Presenter Reminders

- Please **turn on your video** during your assigned session. As a presenter / panelist, your video will be shown to the audience unless you turn it off.

- As a presenter, **you can mute / unmute yourself to speak**. Note that general attendees cannot do this – they can only speak if Peyton identifies an individual to take themselves off mute. If you would like to call on an attendee to speak, please state their first **and** last name.

- Please **say "next slide"** to advance the slides. Laura will be sharing her screen with everyone's presentations already loaded.

- If you do not see the correct slide on your screen, it may be due to internet connectivity issues. Please **say the name of the slide header** that you'd like to see on the screen. As a backup, please **open your slides separately in PowerPoint** to reference the materials in the event internet issues arise.

- Peter or Jakob will chime in if you are over time. Otherwise, it is up to you to stay within your allocated time.

- During the discussion sessions, Peter or Jakob will serve as moderator, and the other will be sifting through the Q&A and feeding questions to the main moderator. However, if you see a question that was submitted by an audience member in the Q&A that pertains to your presentation, please write back to answer it.

- Q&A Chat: Please DO NOT click "answer live" and kindly only type in responses to the questions asked by attendees

COVAX

SARS-CoV-2 variants - Practical considerations for accelerated clinical development in light of current regulatory guidance

Clinical Development & Operations SWAT Team | Thursday March 25, 2021

CEPI

Gavi The Vaccine Alliance

World Health Organization

unicef

Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the "**Q&A**" function. If you see that your question is already asked, you can "like" the question in the "**Q&A**" function.

- This workshop will be **recorded**. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

Workshop Agenda

Time (CET)	Topic	Speaker
14:00-14:20	**Part 1: Welcome and Meeting Objectives**	Peter Dull
14:20-14:35	General Overview of Regulatory Framework for Variant Vaccines	Jakob Cramer
14:35-14:45	Variants and Vaccines: Global Public Health Implications	Sylvie Briand
14:45-14:55	Regulatory Preparedness on Adapting, if Needed, Vaccines for Strain Changes	David Wood
14:55-15:10	US, EU, ACCESS and WHO Guidance on Strain Change	Adam Hacker
15:10-15:15	Break	
15:15-17:00	**Part 2: Use Cases & Panel Discussions**	
	Approach for Vaccines with Acceptable Efficacy Data (with or without EUA / full registration)	
15:15-15:30	Vaccine Clinical Development Plan-Approaches in the context of products with EUA	Anh Wartel
15:30-15:50	Panel Discussion	Moderated by: Jakob Cramer
	Approach for vaccines lacking efficacy data	
15:50-16:10	Pathways for Approval of COVID-19 Vaccines Based on SARS-CoV-2 Variant Strains	Jorge Flores
16:10-16:50	Panel Discussion	Moderated by: Peter Dull
16:50-17:00	Wrap Up & Next Steps	Jakob Cramer

Welcome & Meeting Objectives

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

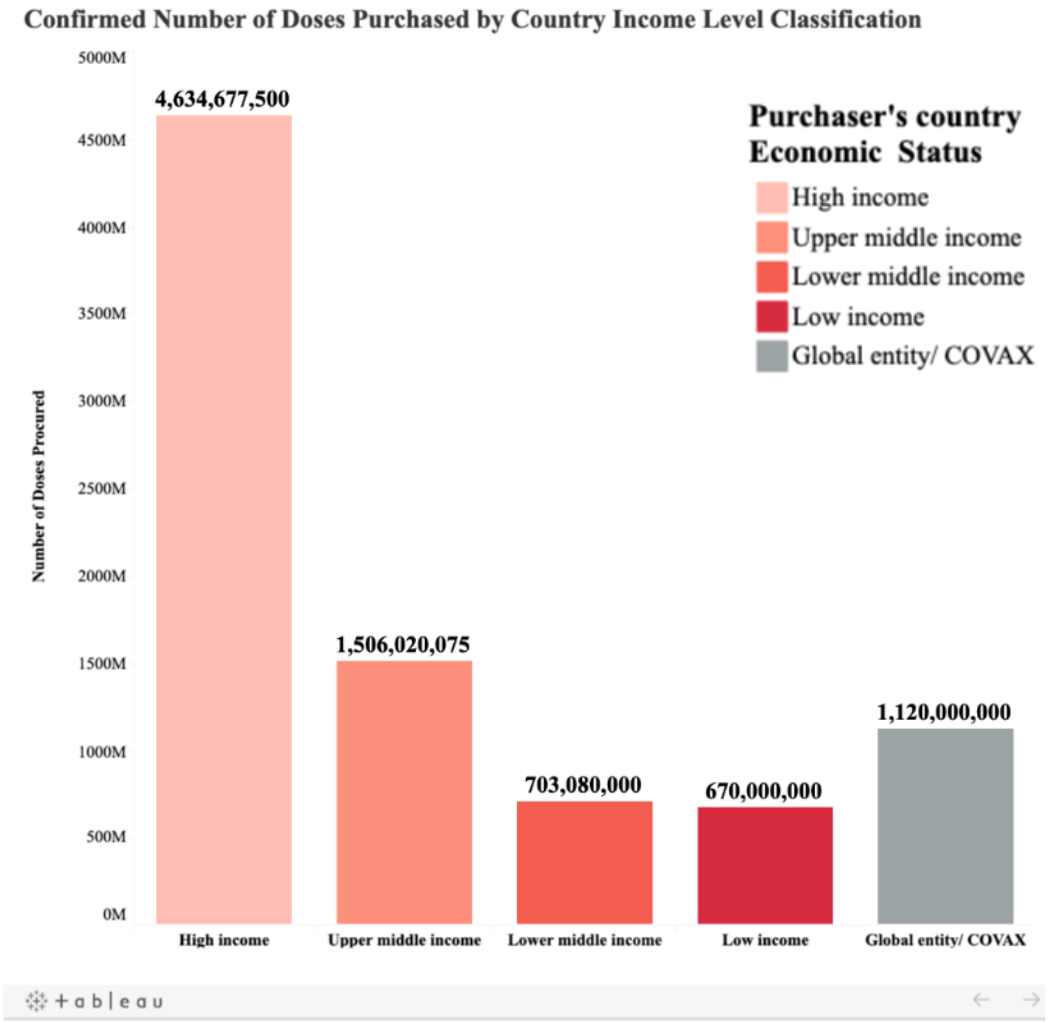
Why do we need more COVID-19 vaccines?

- Current models predict that there will not be enough vaccines to cover the world's population until 2023 or 2024
  - ➢ High-income countries already own more than half of all global doses purchased.

- Manufacturing capacity for existing vaccines has expansion limits
  - ➢ Tech transfers are complicated and scale-up ambitions have not been realized with supply chain bottlenecks for existing products

- Evolving variants are a concern
  - ➢ Emerging variants are spreading rapidly, and early data shows resistance to current vaccines
  - ➢ Urgent need to accelerate vaccine development for the new variants

- The world needs more, and possibly different, vaccines
  - ➢ Recent trans-national limits of vaccine highlight the need for a diversified vaccine supply



Updated: March 19, 2021

[Launch and Scale Speedometer – Duke Global Health Innovation Center]

Correlates of protection – an update on the evidence base

Identification of a biomarker that is reasonably likely to predict protection against COVID-19 would enable accelerated evaluations of high potential new vaccines

Once additional understanding of SARS-CoV-2 immunology, and specifically ***vaccine immune responses that might be reasonably likely to predict protection against COVID-19***, is acquired, **accelerated approval of a COVID-19 vaccine…may be considered** if an applicant provides sufficient data and information to meet the applicable legal requirements.

Source: "Development and Licensure of Vaccines to Prevent COVID-19," FDA Guidance Document

NB: "…companies are still required to conduct studies to confirm the anticipated clinical benefit"

Critical question we must ask as data accumulates:
As we move down the road to a quantitative threshold, have we already arrived at a sufficiently confident relationship between a biomarker and vaccine efficacy ?

Source: "Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry." FDA Guidance Document. Published 30 June 2020.

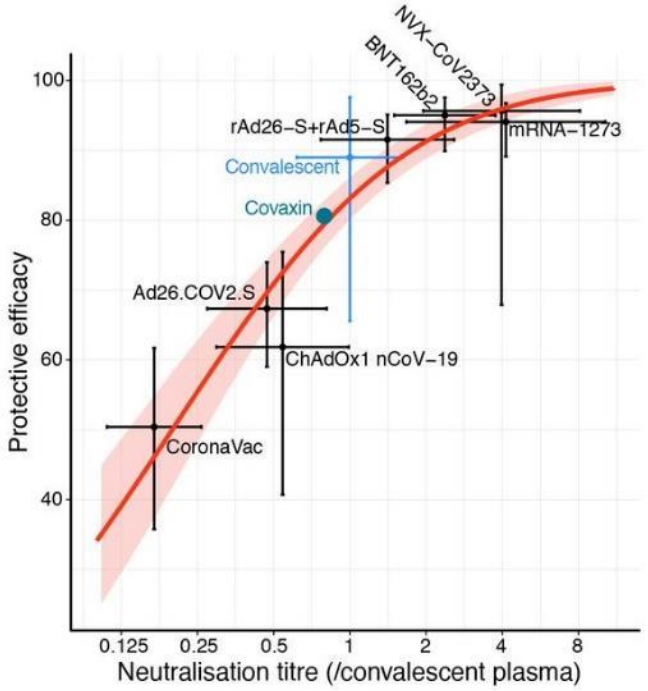
Two independent studies find strong correlation between antibody titers and efficacy, suggesting a potential correlate of protection

What level of neutralizing antibody protects from COVID-19?

