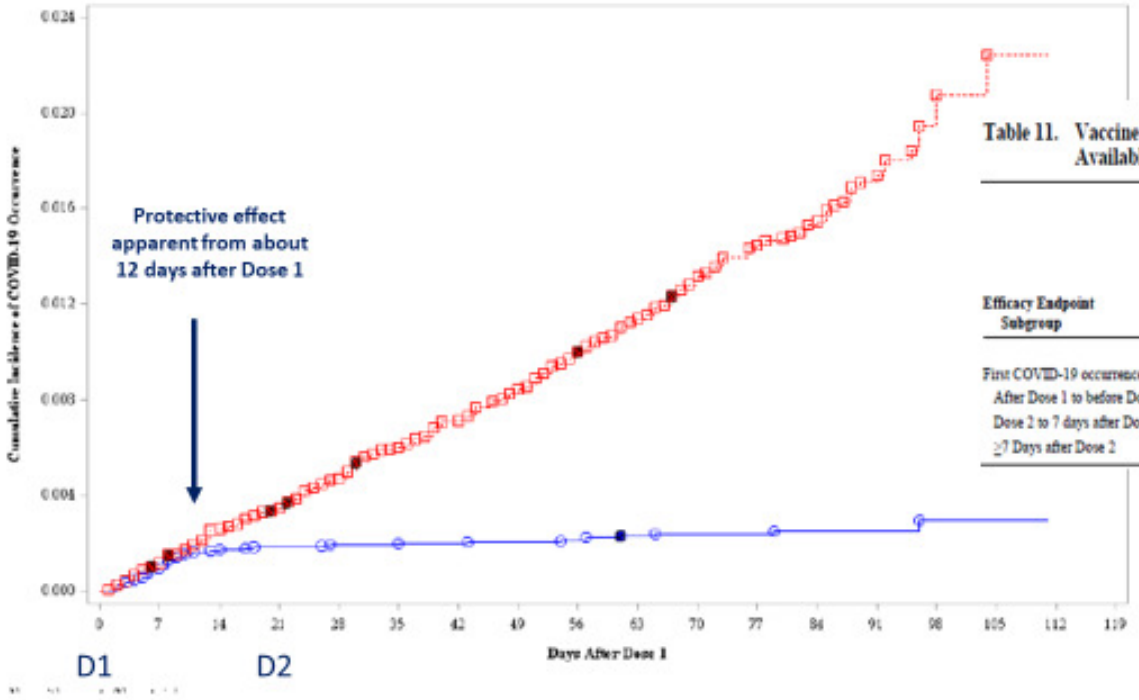

Table 11. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N=21669)		Placebo (N=21686)			
Efficacy Endpoint Subgroup	n[b]	Surveillance Time[c] (n[d])	n[b]	Surveillance Time[c] (n[d])	VE (%)	(95% CI[e])
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)

Vaccine efficacy – one dose (source: JCVI report)

	Pfizer vaccine		Placebo		VE (95% CI)
Post dose 1 interval	N	N	N	N	
15-21 days	2	20481	18	20366	89% (52-97)
22-28 days	2	20481	24	20366	92% (65-98)
15-28 days	4	20481	42	20366	91% (74-97)

Note: Dose 2 given at 21 days

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What is the level of evidence of the harm of the intervention?

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 – Serious Adverse Events (SAEs)

Deaths: 6 total (2 vaccine, 4 placebo)

- Vaccine group deaths (both >55 years of age)
  - Cardiac arrest 62 days after Dose 2; died 3 days later
  - Atherosclerotic disease; died 3 days after Dose 1, with baseline obesity

Non-fatal SAEs

- Appendicitis (8 vaccine, 4 placebo)

Possibly-related SAEs (FDA conclusion)

- Shoulder injury: vaccine administration or vaccine itself

There were no other specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

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.

The potential role of the ALC-0159 containing PEG in the anaphylactic reactions needs to be determined. NIAID and FDA study to analyze the response to the vaccine in people with high levels of anti-PEG antibodies or have experienced severe allergic responses to drugs or vaccines before.

