2021년 한국통계학회 춘계학술대회
기획세션 II-5 Biostatistics Engaged in Fighting the COVID-19 Pandemic

코로나19 백신임상설계시 통계적 고려사항
Statistical Considerations in the Design of COVID-19 Vaccine Trial

28 May 2021

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Epidemiology, Public Health, Impact
International Vaccine Institute

International Vaccine Institute

비전과 사명

비전

감염성 질병으로 인한 개발도상국의 고통 해소

사명

세계 공중보건을 위한 안전하고 효과적이고 저렴한 백신의 발굴, 개발 및 보급

개발도상국을 위한 백신

IVI는 개발도상국의 감염성 질병 예방백신에 중점을 두고 있다. 개발도상국의 전염병 취약지역 주민들이 백신을 활용하고 접근할 수 있도록 하는 것을 목표로 삼고 있다.

세계보건을 위한 백신

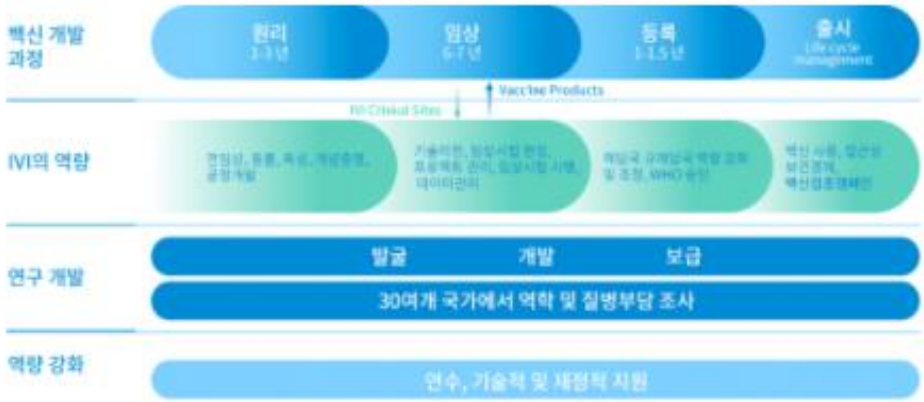
우리는 신종 감염성 질병이 세계보건을 위협할 수 있는 매우 글로벌화된 세계에 살고 있다. IVI는 세계보건에서 주요 문제가 되는 감염성 질병의 예방백신 분야에도 중점을 두고 있다.

IVI의 접근방식

IVI의 접근방식은 다음 세 요소에 기반을 두고 있다.

1. 연구 – 백신 R&D, 중개 연구 및 현장적용 연구
2. 파트너십 – 제품 개발 파트너십, 국제 연구 컨소시엄 및 네트워크
3. 역량 강화 – 교육, 기술 지원 및 기술 이전

IVI 는 시장성은 부족하지만 세계보건에 중요한 감염성 질병들에 대한 백신을 개발 및 보급



백신 제품개발 파이프라인

IVI가 개발중인 몇몇 후보백신

- 백신은 각각 여러 단계의 개발 단계에 있음
- 경구 콜레라 백신은 IVI가 개발하고 WHO가 승인한 첫번째 백신 제품
- Vi-DT 장티푸스 접합백신은 개발중인 2번째 제품 (2020년).

[redacted]

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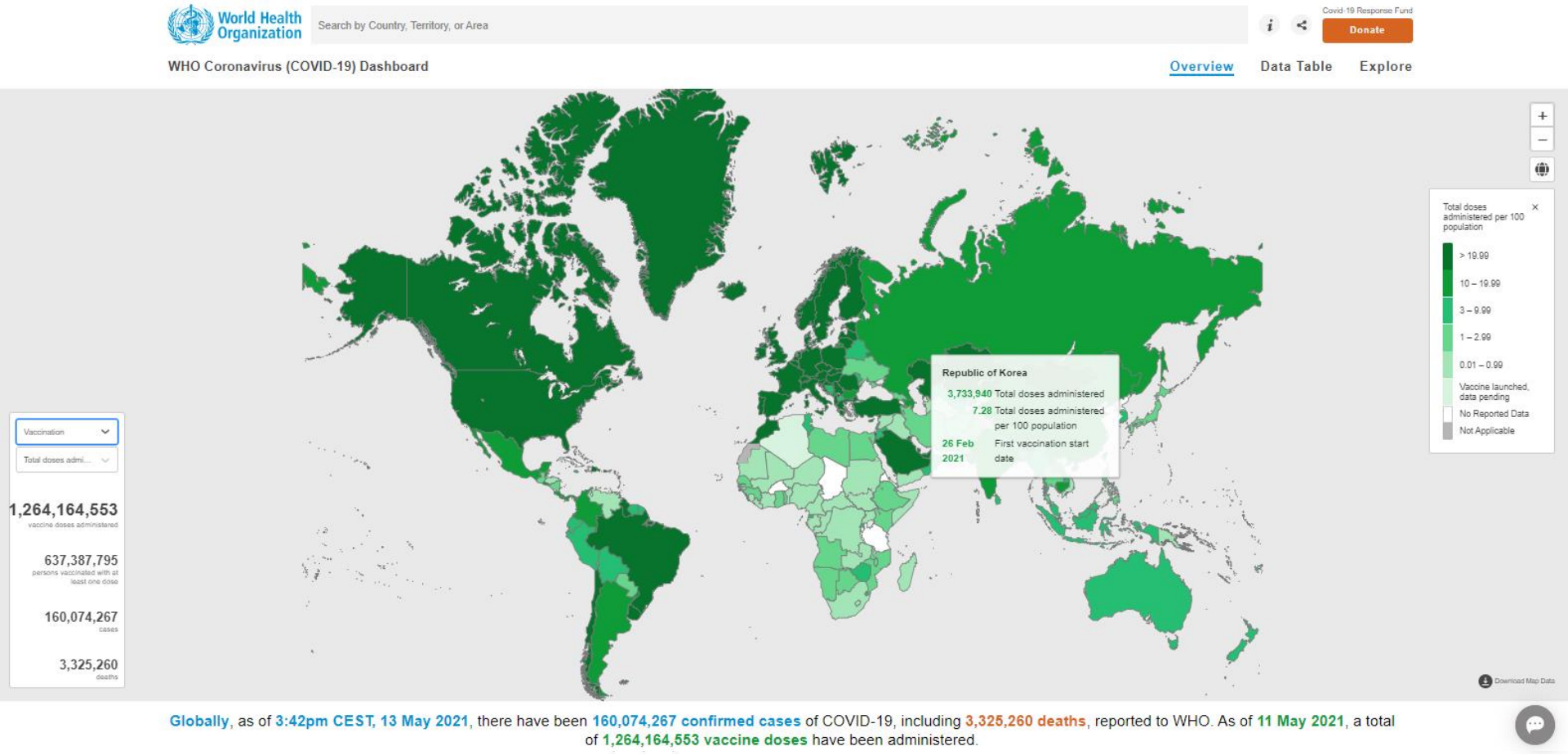
Background