Pre-print posted 11 March 2021

David S Khoury, Deborah Cromer, Arnold Reynaldi, Timothy E Schlub, Adam K Wheatley, Jennifer A Juno, Kanta Subbarao, Stephen J Kent, James A Triccas, Miles P Davenport

doi: https://doi.org/10.1101/2021.03.09.21252641

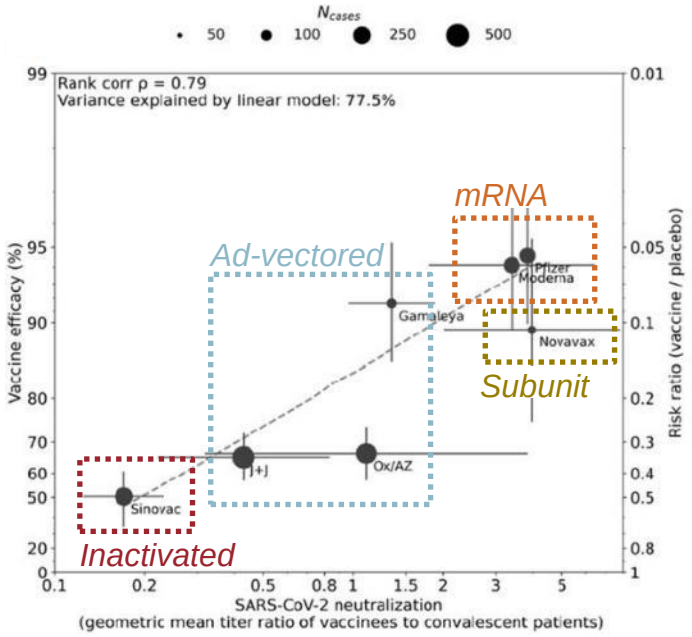


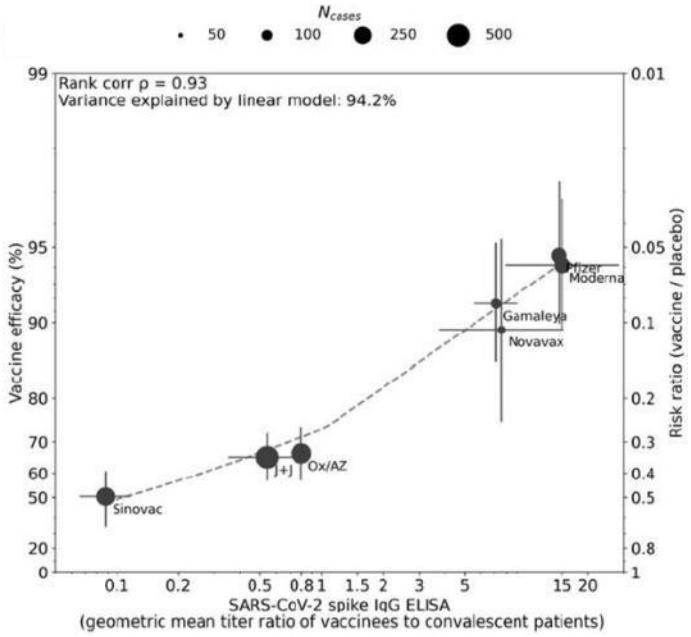
Evidence for antibody as a protective correlate for COVID-19 vaccines

Pre-print posted 20 March 2021

Kristen A. Earle, Donna M. Ambrosino, Andrew Fiore-Gartland, David Goldblatt, Peter B. Gilbert, George R. Siber, Peter Dull, Stanley A. Plotkin

doi: https://doi.org/10.1101/2021.03.17.20200246

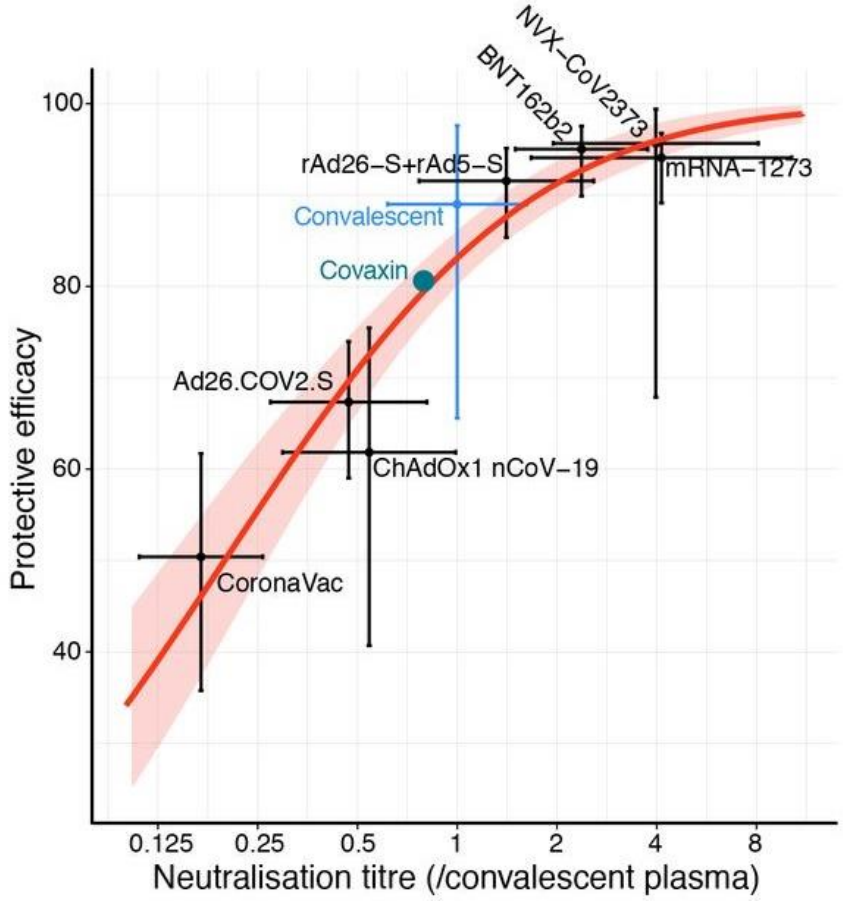




Robust correlation despite diverse study populations subject to different forces of infection and circulating variants, and use of different endpoints, assays, convalescent sera panels and manufacturing platforms

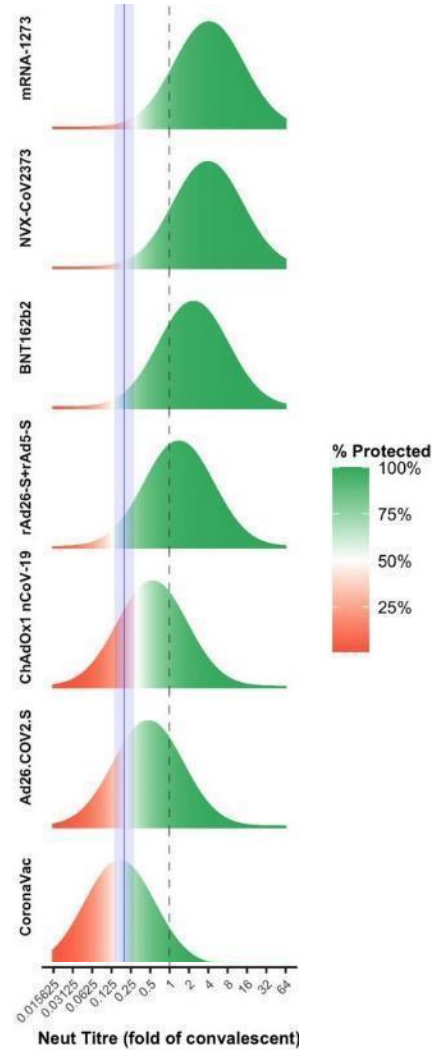
Strong non-linear relationship (ρ = 0.905) between nAbs and efficacy predicts 50% protective neutralization level at 20% average HCS titer

Strong correlation between efficacy and neutralization titers calibrated to HCS panels (ρ = 0.905; p=0.0046)



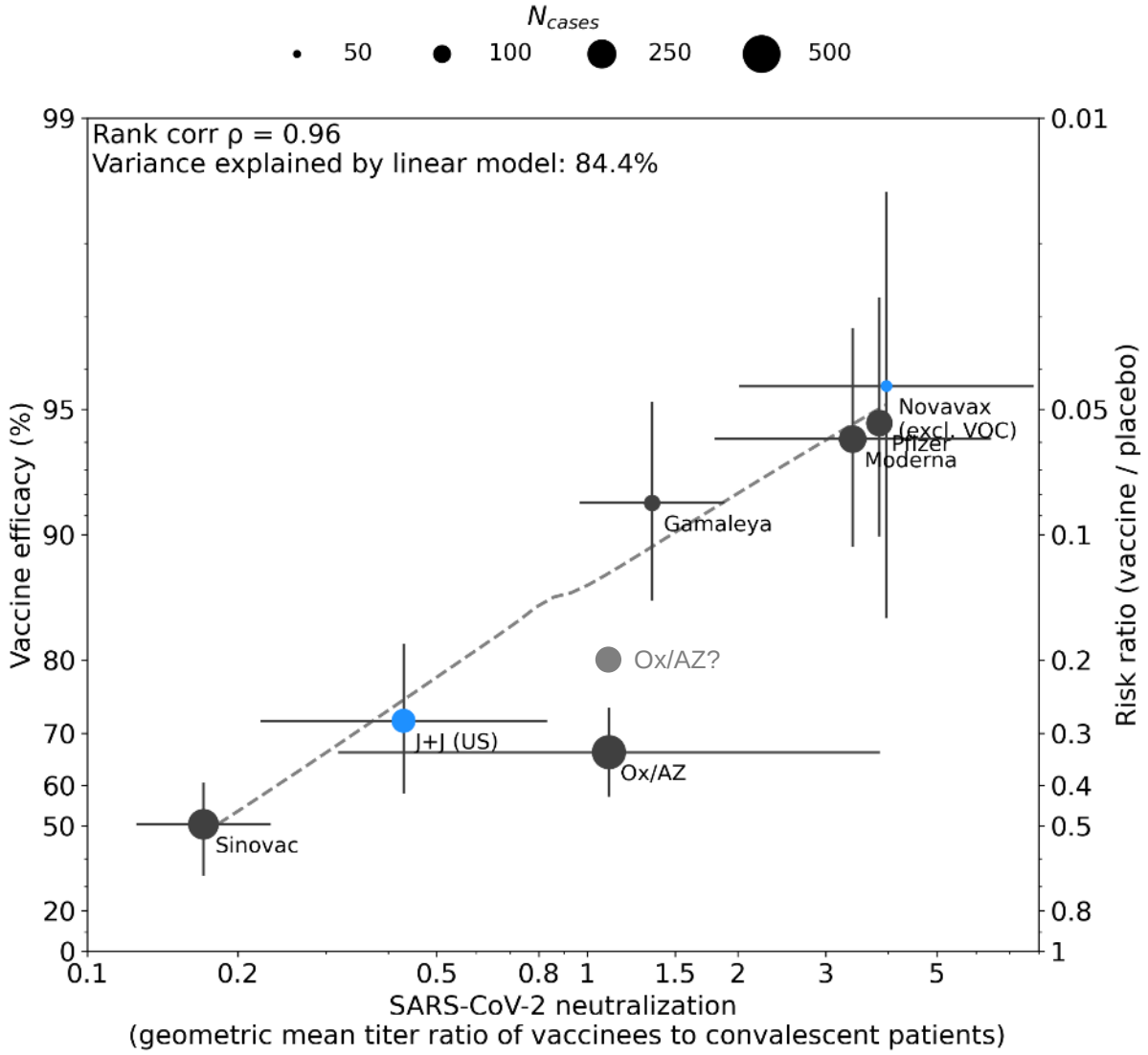
50% protective titer estimated at 19.9% of mean convalescent level