Summary on the Evidence Assessment

Outcome	Importance	Finding	Strength of evidence
BENEFIT			
Symptomatic lab confirmed SARS-CoV-2 infection	Critical	BNT162b2 is effective in preventing symptomatic SARS-CoV-2 infections	high
Hospitalization due to COVID-19	Important	BNT162b2 may prevent hospitalizations due to COVID-19	moderate
Death	Important	BNT162b2 may prevent deaths but the uncertainty is high as death is a rare outcome in the trial	low
Asymptomatic SARS-CoV-2 infection	Important	Not addressed in the trial	no data
HARM			
Serious adverse events	Critical	SAEs were balanced in the intervention and placebo group	moderate
Reactogenicity	Important	Severe reactions were more common in the intervention group; any grade at 3 and above was reported in 8.8% of vaccinees vs 2.1% in placebo recipients	high

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Values

Does the target population feel that the desirable outcome outweighs undesirable outcomes?

Value

Limited available evidence suggests that target populations probably value the desirable effects more than their concern about undesirable effects related to COVID-19 vaccination.

Common concerns include the speed of development, the lack of long-term safety data, conspiracy theories (”mRNA vaccines may genetically modify humans”) and unsubstantiated rumors.

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Acceptability

Is the Pfizer/BioNTech COVID-19 mRNA vaccine acceptable to key stakeholders and the target group?

Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?

No scientific evidence available; 190 economies participating in COVAX suggest a very high acceptability of COVID-19 vaccination in general, although not of this vaccine in particular.

As vaccination is an eagerly awaited tool in combatting COVID-19, it is assumed that key stakeholders, in particular Ministries of Health and Immunization Managers are strongly in favor of COVID-19 vaccination.

Is the intervention acceptable to target groups?

A global survey (19 countries) on acceptance rates in the general population (any COVID-19 vaccine product), revealed that 71.5% of participants reported that they would be very or somewhat likely to take a COVID-19 vaccine. Differences in acceptance rates ranged from almost 55-87%.

Reference: Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2020 Oct 20.

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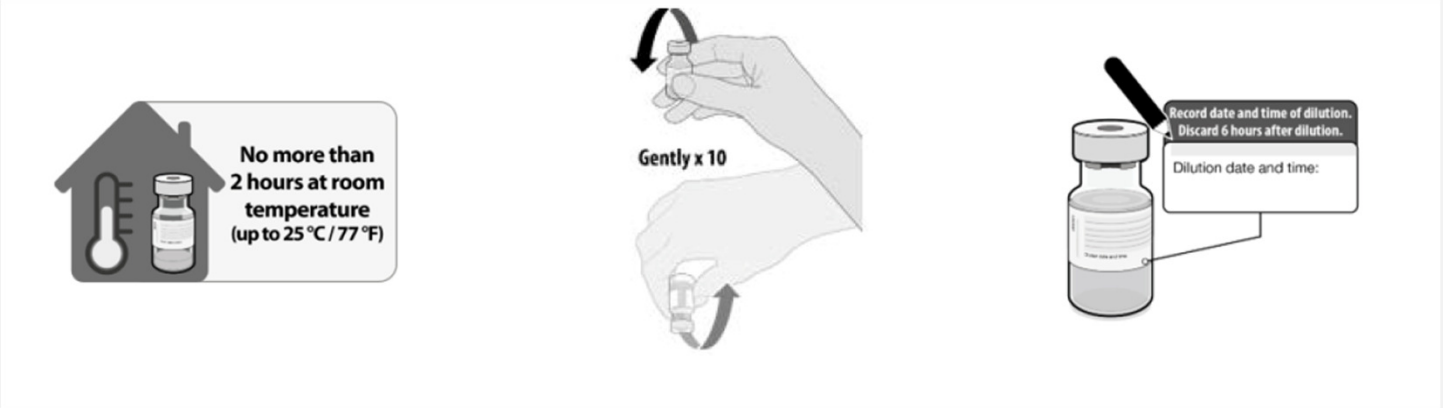
Feasibility

Is BNT162b2 vaccine feasible to implement?