31 Dec 2019. Wuhan Municipal Health Commission, China, reported a cluster of cases of pneumonia in Wuhan, Hubei Province. A novel coronavirus was eventually identified.
07 Jan 2020. Chinese Authorities identified COVID-2019 as coronavirus
11 Mar 2020. Deeply concerned both by the alarming levels of spread and severity, and by the alarming levels of inaction, WHO made the assessment that COVID-19 can be characterized as a pandemic.
18 Mar 2020. WHO and partners launched the Solidarity Trial, an international clinical trial that aims to generate robust data from around the world to find the most effective treatments for COVID-19.
29 Apr 2020. WHO published Target Product Profiles for COVID-19 (version 3)



COVID-19 Vaccines: Target Product Profiles

29 Apr 2020. WHO published Target Product Profiles for COVID-19 (version 3)
16 Sep 2020. COVID-19 Vaccines: Target Product Characteristics by CEPI

Vaccine Characteristic	WHO TPP – Preferred	WHO TPP – Critical	Clinical evidence of vaccines with EUA*
Indication for use	LT: Immunization of at-risk persons to prevent COVID-19	LT: Immunization of at-risk persons to prevent COVID-19	Available with all licensed vaccines. *However, further data in risk populations e.g. older age groups / persons with chronic diseases necessary.*
Contraindication	None	Few (e.g immunocompromised) may be acceptable	Contraindication in persons allergic to vaccine or its component.
Target population	All ages. (including pregnant & lactating women)	Adults including elderly	*EUAs exclude pregnant and lactating women and pediatric population. No trials ongoing among pregnant/lactating women.*
Safety / Reactogenicity	Highly favourable benefit/risk profile in the context of observed VE; with only mild, transient AEs and no SAEs	Outbreak: whereby vaccine benefits outweigh safety risks LT: Highly favourable benefit/risk profile in the context of observed VE; No related SAEs	Available with all licensed vaccines. *Long terms safety lacking.*
Protective efficacy	70% against disease, severe disease, and/or shedding/transmission. Outbreak: 2 week onset	50% against disease, severe disease, and/or shedding/transmission.	>50% efficacy with licensed vaccines against disease / any severity. Promising data against severe disease (however: low number of severe cases) *No data on shedding or transmission available. Evidence related to new variants?*
Dosing regimen	Outbreak: Single-dose primary series LT: Lower frequency (Yearly or less) of booster doses is preferred	Outbreak: No more than two dose regimen LT: Booster doses permitted	*No single dose vaccines licensed; a few under development.* *Limited data post single dose available* *No information on booster dosing, few trials are ongoing.*

** - These include Pfizer/BioNTech, Moderna and Oxford/AZ that have made public detailed and peer reviewed data that formed the basis of Emergency Use Authorisation (EUA)*

Source: https://media.tghn.org/medialibrary/2021/02/20201228_Workshop_Presentation_Materials_FINAL.pdf

COVID-19 Vaccines: Target Product Profiles

29 Apr 2020. WHO published Target Product Profiles for COVID-19 (version 3)
16 Sep 2020. COVID-19 Vaccines: Target Product Characteristics by CEPI

Vaccine Characteristic	WHO TPP – Preferred	WHO TPP – Critical	Clinical evidence of vaccines with EUA*
Durability of protection	Confers protection for at least 1 year	Confers protection for at least 6 months	*Trials ongoing to assess this.* *No data presently on duration of protection.* *Further data will accrue over time.*
Route of administration	Outbreak: Non-parenteral due to ease administration & logistical issues. LT: any route of administration is acceptable	Any route of administration is acceptable, if vaccine is safe and effective	All licensed vaccines (and most in development) are injectable. *No oral or intranasal vaccines in Phase 3 clinical trials presently.*
Co-administration	Outbreak: stand-alone product LT: potential for coadministration with other vaccines that are typically administered in campaigns preferred	Stand-alone product	*No evidence on co-administration of COVID vaccines with other routine vaccines.* *No clinical trials ongoing – evidence may become more important in future?.*
WHO registration and PQ	Outbreak: WHO prequalified and/or made available under EUA/WHO EUL LT: WHO pre-qualified	Outbreak: Meets criteria for EUA/ WHO EUAL LT: WHO pre-qualified	*WHO EUL: One vaccine*

** - These include Pfizer/BioNTech, Moderna and Oxford/AZ that have made public detailed and peer reviewed data that formed the basis of Emergency Use Authorisation (EUA)*