- Assumes normal distribution of neutralization titers
- Suggests efficacy can be predicted by mean and distribution of nAbs – model correctly estimated efficacy of Covaxin
  - Predicted: 79.4% (76.0%-82.8%)
  - Actual: 80.6%



Sources: Khoury et al. 2021. What level of neutralizing antibody protects from COVID-19? medRxiv doi: https://doi.org/10.1101/2021.03.09.21252641; Bharat Biotech Announces Phase 3 Results of COVAXIN®: India's First COVID-19 Vaccine Demonstrates Interim Clinical Efficacy of 81%. (Bharatbiotech Press release 3 March 2021); HCS: Human convalescent sera

Adjusting for efficacy against prototype (ancestral) strain (D614G) strengthens relationship



Incorporated post-hoc analyses of Janssen and Novavax Phase IIIs to remove impact of VOCs

- Janssen: 72% efficacy at US site (96.4% D614G[1])
- Novavax: 95.6% against ancestral strain at UK site[2]

Correlation coefficient = 0.96 with post-hoc analyses; 84.4% variance explained by model

Model may be further strengthened by pending Ox/AZ US Phase III data (76-79% efficacy)

- 4-week interval corresponds better to Phase I schedule
- Potentially less impacted by circulating variants

Source: Earle et al. 2021. Evidence for antibody as a protective correlate for COVID-19 vaccines. medRxiv doi: https://doi.org/10.1101/2021.03.17.20200246

Variant SARS-CoV-2 Vaccine Development (B.1.351) - Latebreaking Data

CpG 1018 adjuvant kindly provided by: DYNAVAX

➢ *Mouse Immunogenicity Study: Preliminary Results*

S.Africa (B.1.351) Spike-Trimer Protein Expression:

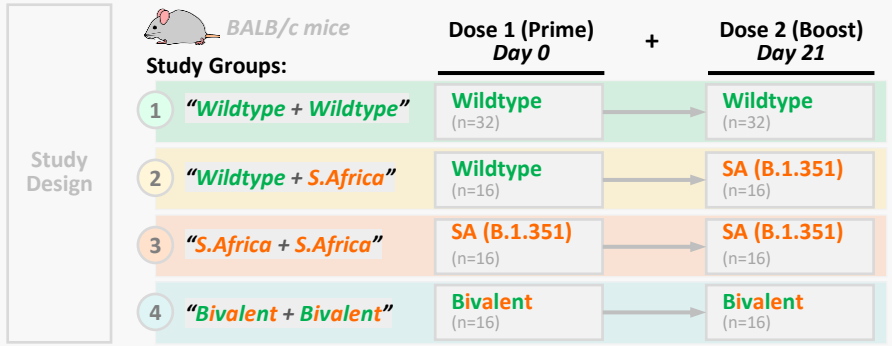
- Utilizing Clover's proprietary Trimer-Tag© technology to achieve stable spike-antigen trimerization and high purity via affinity capture (*same platform as Clover's wildtype SCB-2019 COVID-19 vaccine currently in global Ph 2/3 efficacy clinical study*)
- Early-Jan 2021: Completed construct design
- End-Jan 2021: Initial antigen expression achieved
- Early-Feb 2021: Initial Mouse immunogenicity study initiated
- Ongoing: Stable CHO-cell line development & pilot-scale production

Preliminary Takeaways from Mouse Immunogenicity Study (Day 28 Results):

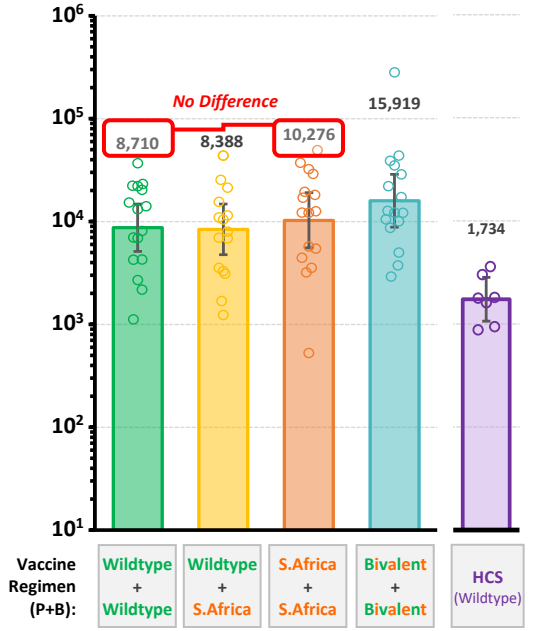
- **Monovalent Wildtype Vaccine:** ~9-fold lower neutralization to B.1.351 observed (although titers are ~6x higher than WT human convalescent sera)
- **Monovalent S.Africa (B.1.351) Vaccine:** Fully cross-neutralizes wildtype strain in this study; ***could be broadly protective against wildtype and all current variants of concern***? Advantageous and simpler CMC versus bivalent/multivalent formulation
- **Original Antigenic Sin?:** Heterologous prime boost (Wildtype Prime + S.Africa Boost) did not induce additional neutralization to S.Africa (B.1.351) pseudovirus compared to two doses of Wildtype vaccine

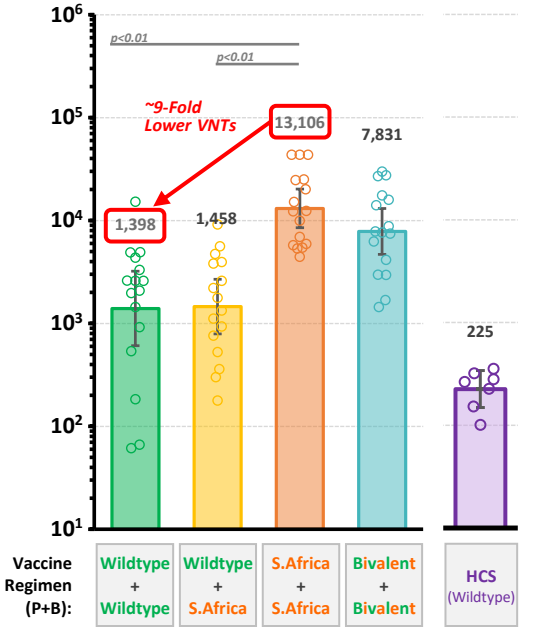
Additional Key Results Expected:

- Cross-neutralization to UK (B.1.1.7) and Brazil (P.1) variants
- Booster dose (Dose 3) to further evaluate 'original antigenic sin'
- Cell-mediated immune responses (variant-specific)



Day 28 VNT Results (1 Week Post-Dose 2)





Notes: Bars represent geometric mean titer (**GMT**) values and error bars represent 95% confidence intervals (**95% CI**) for virus neutralization titers (**VNTs**) based on pseudovirus assays. Prime (**P**) + Boost (**B**) two-dose vaccine regimens. Each dose of monovalent vaccine contains 3 µg of Spike-Trimer antigen for Wildtype (**WT**) or South African (**SA** - B.1.351) strains; each dose of bivalent vaccine contains 3 µg of Wildtype Spike-Trimer + 3 µg of SA (B.1.351) Spike-Trimer antigen. Priming dose in all animals utilized CpG 1018 plus alum adjuvants, and half of the animals in each group received boost dose that was adjuvanted (CpG 1018 plus alum) and half received nonadjuvanted boost. VNT results above represent 4x2 factorial analysis of all animals receiving two doses of vaccine. Human Convalescent Sera (**HCS**) from symptomatic Chinese COVID-19 patients infected with wildtype SARS-CoV-2 (n=7; 1 severe; 4 moderate; 2 unknown).

Adapted Prototype' versus '*Adapted New*' COVID-19 Vaccines – General Overview

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

'Adapted Prototype' versus *'Adapted New'* COVID-19 Vaccines

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General Overview

25th March 2021

New Strains → New Vaccines

- Are approved prototype COVID-19 vaccines **good enough** against currently circulating SARS-CoV-2 variants (of concern) - at least against severe disease?
- We need **more vaccines** but must consider **new circulating virus variants**
    1. Should *new* vaccines be directed against new variants? **Strain change: WHO**
    2. How to approve *prototype* vaccines adapted to new variants? **EMA/FDA/ACCESS guidance**
    3. How to approve *new* vaccines targeting new variants?