Barriers to implementation of mass vaccination

Ultra-cold chain requirement (-60 to 80 Degrees Celsius)
Minimum size of orders
Complex handling requirements
Need for diluent
2 doses
Costs



Implementation challenges

Higher delivery cost	**Non-standard cold chain requirements will require new investments in capital equipment and special equipment for handling deep frozen shipments** **Extra training, supervision, monitoring and logistics will be required for HW as mRNA vaccine have not been used before**	**Delivery of UCC vaccines** **3-6 x more expensive than standard 2-8 Degrees Celsius**
Operational complexity may impact access	Build up of capabilities will be required in countries that have no experience of delivering UCC vaccines Regulatory approval processes may take longer given that no mRNA based vaccines have yet been approved	2-6 months required for ramp up from no UCC capabilities in AMC92

Resource Use

Is BNT162b2 an efficient allocation of resources?

Resource Use

Economic losses from the COVID-19 pandemic and cost-effectiveness of any vaccine programme will differ between countries and regions

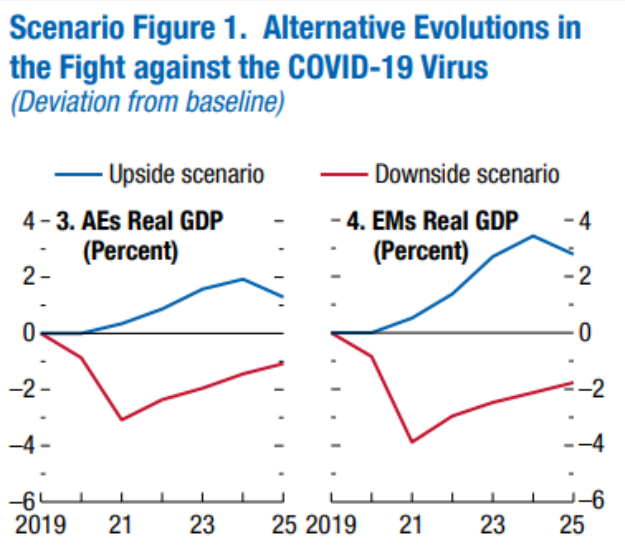
- However, given the magnitude of social and economic impacts, it is expected that COVID-19 vaccination will be cost-effective from a societal perspective in many countries

Cost-effectiveness analyses and economic impact of vaccination will depend on:

- COVID-19 burden
-timing of vaccine roll-out (at time of rise of cases versus decline)
-vaccination coverage levels achieved
-duration of vaccine protection
-vaccination implementation costs
-other mitigation measures used

Cost-effectiveness may not be the primary driver for decision-making during the pandemic

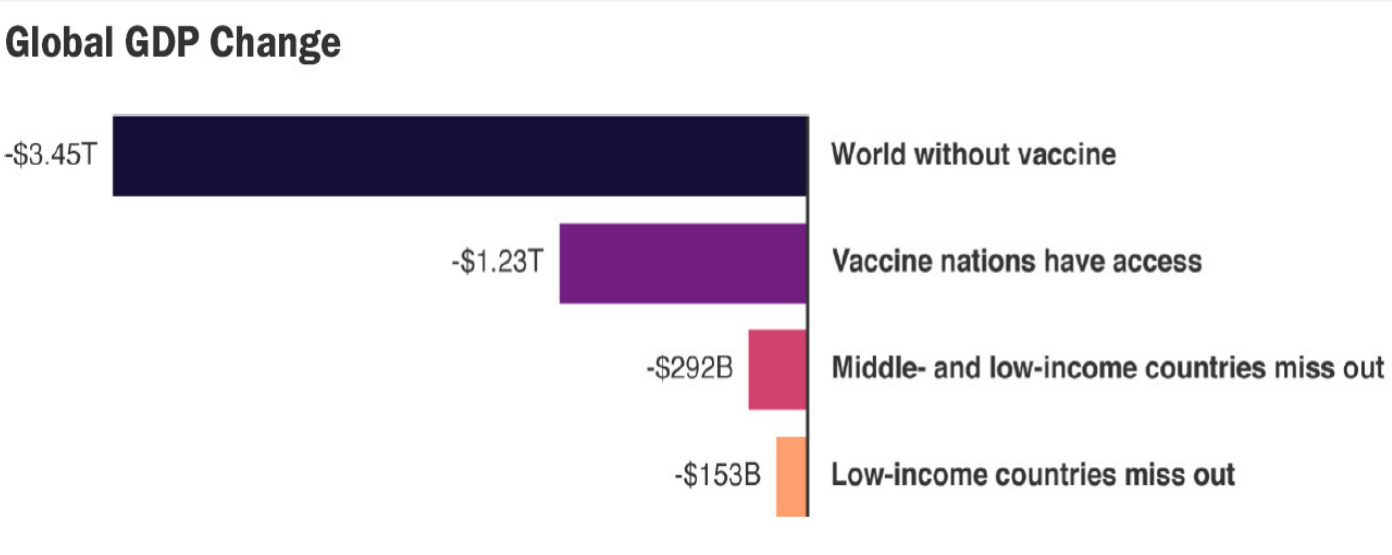
Equitable access to COVID-19 vaccine has large economic impacts