Source: https://media.tghn.org/medialibrary/2021/02/20201228_Workshop_Presentation_Materials_FINAL.pdf

COVID-19 candidate vaccine landscape and tracker

World Health Organization

R&DBlueprint
Powering research to prevent epidemics

COVID-19 - Landscape of novel coronavirus candidate vaccine development worldwide

11 May 2021

Summary Information on Vaccine Products in Clinical Development

1. - Number of vaccines in clinical development 99

2. - Number of vaccines in pre-clinical development 184

3. - Candidates in clinical phase

Filter: All — Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	30	30%
VVnr	Viral Vector (non-replicating)	14	14%
DNA	DNA	10	10%
IV	Inactivated Virus	16	16%
RNA	RNA	16	16%
VVr	Viral Vector (replicating)	3	3%
VLP	Virus Like Particle	5	5%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
		99	

4. - Number of doses, schedule and route of administration of candidates in clinical phase

Number of doses & schedule		Candidate vaccines (no. and %)	
1 dose		**13**	**13%**
Day 0		13	
2 doses		**64**	**65%**
Day 0 + 14		6	
Day 0 + 21		25	
Day 0 + 28		33	
3 doses		**1**	**1%**
Day 0 + 28 + 56		1	
TBD / No Data (ND)		**21**	**21%**
Route of administration			
Oral		**2**	**2%**
Injectable		**83**	**84%**
SC	Sub cutaneous	4	4%
ID	Intra dermal	4	4%
IM	Intra muscular	75	76%
IN	Intra nasal	7	7%
TBD / No Data (ND)		**14**	**14%**

COVID-19 candidate vaccine landscape and tracker

Landscape of candidate vaccines in clinical development

11 May 2021

DISCLAIMER: These landscape documents have been prepared by the World Health Organization (WHO) for information purposes only concerning the 2019-2020 pandemic of the novel coronavirus. Inclusion of any particular product or entity in any of these landscape documents does not constitute, and shall not be deemed or construed as, any approval or endorsement by WHO of such product or entity (or any of its businesses or activities). While WHO takes reasonable steps to verify the accuracy of the information presented in these landscape documents, WHO does not make any (and hereby disclaims all) representations and warranties regarding the accuracy, completeness, fitness for a particular purpose (including any of the aforementioned purposes), quality, safety, efficacy, merchantability and/or non-infringement of any information provided in these landscape documents and/or of any of the products referenced therein. WHO also disclaims any and all liability or responsibility whatsoever for any death, disability, injury, suffering, loss, damage or other prejudice of any kind that may arise from or in connection with the procurement, distribution or use of any product included in any of these landscape documents.

New information that has been added this week is highlighted in yellow

*(NCT04510207 *) This Phase 3 trial assesses both the Wuhan and Beijing vaccine in the same study.*

***Pending confirmation on the phase of study which is not specified in the registry.*

The informaion provided is taken directly from data available in the trial registries. In cases where the trial is registrered as N/A or without a defined clincial phase, it has been listed in the column "Phase not reported".

TBD (To be defined)

Information highlighted in red indicates a change in the development of the vaccine

ID	Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	Number of doses	Schedule	Route of administration	Developers	Phase
1	IV	Inactivated virus	CoronaVac; SARS-CoV-2 vaccine (inactivated)	2	Day 0 + 14	IM	Sinovac Research and Development Co., Ltd	Phase 4
4	VVnr	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222)	1-2	Day 0 + 28	IM	AstraZeneca + University of Oxford	Phase 4
9	RNA	RNA based vaccine	mRNA -1273	2	Day 0 + 28	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4
10	RNA	RNA based vaccine	BNT162b2 (3 LNP-mRNAs), also known as "Comirnaty"	2	Day 0 + 21	IM	Pfizer/BioNTech + Fosun Pharma	Phase 4

ID	Vaccine platform acronym	Vaccine platform description	Current status of clinical evaluation (Trial registries and public reports)						
			Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Phase 4	Phase not reported
1	IV	Inactivated virus		NCT04383574	NCT04800133		NCT04456595	NCT04756830	ChiCTR2100045109
4	VVnr	Viral vector (Non-replicating)	PACTR202005681895696	PACTR202006922165132	NCT04686773	NCT04400838	ISRCTN89951424	NCT04760132	NCT04794946
9	RNA	RNA based vaccine	NCT04283461	NCT04677660	NCT04405076	NCT04649151	NCT04470427	NCT04760132	
10	RNA	RNA based vaccine	NCT04523571	2020-001038-36	NCT04649021	NCT04754594	NCT04368728	NCT04760132	NCT04844489

ID	Vaccine platform acronym	Vaccine platform description	Phase 3 endpoints as per protocol								
			Number of virologically confirmed (PCR or NAAT positive) symptomatic cases of COVID-19	Efficacy compared to placebo for the prevention of SARS-CoV-2 infection	Efficacy against severe and non-severe COVID-19: hospital admissions	Efficacy for the prevention of COVID-19-related Emergency Department visits	Efficacy of vaccine against severe and non-severe COVID-19	Efficacy of vaccine against severe and non-severe COVID-19: number of deaths	Efficacy: seroconversion rates	Assess humoral immunogenicity : antibody quantification	Safety and immunogenicity of a booster dose
1	IV	Inactivated virus	X	X			X		X	X	X
4	VVnr	Viral vector (Non-replicating)	X				X	X	X	X	X
9	RNA	RNA based vaccine	X	X			X		X	X	X
10	RNA	RNA based vaccine	X	X				X	X	X	X