Many additional challenges (to be addressed in subsequent workshops):

- Vaccinating seropositive versus seronegative individuals
- Booster vaccination: homologous vaccine or vaccine adapted to new viruses given months after primary immunization with prototype vaccine (against original virus)
- Multivalent vaccines
- Mix and match vaccine regimens…

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Challenging Terminology

	Term	Explanation	Other terms
Vaccine	*'prototype'*	Vaccine approved and/or with demonstrated clinical vaccine efficacy against *original* SARS-CoV-2 virus	'parent', 'original', 'current'
	'new'	Vaccine without approved *prototype* based on the identical product/platform	
	'adapted'	Vaccine against *variant strain –adapted* based on either *prototype* or *new* vaccine	'modified', 'variant', 'updated'
Virus	*'original strain'*	Initial SARS-CoV-2 virus (included in *prototype* vaccines)	'parent', 'initial',
	'variant strain'	Mutated SARS-CoV-2 virus with significant modified characteristics that has emerged from the *original* virus	'new'

Comparing *prototype* / *adapted* vaccines:

- Same vaccine product (identical platform)
- Same / comparable platform
- Across platforms

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CDP for New Vaccines

Option	Vaccine Efficacy demonstrated based on	CDP	Risks / challenges
A) No evidence for correlation between immune response and vaccine efficacy (alternative platform / route of administation)			
1a)	Superiority to inactive-comparator (placebo)	• Randomized controlled trial • Primary objective in seronegatives • Target VE: ≥50% (LB 95%CI >30%)	• Large sample size • Placebo-controlled VE trials increasingly challenging
1b)	Non-inferiority (NI) to active-comparator	• Randomized controlled trial • Primary objective in seronegatives • Target VE: -10% margin	• Access to comparator vaccine • Time to recruit very large sample size • Practical challenges
B) Evidence for correlation between immune response and vaccine efficacy available and accepted by NRAs / WHO PQ			
2)	Immunobridging (NI) followed by clinical vaccine efficacy	• NI to appropriate/ approved comparator vaccine based on pre-defined margins for SCRs / GMTs • Primary objective in seronegatives • Clinical VE based on less stringent requirements (e.g. LB 95% CI = 0%)	• Clin. VE based on less stringent criteria probably not acceptable by NRAs / WHO PQ • Access to comparator, size/time (see 1b) • May still require post-authorisation vaccine effectiveness
3)	Immunobridging (NI) with post-authorisation vaccine effectiveness	• NI to appropriate/ approved comparator vaccine based on pre-defined margins for SCRs / GMTs • (Prim. objective in seronegatives) • Post-authorisation vaccine effectiveness study	• Within identical product/platform *versus* between products/platforms
C) Immune quantitative Correlate of Protection (CoP) available and accepted by NRAs / WHO PQ			
4)	Demonstrate adequate SPR	• Establish level of SPR (control group [placebo or active control] only needed for comparing safety / reactogenicity]	• NRAs / WHO PQ may still require NI based on SPR

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NI – non-inferiority; SCR = seroconversion rate; SPR = seroprotection rate

Scenarios for Establishing Vaccine Efficacy
directly (via clinical efficacy) / indirectly (via immunobridging)

Assumption: Supportive evidence re correlation of immune response with Vaccine Efficacy [no CoP]

	Scenario	Vaccine type	SARS-CoV-2	Vaccine against original strain authorised?	Pivotal clinical trial ?	Comparator vaccine ?
default	1-1)	'prototype'	'original' strain	n.a.	Conventional vaccine efficacy trial (data available or expected in near future)	n.a. (placebo) (vaccine already approved or approved in near future) **[= default scenario]**
IVI:	1-2)	'adapted'	'variant' strain	yes	Immune bridging based on NI	'prototype' vaccine against original SARS-CoV-2 strain **(*identical* platform)**
PATH:	1-3)	'new'	'variant' strain	no	1. Immune bridging based on NI [followed by post-authorisation vaccine effectiveness study] 2. Conventional vaccine efficacy trial	1. 'prototype' vaccine against original SARS-CoV-2 strain **(*comparable* platform*)** 2. placebo
	1-4)	'new'	'original' strain	no	1. Immune bridging based on NI [followed by post-authorisation vaccine effectiveness study] 2. Conventional vaccine efficacy trial	1. 'prototype' vaccine against original SARS-CoV-2 strain **(comparable platform*)** 2. placebo

*)
- *Identical* platform = same 'product'
- *Comparable* platform = in terms of putative mechanism of protection (i.e. protective immune response primarily based on nAbs / strong T cell response, …)

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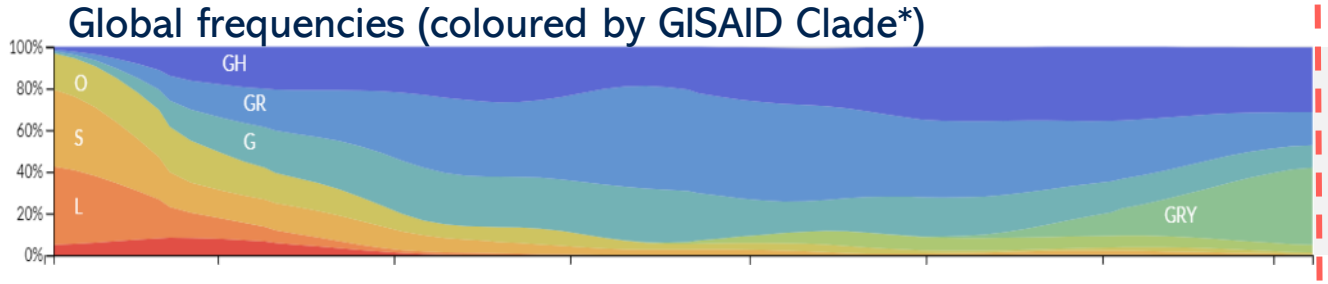
Planning Pivotal Trials to Establish VE

Adapted versus new COVID-19 vaccines



???

*) GISAID clades:
S – original strain
GH – includes B.1.351 lineage
GR – includes B.1.1.7 and P1 lineages

Jan 2020 | Jul 2020 | Jan 2021 | today | Jul 2020 | Jan 2022

Wave 1 | **Wave 1a** | **Wave 2**

Pfizer/BNT
Moderna
Gamaleya
AstraZeneca
J&J
Sinovac
Cansino

X

Y

Proportion of seropositives, illustrative (original SARS-CoV-2 strain)

???

Potential recommendation to adapt COVID-19 vaccines to new SARS-CoV-2 strain

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= Ph3 VE IA data published | = Ph3 'wave 1' | = Ph3 'wave 1a' | = Ph3 'wave 2'

For illustration / discussion purposes only

PLATFORM TECHNOLOGY

	Wave 1: 'Prototype' approved / with clinical efficacy	Wave 1a: Ph3 VE data expected soon	Wave 2: VE: Immunobridging?
mRNA	• BNT/Pfizer, Germany/USA • Moderna, USA	• CureVac, Germany	• SP/TBio, USA/France • Walvax, China • Imp. Coll., UK [saRNA] • Gennova, India [saRNA]
Viral vector	• AZ/Uo Oxford, UK • J&J, USA • CanSino, China • Gamaleya (Sputnik V), Russia		• Altimmune, USA • Gritstone, USA
Protein	• Novavax, USA	• Clover, China • BioE*, India • Medicago, Canada • Zhifei*, China	• SK Bio*, SK • SP/GSK, France/UK • COVAXX, USA • VBI, USA • SII, India [VLP]*
Whole inactivated virion	• Sinovac, China • Sinopharm (BIBP), China • Bharat, India	• IMB, China	• Valneva, Austria
Other	• none	• Inovio, USA [DNA] • Zydus, India [DNA]	

*) RBD-based

[**Assumptions** made based on publicly available data:
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Protein-based COVID-19 Vaccines

Developer	Construct	Antigen	Adjuvant	No. doses / interval
Novavax, USA	Nanoparticle	FL spike gp	MatrixM	2 doses, 3 weeks
Clover, China	S-trimer	FL spike gp	CpG, aluminum phosphate	2 doses, 3 weeks
BioE, India	RBD N1C1 (Pichia pastoris)	RBD	CpG, aluminium hydroxide	2 doses, 4 weeks
Medicago, Canada	Plant-based	FL spike gp	ASO3	2 doses, 3 weeks
SKBio, South Korea	Nanoparticle	RBD	ASO3	2 doses, 4 weeks
Sanofi Pasteur, France	Recombinant protein	FL spike gp	ASO3	2 doses, 3 weeks
COVAXX, USA	Multitope peptide based S1-RBD-protein	Parts of several viral Ag	Aluminium phosphate	2 doses, 4 weeks
VBI, USA	VLP	Modified spike gp	Aluminum phosphate	2 doses, 4 weeks
Anhui Zhifei, China	Recombinant protein (Chinese Hamster Ovary-CHO Cell)	RBD	Aluminium hydroxide	3 doses, 4 weeks
Serum Institute of India	VLP (Pichia pastoris)	RBD	Alum vs. CpG	

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(Placebo-) Controlled Efficacy Trials: Increasingly Difficult

- Vaccination campaigns targeting **high risk groups** for clinical / complicated COVID-19
- Recruiting younger (non-high-risk) population groups: **Significant / increasing practical challenges**
  - Individuals chose not to participate but **wait to be vaccinated with approved vaccine**
  - Even in countries with limited vaccine supply **enrolment of volunteers slows down** → extended recruitment times
  - **Increasing rate of drop-outs** expected over time / as approved vaccines become available
  - **Compromised data quality** (e.g. no local reaction: subjects feel they got placebo and seek vaccination elsewhere)
- Rapidly increasing proportion of trial **population being seropositive**

⇒Increasing unwillingness of developers to consider / conduct conventional vaccine efficacy trials.

⇒Window for pre-licensure vaccine efficacy trial closing?

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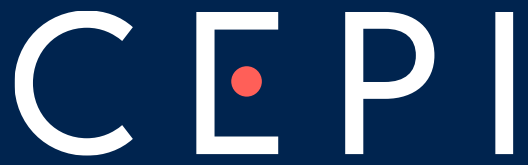
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Variants and Vaccines: Global Public Health Implications

Sylvie Briand, MD

Director, Global Infectious Hazards Preparedness (GIH)

Health Emergencies Programme

World Health Organization (WHO)

Variants and vaccines: global public health implications.