AE: Advanced Economies
EM: Emerging Markets

IMF World Economic Outlook October 2020. https://www.imf.org/en/Publications/WEO/Issues/2020/09/30/world-economic-outlook-october-2020

Note: estimates are not specific to BNT162b2 or any other COVID-19 vaccine product.



RAND Europe. 2020. COVID-19 and the cost of vaccine nationalism. https://www.rand.org/pubs/research_reports/RRA769-1.html

- **GDP is projected to recover faster if COVID-19 vaccination roll-out permits reduction in physical distancing, and travel and trade interruptions.**
- **Slower vaccination roll-out and inequitable vaccine access globally will result in greater GDP losses, including for high-income countries.**

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What would be the impact of BNT162b2 on health equity?

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

14 September 2020

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Executive Summary

This Values Framework offers guidance globally on the allocation of COVID-19 vaccines between countries, and to offer guidance nationally on the prioritization of groups for vaccination within countries while supply is limited. The Framework is intended to be helpful to policy makers and expert advisors at the global, regional and national level as they make allocation and prioritization decisions about COVID-19 vaccines. This document has been endorsed by the Strategic Advisory Group of Experts on Immunization (SAGE).

The Framework articulates the overall goal of COVID-19 vaccine deployment, provides six core principles that should guide distribution and twelve objectives that further specify the six principles (Table 1). To provide recommendations for allocating vaccines between countries and prioritizing groups for vaccination within each country, the Values Framework needs to be complemented with information about specific characteristics of available vaccine or vaccines, the benefit-risk assessment for different population groups, the amount and pace of vaccine supply, and the current state of the epidemiology, clinical management, and economic and social impact of the pandemic. Hence, the final vaccination strategy will be defined by the characteristics of vaccine products as they become available.

SAGE is currently engaged in the process of applying the Values Framework to emerging evidence on specific vaccines, and the evolving epidemiology and economic impact of the pandemic. The first stage of this process was the identification of populations and sub-populations which would be appropriate target groups for prioritization under the various values-based objectives in the Framework (Table 2), before data on Phase 3 vaccine performance are not yet available. Specific priority group recommendations for specific vaccines will be made as vaccine products become authorized for use; initial vaccine specific policy recommendations are expected in the final quarter of 2020 or early 2021, depending on timing of and findings from phase 3 vaccine trials.

The Framework also complements the principles on equitable access and fair allocation of COVID-19 health products developed for the ACT Accelerator COVAX facility.

https://apps.who.int/iris/bitstream/handle/10665/334299/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf?sequence=1&isAllowed=y