COVID-19 new variants: Knowledge gaps and research

12 Jan 2021. At a global discussion meeting organized by the WHO R&D Blueprint initiative, discussed the threat posed by SARS-CoV-2 variants and the research response required to control them.
11 May 2021 Weekly epidemiological update on COVID-19 includes SARS-CoV-2 variants of concern:

Special Focus: Update on SARS-CoV-2 variants

WHO, in collaboration with national authorities, institutions and researchers, routinely assesses if variants of SARS-CoV-2 result in changes in transmissibility, clinical presentation and severity, or if they result in changes in public health and social measures (PHSM) implementation by national health authorities. Systems have been established to detect "signals" of potential variants of concern (VOCs) or variants of interest (VOIs) and assess these based on the risk posed to global public health (see also working definitions). National authorities may choose to designate other variants of local interest/concern. Detailed information on currently circulating VOCs and VOIs is available in previously published editions of the Weekly Epidemiological Update. Here we provide information on a newly designated VOC within lineage B.1.617, and provide an update on the geographical distribution, and emerging evidence surrounding phenotypic characteristics of all designated VOIs and VOCs.

Newly designated VOC within lineage B.1.617

In consultation with the WHO SARS-CoV-2 Virus Evolution Working Group, WHO has determined that viruses within the lineage B.1.617 have been characterized as a VOC. B.1.617 contains three sub-lineages (Table 2), which differ by few but potentially relevant mutations in the spike protein as well as prevalence of detection globally. As of 11 May, over 4500 sequences have been uploaded to GISAID and assigned to B.1.617 from 44 countries in all six WHO regions, and WHO has received reports of detections from five additional countries (Figure 3). Though there may be important differences among the three sublineages, currently available evidence is too limited for VOI/VOC characterization by sublineage. Future delineation of sublineages as VOIs/VOCs may be possible as our understanding by sublineage and relative importance of their epidemiology increases. At the present time, WHO has designated B.1.617 as a VOC based on early evidence of phenotypic impacts compared to other circulating virus variants, namely:

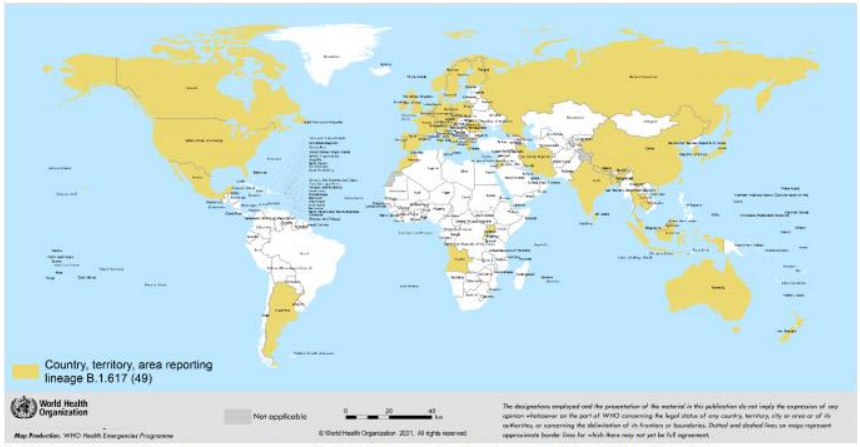
- B.1.617 sublineages appear to have higher rates of transmission, including observed rapid increases in prevalence in multiple countries (moderate evidence available for B.1.617.1 and B.1.617.2), and
- Preliminary evidence suggests potential reduced effectiveness of Bamlanivimab, a monoclonal antibody used for COVID-19 treatment, and potentially slightly reduced susceptibility to neutralisation antibodies (limited evidence available for B.1.617.1).

Table 2: Overview of B.1.617 sublineages, as of 11 May 2021

Sublineage	B.1.617.1	B.1.617.2	B.1.617.3
Sequences in GISAID	2001	2507	67
Number of countries reporting detections	34 (in 6 WHO regions)	31 (in 5 WHO regions)	4 (in 3 WHO regions)
Number of lineage-defining spike mutations*	7	8	6
Characteristic spike mutations*	G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	T19R, G142D, del157/158, L452R, T478K, D614G, P681R, D950N	T19R, L452R, E484Q, D614G, P681R, D950N

Mutations found in >60% of sequences

Figure 3. Countries, territories and areas with B.1.617.1, B.1.617.2 or B.1.617.3 sequences uploaded to GISAID and/or reported to WHO as of 11 May 2021*



** Unverified detections based primarily on GISAID, subject to change as WHO validates detection with Member States.*

Table 4. Summary of vaccine performance against variants of concern (VOC) relative to ancestral stains

VOC 202012/01 (B.1.1.7)	501Y.V2 (B.1.351)	P.1 (B.1.1.28.1)
Efficacy/effectiveness against disease or infection		
Protection retained against disease • Severe disease: No/minimal loss: Pfizer BioNTech-Comirnaty[1-3] • Infection & symptomatic disease: o No/minimal loss: AstraZeneca-Vaxzevria, Novavax-Covavax, Pfizer BioNTech-Comirnaty[2-13] • Asymptomatic infection: o No/minimal loss: Pfizer BioNTech-Comirnaty[2,14] o Inconclusive/moderate/substantial loss, limited sample size: AstraZeneca-Vaxzevria[5]	Reduced protection against disease, limited evidence • Severe disease: No/minimal loss: Janssen Ad26.COV 2.5, PfizerBioNTech-Comirnaty[3,35] • Mild-moderate disease: o Moderate loss: Janssen-Ad26.COV 2.5, Novavax-Covavax[35,36] o Inconclusive/substantial loss, limited sample size: AstraZeneca-Vaxzevria[37] • Infection: Moderate loss: Pfizer BioNTech-Comirnaty[3] • Asymptomatic infection: No evidence	Limited evidence • No/minimal loss: Sinovac-CoronaVac [44]
Neutralization		
• No/minimal loss: Bharat-Covaxin, Gamaleya-Sputnik V, Moderna-mRNA-1273, Novavax-Covavax, Pfizer BioNTech-Comirnaty, Beijing CNBG-BBIBP-CorV, Sinovac-CoronaVac[16-35] • Minimal/moderate loss: AstraZeneca-Vaxzevria[5,31]	• Minimal/modest loss: Beijing CNBG-BBIBP-CorV, Sinovac-CoronaVac[39,40] • Minimal to large loss: Moderna-mRNA-1273, Pfizer BioNTech-Comirnaty[15,16,20-22,24-27,29-32,38,40-43] • Moderate to substantial loss: AstraZeneca-Vaxzevria, Gamaleya-Sputnik V, Novavax-Covavax[22,30,33,42]	• No/Minimal reduction: AstraZeneca-Vaxzevria, Sinovac-CoronaVac[30,45] • Minimal/moderate reduction: Moderna-mRNA-1273, Pfizer BioNTech-Comirnaty [16,17,24,27,29,30,41,43,45,46]