World Health Organization

WORKSHOP - 25 March 2021
SARS-CoV2 variants -
Practical considerations for accelerated clinical development in light of current regulatory guidance

Dr Sylvie Briand,
Director Global Infectious Hazards Preparedness (GIH)
Health Emergencies Programme
World Health Organization

Update on key VOCs

(as of 23 March)

Table 2: Overview of emerging information on key variants of concern, as of 23 March 2021*

Nextstrain clade	20I/501Y.V1	20H/501Y.V2†	20J/501Y.V3
PANGO lineage	B.1.1.7	B.1.351	B.1.1.28.1, alias P.1†
GISAID clade	GR	GH	GR
Alternate names	VOC 202012/01†	VOC 202012/02	-
First detected by	United Kingdom	South Africa	Brazil / Japan
First appearance	20 September 2020	Early August 2020	December 2020
Key spike mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; and P681H	L242/A243/L244 deletion; K417N E484K, N501Y	K417T, E484K; N501Y
Key mutation in common	S106/G107/F108 deletion in Non-Structural Protein 6 (NSP6)		
Countries reporting cases (newly reported in last week)**	125 (7)	75 (11)	41(3)

†*While work is ongoing to establish standardized nomenclature for key variants, these are the names by which WHO will refer to them in this publication.*
**Generalized findings as compared to non-VOC viruses. Based on emerging evidence from multiple countries, including nonpeer-reviewed preprint articles and reports from public health authorities and researchers – all subject to ongoing investigation and continuous revision.*
***Includes official and unofficial reports of VOCs detections in countries among either travellers (imported cases only) or community samples (local transmission).*

Figure 5. Countries, territories and areas reporting SARS-CoV-2 VOC 202012/01 as of 23 March 2021

Figure 6. Countries, territories and areas reporting SARS-CoV-2 501Y.V2 as of 23 March 2021

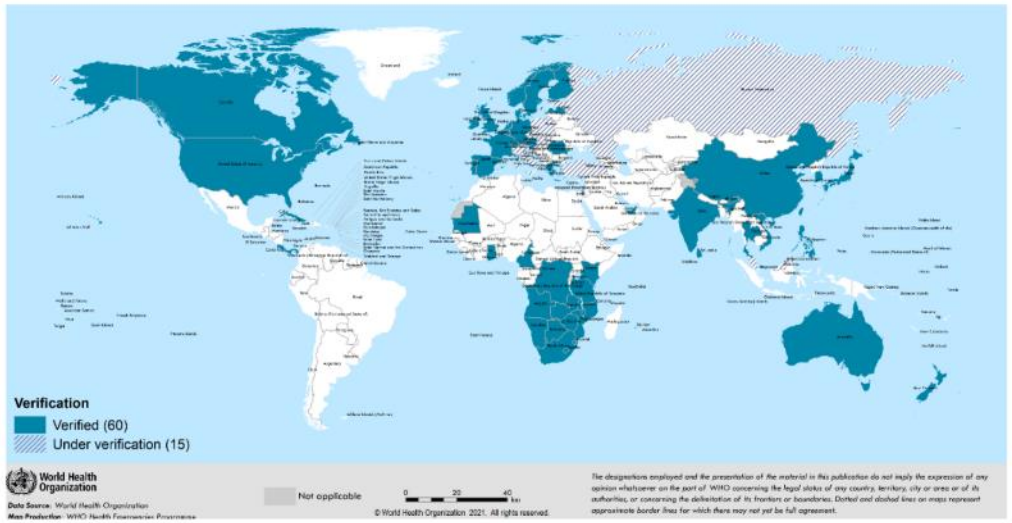
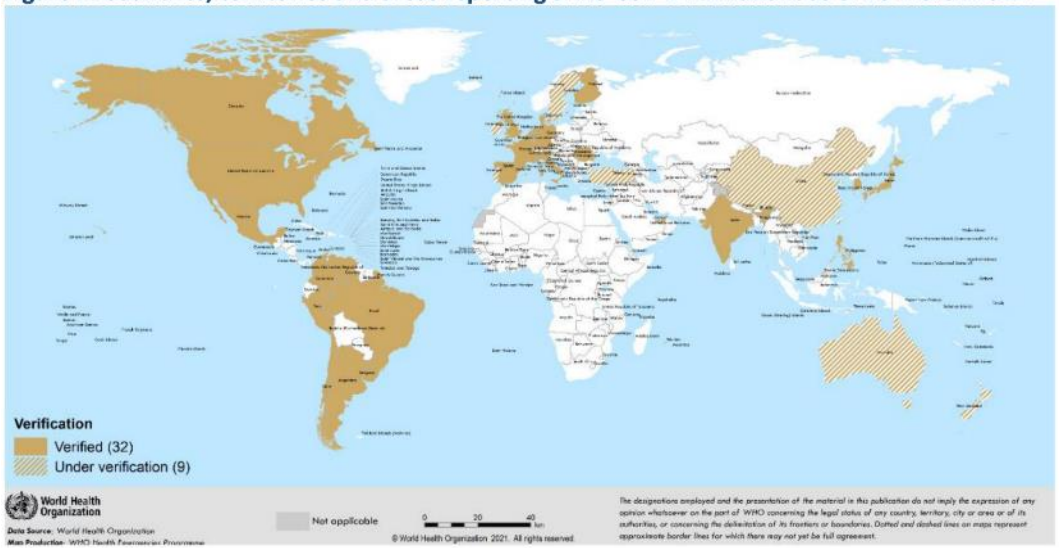


Figure 7. Countries, territories and areas reporting SARS-CoV-2 P.1 variant as of 23 March 2021



https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-march-2021

Filling knowledge gaps and rapid evidence-based decisions

- How long does the natural immunity last?
- How long does the immunity conferred by vaccines last?
- Can people be re-infected, how often?
- What is the impact of each SARS-CoV-2 variant on transmissibility and disease severity? What is the impact on risk groups?
- What is the impact of the variants on public health and social measures, the testing strategy or the tests in use, the management of patients, …?
- What is the impact of each variant on vaccine efficacy and effectiveness? And does it require to change the vaccine composition?
- What is the impact on research? …

World Health Organization

LEGEND
Epidemic
Pandemic

MAJOR EPIDEMIC THREATS SINCE 2000

COVID-19
Ebola (DRC)
Yellow fever (Central Africa, Brazil)
Zika
H7N9
Ebola (West Africa)
H1N1
H5N1
MERS
SARS
Cholera (Haiti)
Cholera (Yemen)
Plague (Madagascar)

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020

INTERNATIONAL COLLABORATION EFFORTS TO FIGHT EPIDEMIC THREATS

GAVI

Gavi, the Vaccine Alliance, is an international organisation that was created in 2000 to improve access to new and underused vaccines for children living in the world's poorest countries.

GOARN

The **Global Outbreak Alert and Response Network (GOARN)** is a technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance.

IHR (2005)

The **International Health Regulations (2005)** or IHR (2005) are an international law which helps countries work together to save lives and livelihoods caused by the international spread of diseases and other health risks. The IHR (2005) aim to prevent, protect against, control and respond to the international spread of disease while avoiding unnecessary interference with international traffic and trade.

PIP Framework

The **Pandemic Influenza Preparedness (PIP) Framework** brings together Member States, industry, other stakeholders and WHO to implement a global approach to pandemic influenza preparedness and response. Its key goals include:
- to improve and strengthen the sharing of influenza viruses with human pandemic potential; and
- to increase the access of developing countries to vaccines and other pandemic related supplies.

R&D Blueprint

R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of research and development activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crises.

PIP Review

IHR Review

Access to COVID-19 Tools (ACT) Accelerator is a global collaboration to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines.

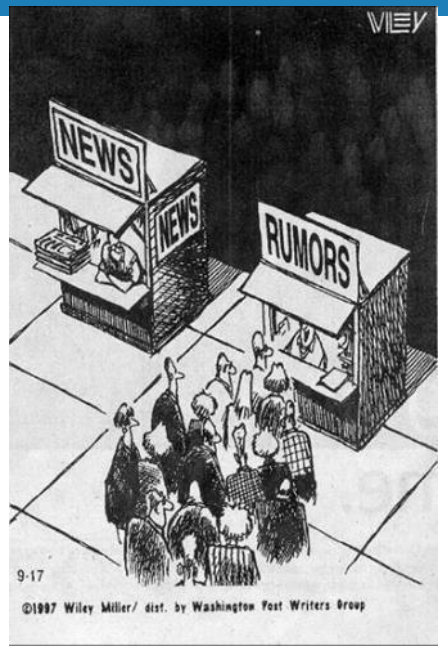
ACT Accelerator

Timeline

Major infectious threats in the 21st Century & collaboration mechanisms to fight against them

Last update: 08 May 2020

How to build trust during pandemic ?