6 main principles

-Human well being

-Equal respect

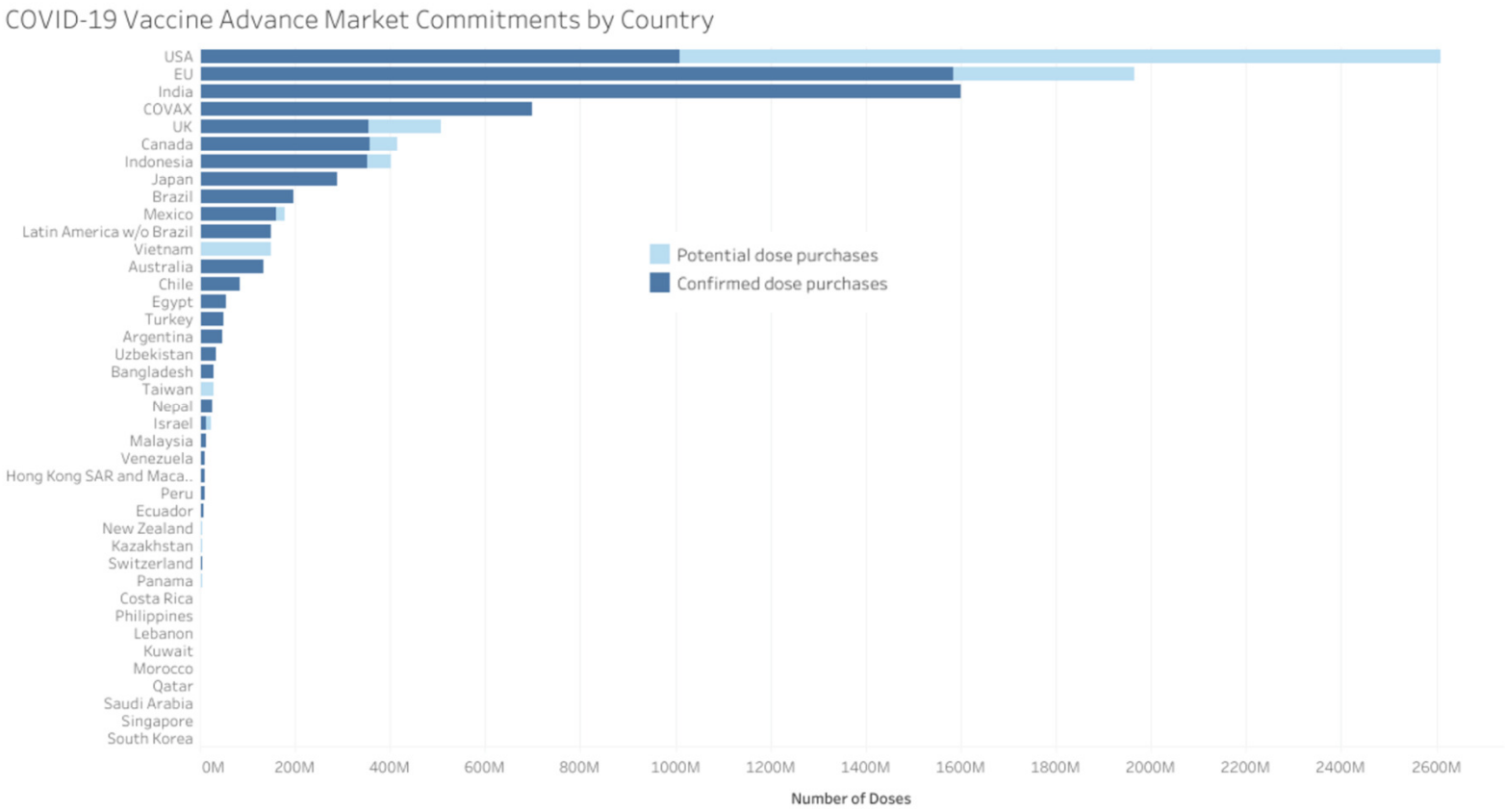
-Global equity

-National equity

-Reciprocity

-Legitimacy

Countries with Advance Commitments to COVID-19 Vaccines



Accessed 10Dec2020: https://launchandscalefaster.org/COVID-19

Equity concerns of BNT162b2

Several factors may increase inequity: cost, ultra-cold chain storage and transportation, minimum number of doses per shipment, need to administer a whole batch of vaccines within a short time frame, need for diluent. Conditions must be met to avoid exposure of vials to sun light and ultraviolet light.

Appropriate medical treatment to manage anaphylaxis must be immediately available. Hence, this vaccine should only be administered in settings with the necessary resources and trained health workers, and in settings that allow for 30 minutes of post-vaccination observation and immediate care, if required.

Need for 2 dose series may disadvantage homeless, nomads, persons living in remote places, and those with limited access to health care.

Programmatic implications require particular attention to equity, including the feasibility, acceptability, and effectiveness in resource-constrained settings

Addressing inequity within and between countries

"…increasing the availability of an effective intervention within a country or region is not necessarily enough to reduce inequities. The intervention has to be accessible, acceptable, effective in, and used by the most disadvantaged groups within that population to be truly effective at reducing inequities in health".[1]

[1]O'Neill J, Tabish H, Welch V, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J Clin Epidemiol. 2014; 67: 56-64.

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