Source: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20210511_weekly_epi_update_39.pdf?sfvrsn=b66ba70d_11&download=true

The next steps for a COVID-19 vaccine

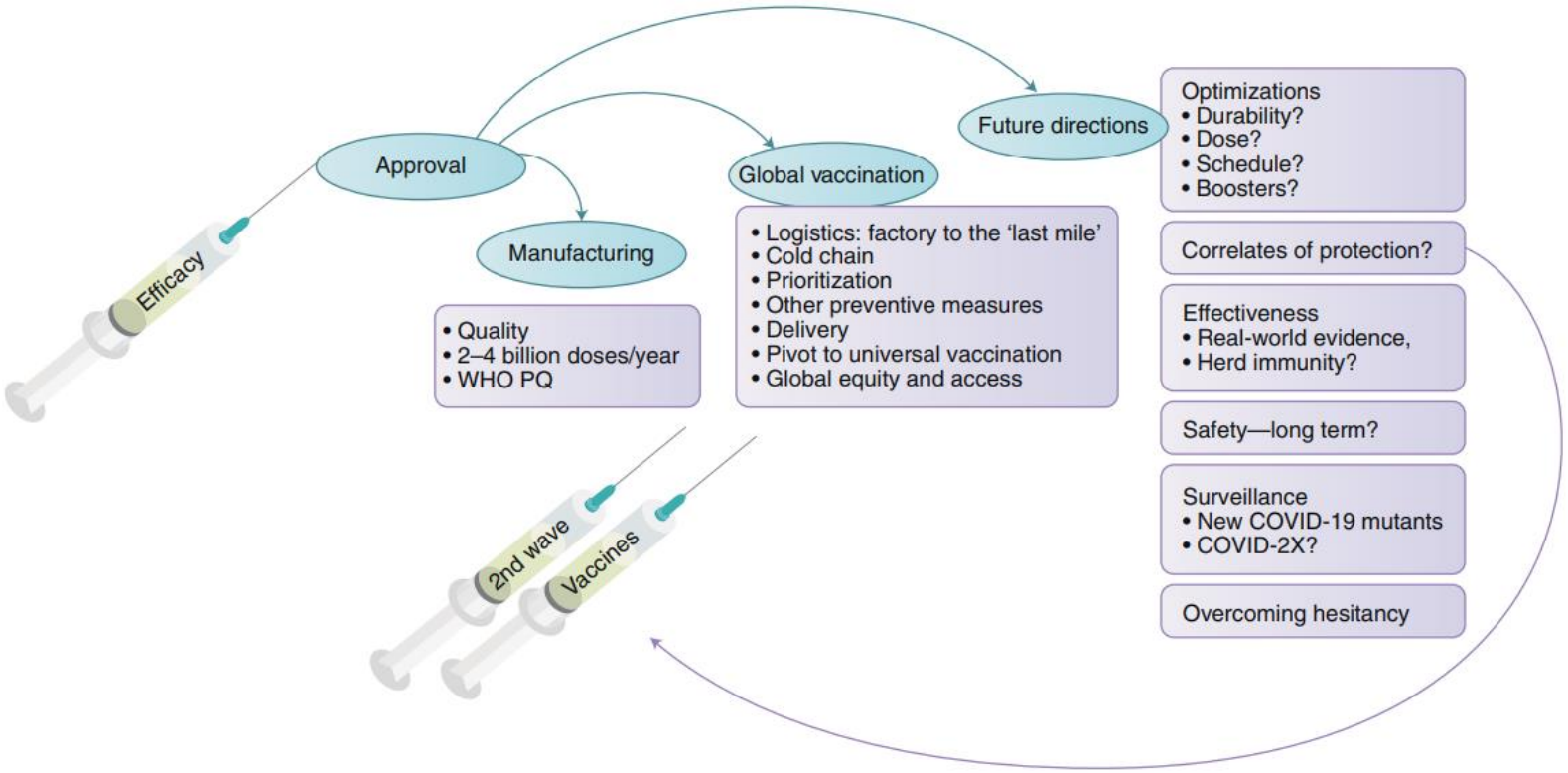


Fig. 1 | The next steps for a COVID-19 vaccine. After a COVID-19 vaccine has demonstrated efficacy in a clinical trial, the vaccine must be approved and manufacturing scaled up, according to an international standard known as CGMP. The transportation of the vaccine must respect the cold-chain requirements. COVID-19 vaccines should be allocated with respect to equity and access for LMICs. Several scientific questions around optimization of the vaccine(s) dose and schedule, boosting and correlates of protection must be answered, particularly if testing of the 'second wave' of vaccines cannot be accomplished with a placebo group (owing to licensure or approval of first-wave vaccines). Collection of effectiveness data and understanding indirect protective effects of vaccination will allow countries to make rational plans for maintaining herd protection. Surveillance for COVID-19 mutations and the sensitivity of those mutations to vaccine-induced immune responses will be necessary, as will continued vigilance for the emergence of new zoonotic coronavirus infections. Finally, for effective control of COVID-19 transmission, countries will need to address issues around vaccine hesitancy; increasing uptake of vaccines will be a priority before control over COVID-19 can be gained.