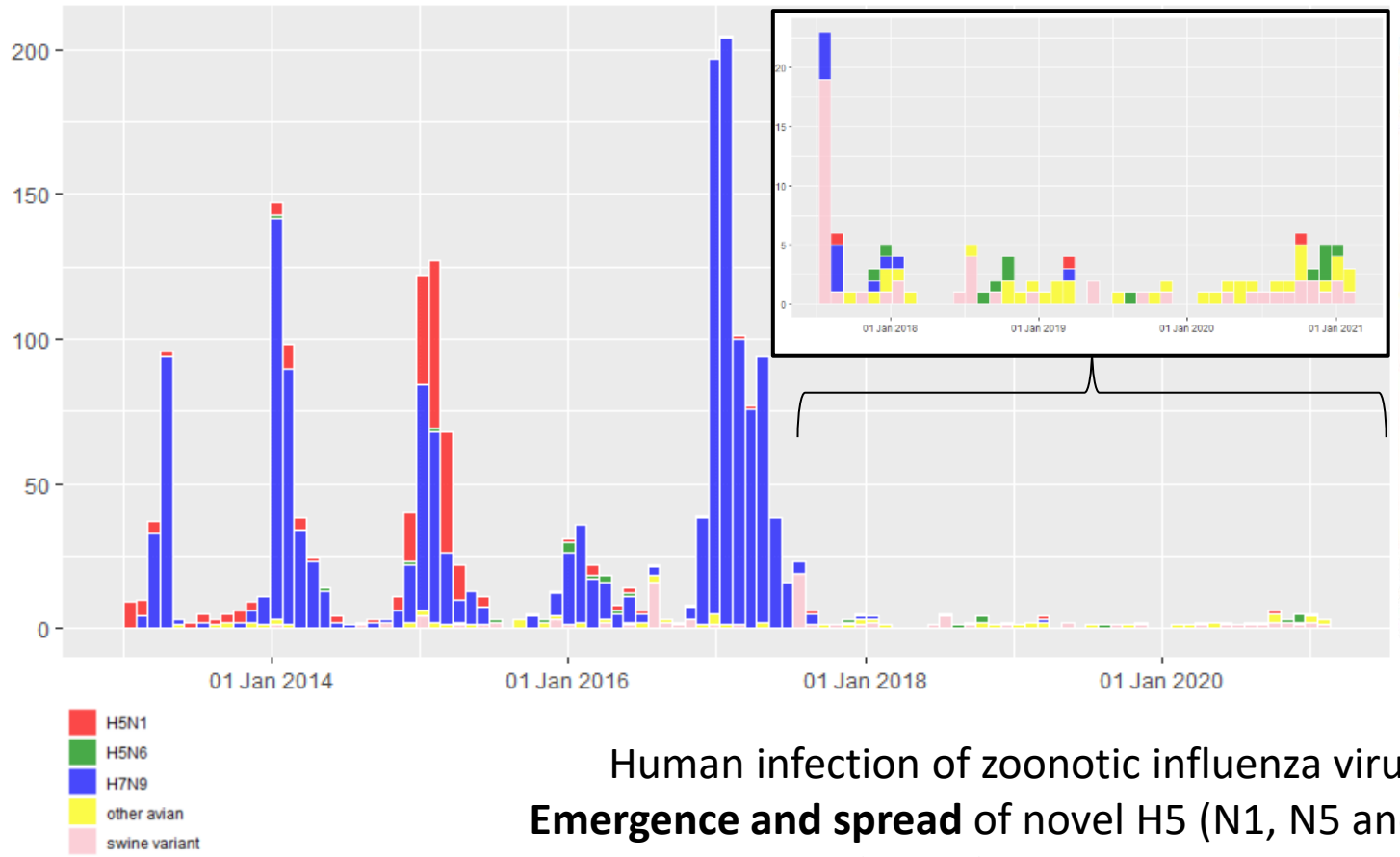
WHO advisors paid by VACCINE COMPANIES-Danish media.

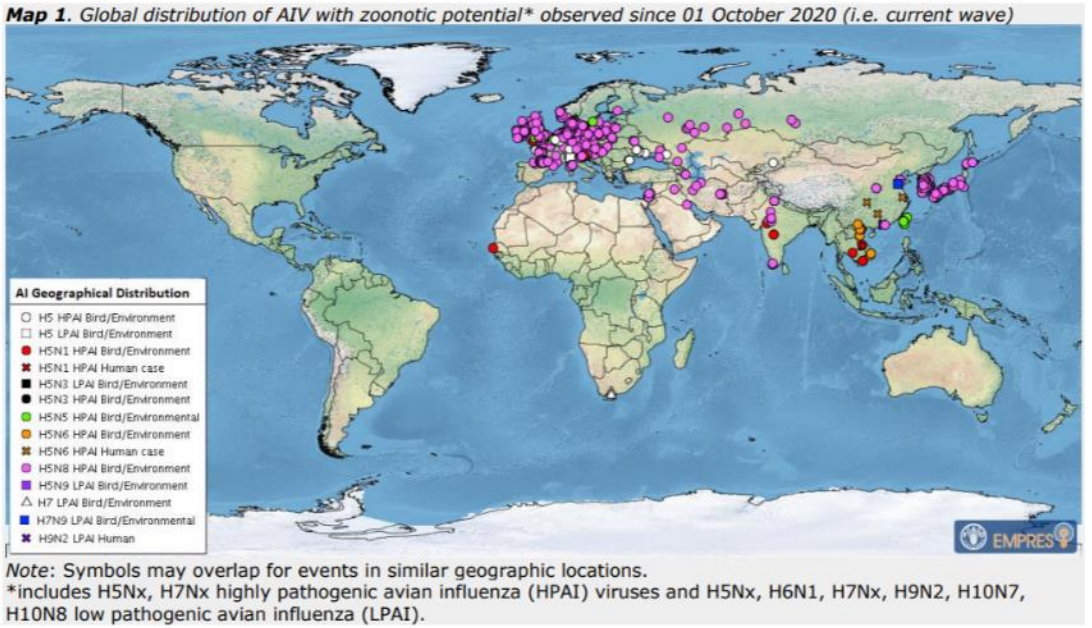
World Health Organization

HEALTH EMERGENCIES programme

Existing global systems for pandemic vaccine decision: e.g. Seasonal and Non-seasonal (zoonotic) influenza outbreaks

Human infections of non-seasonal influenza reported to WHO, by month of onset





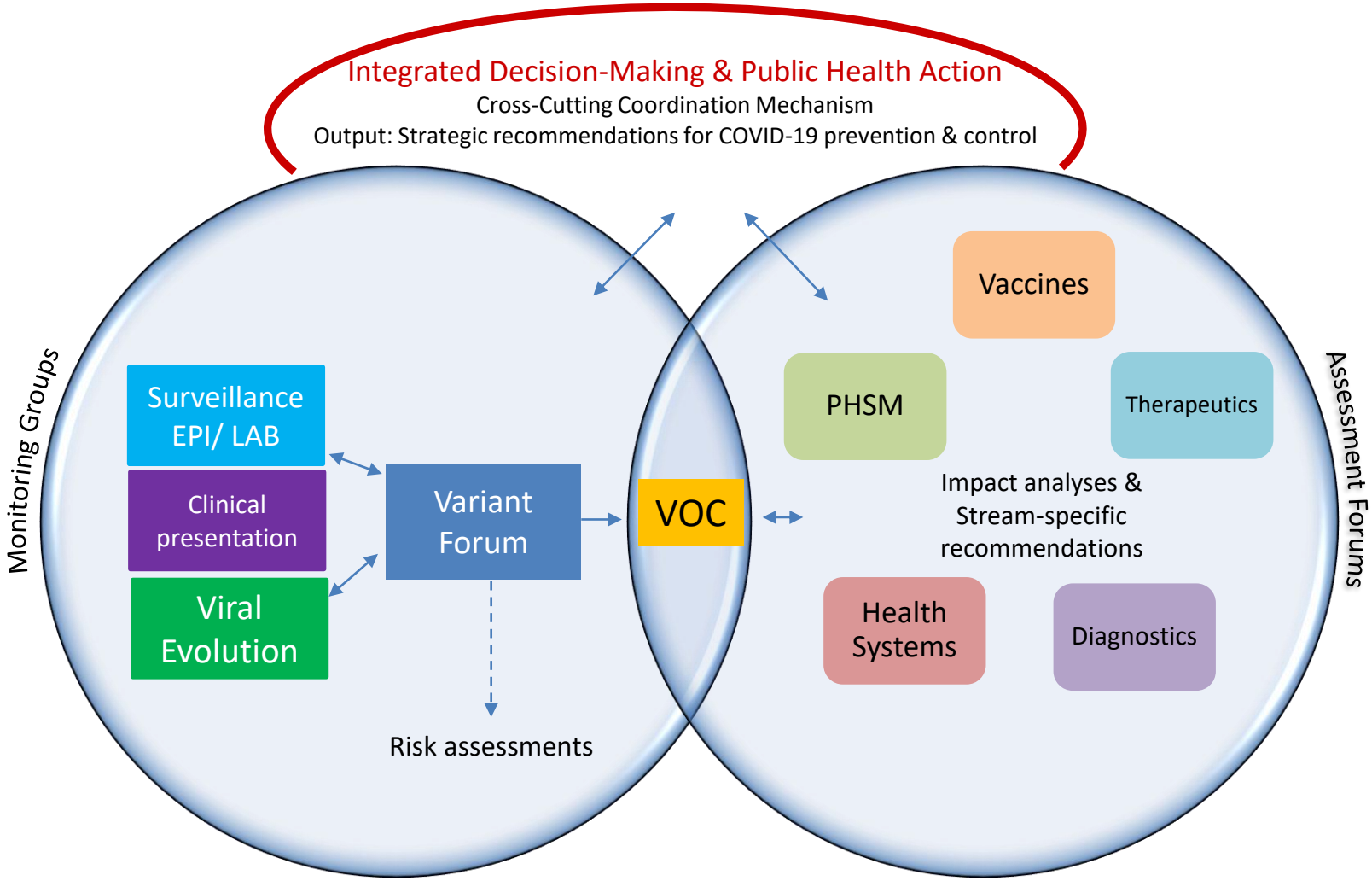
Source: FAO global AIV update, 27 Jan 2021

Human infection of zoonotic influenza viruses – **continuous, sporadic**

Emergence and spread of novel H5 (N1, N5 and N8) genetic clade 2.3.4.4 HPAI

Threat of an influenza pandemic – **PERSISTENT – NO Change**

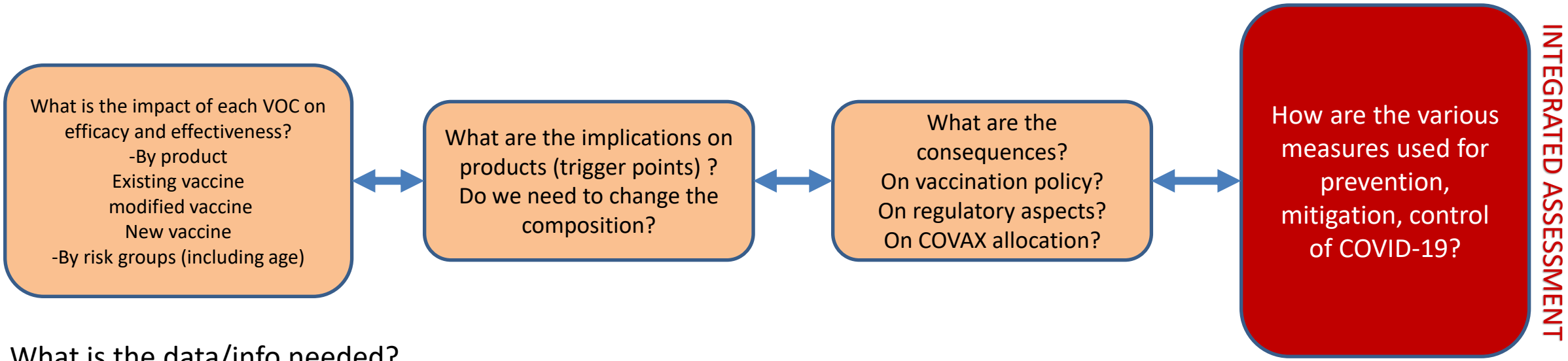
COVID-19 global monitoring and PH action