Source: https://www.nature.com/articles/s41591-021-01230-y.pdf

Clinical Trial Design – Phase IIB/III efficacy trials

- **Randomized, blinded, and placebo controlled**
  - Active controlled when a safe and effective COVID-19 vaccine is available.
- **Individually randomized trial** with 1:1 or 2:1 randomization between vaccine and placebo groups.
  - Cluster randomization if there is evidence that potential biases have been avoided.
- **Pre-specified criteria** for critical decision
  - Frequent interaction with NRA may be needed to guide decision making in adaptive or seamless trials
- Ideally, **at least one or two years of follow-up** of study participants for COVID-19 outcomes (especially, severe COVID-19 manifestations)
  - Adequate assessment on the duration of protection and potential for vaccine-associated Enhanced Disease as immune responses to the vaccine wane.
- **Contingency plan** for continued follow up and analysis of safety and efficacy outcomes in the event that a safe and effective vaccines available and the study stopped.
  - As demonstrated in a planned interim analysis or as demonstrated in another clinical trial.
  - Discussion with the NRA may be necessary to address ethical issues of breaking the blind and offering vaccine to placebo recipients.
- **Establish a Data and Safety Monitoring Board**
  - A periodic independent review of safety data at appropriate intervals
  - A review of any interim efficacy data

Endpoints - Phase IIB/III efficacy trials

- **Clinically driven primary efficacy endpoint**
  - Laboratory confirmed first episode of COVID-19
  - Immunogenicity if an immune correlate of protection becomes established.

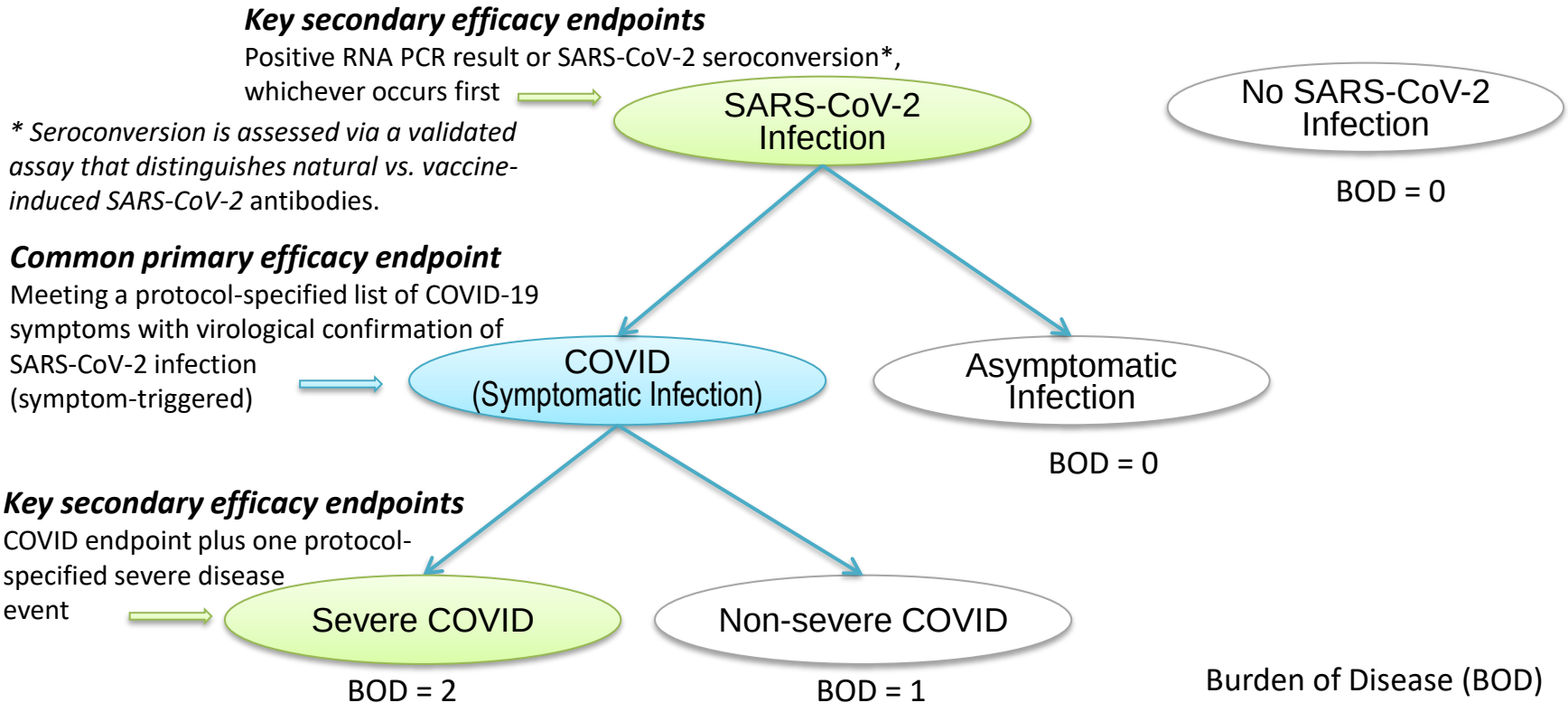


Figure 1. Clinical endpoint relationships, definitions, and example sampling scheme for diagnosed COVID-19 cases.

Source: https://www.acpjournals.org/doi/full/10.7326/M20-6169?journalCode=aim

Primary Analysis and Success Criteria - Efficacy Trials

- **Vaccine Efficacy (VE)**
  - VE = [1 – Endpoint hazard ratio (vaccine/placebo)] x 100%
  - Assess by proportional hazards model with separate placebo arm baseline hazard function for each study site x randomization stratum (anticipate heterogeneity in epidemics across sites)

- **Primary Analysis cohort**
  - Participants baseline negative for SARS-CoV-2 (PCR/Serology) in Full Analysis Set (FAS) [enrolled participants receiving 1+ dose], counting events 15+ days after last dose.
  - A statistical model with treatment group as fixed effect and adjust for stratification factor
  - Sensitivity analysis using the same model based on the PP Set

- **Success Criteria**
  - >50% of VE point estimate
  - >30% of the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate.
  - Per FDA guidance and satisfies WHO TPP

Total Sample size and target endpoints - Efficacy Trials

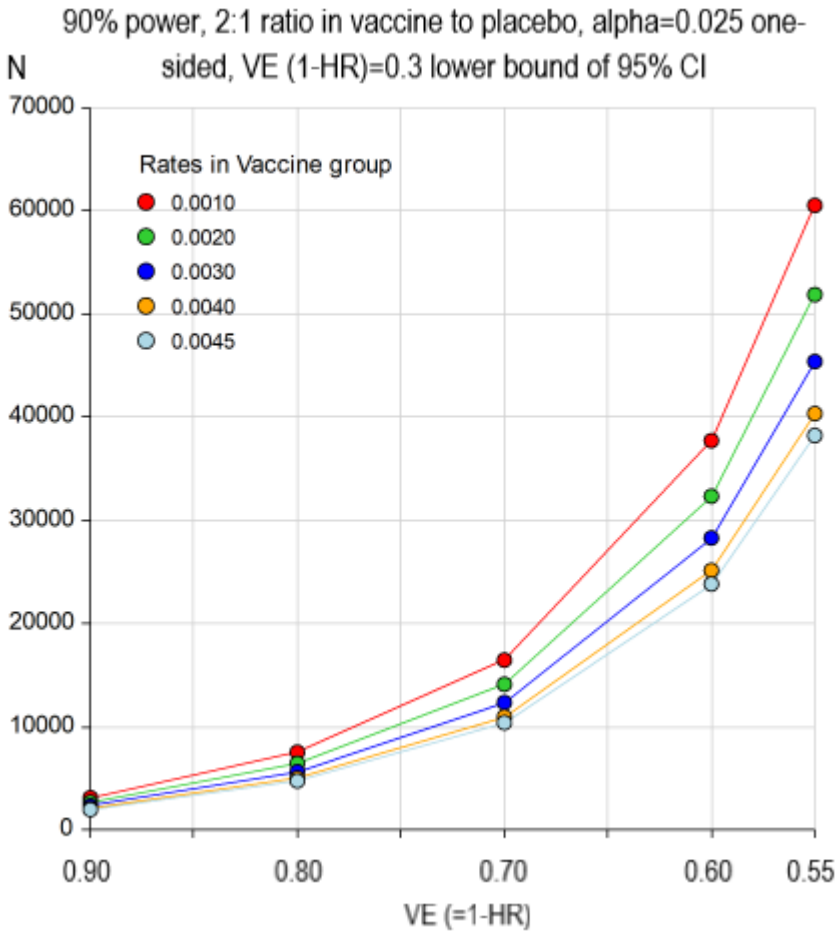
- **Assumptions**
  - Tests for Two Survival Curves Using Cox's Proportional Hazards Model
  - H0: HR ≥ 0.7 (equivalently, VE (=1-HR) ≤ 0.3 lower bound)
  - 90% power
  - Significance level: 0.025 (one-sided)
  - Target VE: 0.6
  - Incidence rate in placebo group: 0.01
  - 2:1 randomization ratio in vaccine to placebo

  ⇒ **152 primary endpoints needed**

Target VE	Lower Bound	Randomization Ratio	Total #of Cases	Incidence Rate		Total Sample size
				Placebo	Vaccine	
60%	30%	2:1	152	1%	0.40%	25164

- **Additional assumptions**
  - Account for participants to be excluded from the PP set due to baseline SAR-CoV-2 positive
  - Dropout rate (loss of evaluable participants)

Applied 15% baseline SARS-CoV-2 positive	Applied 5% dropout rate
28000	30000



Publicly available efficacy trials

	Moderna	BNT/Pfizer	AZ (US trial)	Janssen
Primary efficacy objective/endpoint	**First occurrence of COVID-19:** a. Positive RT-PCR **AND** b. At least 1 of: cough, SOB, clinical/radiographic pneumonia **OR** c. At least 2 of: fever, chillis, myalgia, headache, sore throat, olfactory & taste disorder	**Confirmed COVID-19:** a. Positive RT-PCR or other NAAT **AND** b. At least 1 of: fever, cough, SOB, chillis, muscle pain, sore throat, anosmia/ ageusia, diarrhea & vomiting	**First occurrence of COVID-19:** a. Positive RT PCR **AND** b. At least 1 of Pneumonia (CXR/ CT); SPO2 ≤ 94% or need for O2; SOB **OR** c. At least 2 of fever; cough; myalgia; fatigue; vomiting/diarrhea*; anosmia/ageusia*	**First occurrence of COVID-19:** a. Positive RT PCR **AND** b. Any 1 of: RR ≥ 20 breaths/min, abnormal SpO2 but still >93%, clinical/ radiologic pneumonia, radiologic DVT, shortness of breath **OR** c. Any 2 of: fever, HR ≥ 90 BPM, shaking chills/rigors, sore throat, cough, malaise, headache, myalgia, GI symptoms, olfactory/ taste disorder, red/bruised feet/toes
Follow-up start	14 days post dose 2	7 days post dose 2	15 days post dose 2	15 days post single dose
Stratification on baseline serostatus	Only seronegative in primary VE analysis; Separate analysis for seropositive	2 primary endpoints a. without evidence of past infection & b. with or without evidence of past infection	Only seronegative in primary VE analysis; Separate analysis for seropositive	Only seronegative in primary VE analysis; Secondary efficacy analyses include all regardless of serostatus
Age range	Age based analysis 18-64 & ≥ 65 (25- 40% either ≥ 65 or <65)	Age based stratification: 16-55 & >55 (~40% of total enrollment)	Stratified randomization: 18-55; 56-69 & ≥ 70; age-based analysis planned	Age based analysis: 18-60 & >60 (~30% ≥ 60, 20% between 18-40)
VE & LB 95% CI	≥50% & >30%	≥50% & >30%	≥50% & >30%	≥60% & >30%
Total N (V:P)	30000 (1:1)	43998 (1:1)	30000 (1:1)	60000 (1:1)
Analysis set	- All doses received - No significant PDs - No evidence of infection or COVID-19 at baseline	-All doses received -No significant PDs -All eligible randomized subj. 1. Received ≥1 dose; 2. received both doses	-Received at least one dose -Not seropositive -Not withdrawn or no COVID-19 before Day 15 post dose 2	-Received study vaccine -Seronegative at time of vaccination -No other major PDs
Analysis method	Cox PH regression	Beta-Bionomial model	Poisson regression model	Sequential probability ratio test
Cases needed	151	164	150	154
#IAs planned (cases)	2 (53/106)	4 (32/62/92/120)	1 (75)	1+ (20/at least once a week after)

Mix & Match Vaccination

Examples of Clinical gaps CEPI aims to address particularly for LMICs

GAPS

- Studies in pregnant and lactating women
- Paediatric studies
- Other special populations (e.g., immunocompromised)
- Booster studies
- Increasing / broadening the immune response, for example
- Prolonged dosing interval for primary immunisation
- Heterologous prime-boost regimen (also addresses 'mix-&-match')
- Dose sparing strategies including single-dose primary vaccination regimens
- Concomitant administration of routine immunizations
- Vaccine efficacy against viral shedding, asymptomatic infection and transmission
- Vaccine efficacy against new SARS-CoV-2 variants: Sequencing breakthrough cases in clinical trials
- Correlate-of-Protection studies

Study design – Mix & Match Vaccination

- A **single-blind**, randomized, phase 2 study to determine immunogenicity of heterologous Prime-Boost COVID-19 vaccine schedules
- Primary objective is to determine whether the immune response in COVID-19 seronegative participants administered heterologous prime/boost COVID-19 vaccines regimens is **non-inferior** to that observed following administration
- Hypothesis H0: $GMT_{heterogolous} / GMT_{homologous} \leq 0.63$; H1: $GMT_{heterogolous} / GMT_{homologous} > 0.63$
- **Study arms**
  - A total of 1200 participants (150 per arm)
  - Participants boosted at either Day 28 or Day 84

Group	Arm	Prime (Day 0)	Boost (Day 28)	Boost (Day 84)
A – Gamaleya Sputnik (n=300)	A1-28 (n=150)	Gamaleya Sputnik V Ad26	AstraZeneca ChAdOx1	-
	A2-28 (n=150)	Gamaleya Sputnik V Ad26	Gamaleya Sputnik V Ad5	-
B - AZ ChAdOx1 (n=300)	B1-28 (n=150)	AstraZeneca ChAdOx1	Gamaleya Sputnik V Ad26	-
	B2-28 (n=150)	AstraZeneca ChAdOx1	AstraZeneca ChAdOx1	-
A – Gamaleya Sputnik (n=300)	A1-84 (n=150)	Gamaleya Sputnik V Ad26	-	AstraZeneca ChAdOx1
	A2-84 (n=150)	Gamaleya Sputnik V Ad26	-	Gamaleya Sputnik V Ad5
B - AZ ChAdOx1 (n=300)	B1-84 (n=150)	AstraZeneca ChAdOx1	-	Gamaleya Sputnik V Ad26
	B2-84 (n=150)	AstraZeneca ChAdOx	-	AstraZeneca ChAdOx1

Sample size and Primary analysis – Mix & Match Vaccination

- **Sample size Assumptions**
  - Non-inferiority margin for fold-difference: 0.63
  - Coefficient of Variation: 1.15 conservatively (from current available data)
  - True fold-difference: 1
  - 90% power
  - One-sided 2.5% alpha

  → Under the assumptions above, **84 participants who are seronegative at baseline in each arm**

  By accounting for
  - ~25% seropositivity rate at baseline
  - ~25% attrition rate,

  → **150 participants per arm (Total sample size = 1200 (=150x8arms))**
- **Primary Analysis**
  - Non-inferiority comparison between heterologous and homologous boost schedules, i.e., Groups A1-28 vs. A2-28, B1-28 vs. B2-28, A1-84 vs. A2-84, B1-84 vs. B2-84.
  - Among the seronegative population at baseline.
  - Claim heterologous boost group is non-inferior to homologous boost group if the lower limit of one-sided 97.5% CI of GMR between heterologous boost group and their corresponding homologous group lies above 0.63.
  - The analysis will be done to estimate the adjusted GMR with 97.5% CI after controlling for the design factors, including age strata and study sites.

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Q&A