Upcoming global consultation: 29 March 2021

- Global Consultation on a Decision Framework for Assessing the Impact of SARS-CoV-2 Variants of Concern on Public Health Interventions
  - 29 March, 13:00-16:30 CET
- Objectives:
  - Review and summarize the existing evidence of the impact of VOCs on public health interventions
  - Engage global stakeholders to outline the information needs and decision-making processes for assessing the impact of VOCIs on public health interventions
  - Using COVID-19 vaccines as an example, review how a decision-making process could look with respect to analyzing the impact of VOCs and issuing policy recommendations
- Outcomes:
  - Established global forum for harmonized coordination and communications regarding VOCs and their impact on public health interventions
  - Decision-making framework that outlines the critical triggers, roles and responsibilities, and information needs and standards to guide policy recommendations regarding the impact of VOCs
  - Common understanding of the current evidence, challenges, and solutions for VOCs and their impact on current and future COVID-19 vaccines

Zooming in: Vaccine & vaccination stream - decision points



What is the data/info needed?
What are the methodologies for obtaining data/info?
What groups are involved?

e.g. Vaccination
and
Public Health measures ?


World Health
Organization
Thank You

Regulatory Preparedness on Adapting, if Needed, Vaccines for Strain Changes

David Wood, PhD, Independent consultant

Rogerio Gaspar, PhD
Regulation and Prequalification, WHO

Regulatory preparedness on adapting, if needed, vaccines for strain changes

World Health Organization

COVAX Workshop

SARS-CoV2 variants - Practical considerations for accelerated clinical development in light of current regulatory guidance

25 March 2021

Rogerio Gaspar / David Wood / Regulation and Prequalification, WHO

What are regulators preparing for?

- A coordinated public-health driven approach on strain composition for modified/new SARS CoV-2 vaccines – **if needed**
- Good linkages with public health authorities
- Three scenarios to consider:
  - Vaccines currently in use – what evidence is needed to decide if modifications are needed – guidance to come from WHO
  - Modifications to vaccines with established vaccine efficacy – guidance already available from regulators and WHO
  - Completely new vaccines – guidance under development

World Health Organization

Regulatory guidance to evaluate modifications to vaccines with established efficacy

- Regulators have rapidly developed guidance on evaluation of changes, **if needed,** to SARS CoV-2 vaccines with established vaccine efficacy
- US FDA, the EMA and the ACCESS consortium (Australia, Canada, Singapore, Switzerland, UK) have published guidance
- WHO has published guidance for PQ/EUL assessments
- Key features of guidance **shared during the development process** in vaccine cluster (EMA, FDA, HC, WHO), ICMRA and WHO R&D Blueprint meetings
- High level of alignment between regulators on key features
- All guidance's will be "living guidance" to be modified, if needed, as our knowledge of variants increases

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Features of the good alignment between regulators

Assumptions:

- ✓ Modified vaccine is developed by the same manufacturer and the same manufacturing process;
- ✓ Neutralizing antibodies are important to protection

- Non-inferiority of the neutralizing antibody response of the modified vaccine compared to the original vaccine
- Primary series to be tested, as well as the effect of a booster dose
- Clinical efficacy will not be required
- Large safety database will not be required

World Health Organization

Manufacturers are already developing modified vaccines

- Some manufacturers of vaccines with established efficacy are developing modified vaccines “at risk”
- This is useful, since will identify possible manufacturing and evaluation challenges with developing modified vaccines against variants
- Will also help to understand how long the process will take
- Some regions/countries are moving ahead on preparedness for access to modified vaccines e.g. European Commission has launched the “HERA incubator” to develop vaccines against variants, and ramp up industrial production

Completely new vaccines

- WHO will modify its Target Product Profile based on global public health considerations to guide what is needed
- ACCESS and EMA guidelines already provide some guidance for multivalent COVID vaccines
- Regulators have recognized the need that additional regulatory guidance is required for new vaccines and are actively working on guidance for new vaccines

Key messages

- A globally coordinated response is essential for
  - identifying variants of concern,
  - their impact on vaccines, and
  - any modifications to vaccine composition
- Regulatory alignment to assess modifications to SARS CoV-2 vaccines with established efficacy is largely achieved
- Further regulatory guidance is needed for vaccine candidates that are in earlier stages of development
- Careful messaging is essential on variants so as not to disturb public trust in COVID-19 vaccines

World Health Organization

US, EU, ACCESS and WHO Guidance on Strain Change

Adam Hacker, PhD
Head of Global Regulatory Affairs
CEPI

US, EU, ACCESS and WHO Guidance on strain change

Adam Hacker

Head of Global Regulatory Affairs, CEPI

25 March 2021

Features of the good alignment between regulators

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- clinical efficacy will not be required
- large safety database will not be required

World Health Organization

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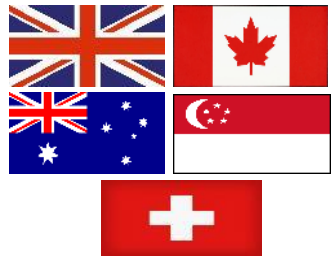
From David Wood, Regulation and Prequalification, WHO

Scope

- Scope is similar with a requirement for:
  - Parent / prototype vaccine to be approved and
  - The variant / modified vaccine to use the same manufacturing process and sites etc.
  - Assumes that there is no correlate of protection

- US Emergency Use Authorization for Vaccines to Prevent COVID-19 APPENDIX 2: EVALUATION OF VACCINES TO ADDRESS EMERGING SARS-COV-2 VARIANTS ver 22 February 2021
- EU Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 ver 25 February 2021
- ACCESS (UK, Australia, Canada, Singapore and Switzerland), Guidance on strain changes in authorised COVID-19 vaccines ver 4 March 2021
- WHO ADDENDUM to Considerations for Evaluation of COVID-19 Vaccines for Prequalification or Emergency Use Listing. Considerations for evaluation of modified COVID-19 vaccines ver 12 March 2021



Terminology

Situation	EU	US	ACCESS	WHO
Original SARS-CoV-2 strain	Parent strain	Original virus Original strain	Initial strain	Original virus
Original licensed/authorized vaccine (designed against original SARS-CoV-2 strain)	Parent vaccine	Prototype vaccine	Current vaccine	Prototype vaccine
SARS-CoV-2 variants	Variant strain	Variant of concern Variant of interest	New variant	Variant of concern
New vaccine designed to protect against one or more SARS-CoV-2 variants	Variant vaccine	Modified vaccine	Updated vaccine New vaccine version Variant vaccine	Modified vaccine
Original vaccine regimen	Primary series	Primary series	Not explicitly referred to	Not explicitly referred to

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CMC

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CMC

- Facilities and manufacturing process and control will be identical to that used for the prototype vaccine
- Details of manufacturing development and changes to the manufacturing process necessary due to the novel sequence
- Details of critical aspects of product characterization, sequence identity, potency assay and necessary re-validation of assays and standards required due to the novel sequence
- Shelf life – based on original licensed vaccine, supplement with real time stability

- EU
  - Some guidance on multi-valent considerations
- US
  - Any changes made to the manufacturing process and process control should be discussed with FDA in advance of the EUA amendment submission.
- ACCESS
  - A sufficient number (at least two) commercial scale (pre-) PPQ batches per manufacturing facility (possibly with supporting smaller development batches)
  - If same manufacturing line, adequate data on avoidance of cross-contamination (identity).
- WHO
  - Phylogenetic assessment re “distance” from prototype, for the sequences of the antigenic sites (protein S, protein N) should be provided. Sequence should be comparable to the VoC

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Non-Clinical

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Non-clinical

- Generally minimal requirements for non-clinical data but should be justified and dependent on platform experience

- EU
  - Bold statement – “No requirement to conduct any further in-vitro or in-vivo nonclinical testing”
- US
  - Immuno data from **suitable animal model challenge studies are encouraged and may contribute where clinical immunogenicity studies are ambiguous** (can be performed in parallel to clinical studies)
- ACCESS
  - Immunogenicity data, both humoral and cellular, in a relevant animal model will be informative. Comparisons of the prototype and variant vaccines are recommended.
  - Non-clinical protection data from a suitable challenge model may be useful additional data. Where justified, such studies can be performed in parallel to clinical studies. **Cross-protection data in animals could test whether the new version of the vaccine is able to provide protection against the existing virus to inform on whether vaccination against both versions of virus should be considered**.
- WHO
  - Data on the impact of the antigen change to the immune response may be required. Data should be generated using validated methods
  - Describes immuno data that should be evaluated but also indicates that data on the prototype vaccine may be acceptable
  - Similar statement to FDA re potential to support clinical immunogenicity data

Clinical

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Clinical - overview

- Conduct a non-inferiority study comparing the immune response induced by the modified / variant COVID-19 vaccine to that by the prototype / parent COVID-19 vaccine.
    - If unethical to vaccinate with the prototype / parent then the use of historical samples may be possible (link to animal data)
- Primary analysis
    - neutralizing antibodies elicited by the modified / variant COVID-19 vaccine against the variant strain compared to the neutralizing antibodies elicited by the prototype / parent COVID-19 vaccine against the original virus
    - Non-inferiority margin of -10%
    - Lower bound of the 95% confidence interval around the geometric mean (GMT) ratio should be at least 0.67
- Importantly, where possible should be conducted in unvaccinated subjects with no history of prior Covid-19 infection
- Acceptable to conduct in non-priority groups i.e., in 18- to 55-year-olds
- Booster data required
- Use or calibrate against the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody

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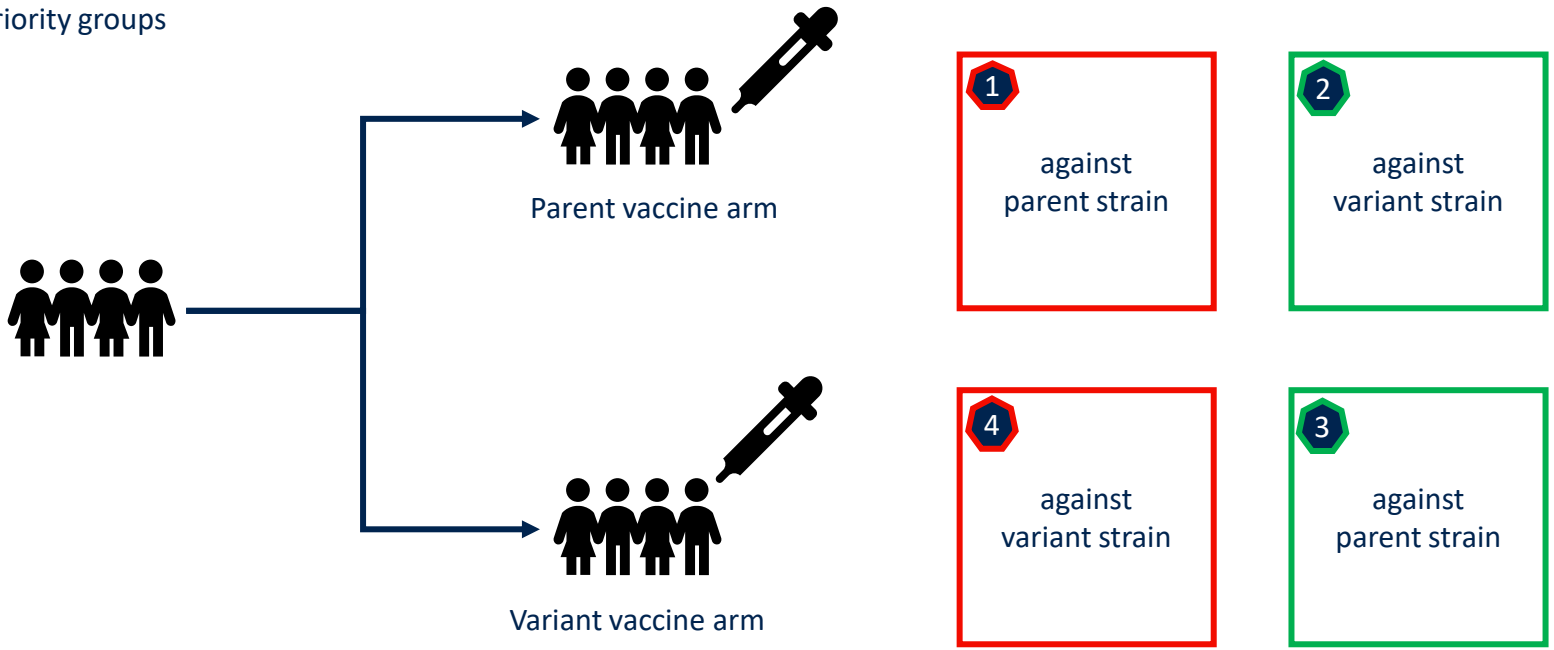
SARS-CoV-2-naïve subjects
i.e., unvaccinated and with no evidence of prior infection

Inclusion criteria

Unvaccinated
No prior Covid-19 infection
Do not have to include priority groups

Vaccination

Same dose schedule as approved for parent
Same blood sampling as parent efficacy data



Neutralizing antibody titres

- **Primary analysis**
  - Difference in seroconversion rates for ❶ vs. ❹ lower bound of 95% CI < -10%.
  - The lower bound of the 95% CI around the GMT ratio ≥ 0.67

  Definitions
  - *Seroconversion ≥ 4-fold increase in titre from pre-vaccination to post-vaccination*
  - *Since the primary analysis will be in seronegative subjects, a nominal value should be applied to the pre-vaccination samples to calculate the seroconversion rate.*

- **Secondary Analysis**
  - ❷ vs. ❸ <<interesting comparison!>>
  - For vaccines with 2-dose primary schedules, the immune responses after the first dose should be compared along the same lines as for the primary analysis.
- Present reverse cumulative distribution

- If administering parent vaccine is unethical: compare ❹ versus previously obtained data from ❶. Ensure same assays, matched population etc.
- **If ICP specific to vaccine construct**, vaccine as above with just the variant vaccine. The percentage of subjects that achieve titres at or above the ICP (i.e. the seroprotection rate) against the variant strain(s) (i.e. ❹) should be determined. Lower bounds of the 95% CI to be agreed with CHMP

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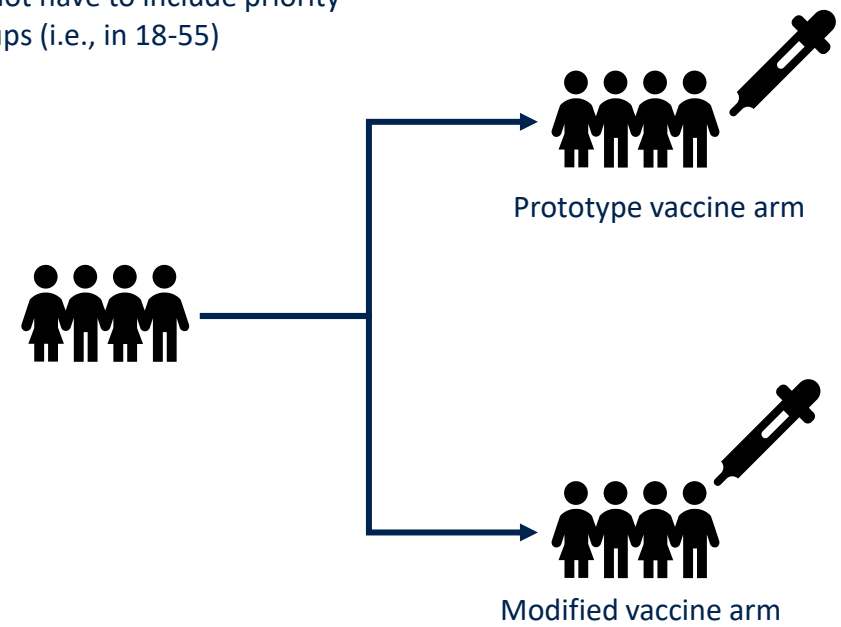
SARS-CoV-2-naïve subjects
i.e., unvaccinated and with no evidence of prior infection

Inclusion criteria

Unvaccinated
No prior Covid-19 infection
Do not have to include priority groups (i.e., in 18-55)

Primary series vaccination

Same dose schedule as approved for prototype



Neutralizing antibody titres

1 against prototype strain (original virus)	2 against variant of concern (interest)
4 against variant of concern (interest)	3 against prototype strain (original virus)

- **Primary analysis**
  - nAb seroresponse rate and GMTs for ❹ vs. ❶
  - non-inferiority margins of -10% for seroresponse rates and 1.5-fold for GMTs
- Additional Analyses (similarly specified for WHO guideline)
  - ❸ vs. ❶
  - ❹ vs. ❷

- If high SARS-CoV-2 seroprevalence precludes conducting studies in a SARSCoV-2 naïve population, then further considerations for characterization of baseline serostatus and vaccine-elicited antibody responses would be needed to ensure that data are interpretable
- Instead of prototype vaccine arm, may use serum samples from a previous study. Ensure same assays, matched population etc.

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Subjects previously vaccinated against SARS-CoV-2 i.e., “booster” strategy

Inclusion criteria

Previously vaccinated with parent vaccine primary series

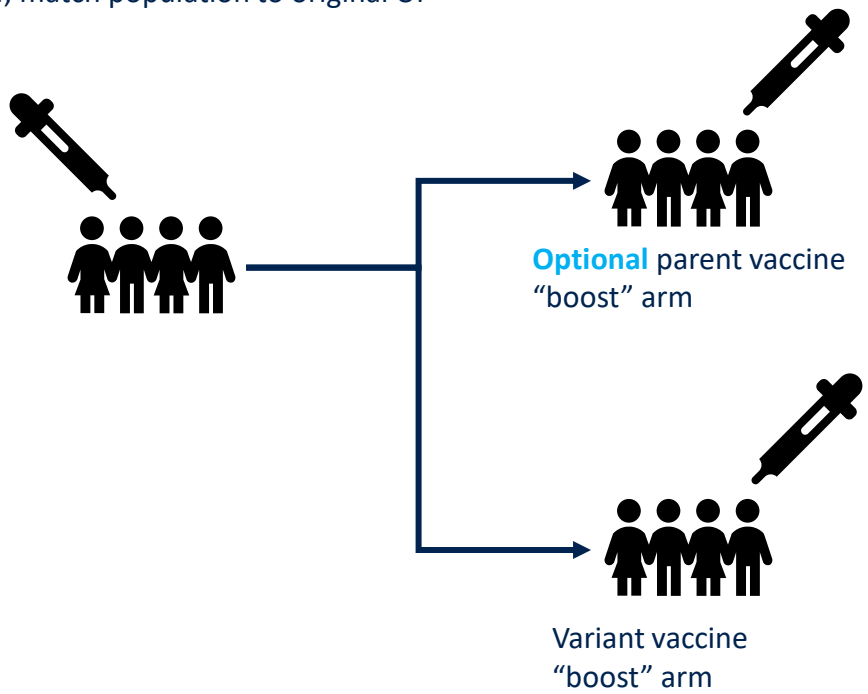
No prior Covid-19 infection

- *Data from previous CT so nAb titres available
- If data not available from previous CT, match population to original CT

Vaccination

Single dose “boost” vaccination

Justify interval between primary series and “boost”



Neutralizing antibody titres

5 ***Previous CT samples** against parent strain

6 ***Previous CT samples** against variant strain

2 Parent vaccine “boost” arm samples against variant strain

1 Parent vaccine “boost” arm samples against parent strain

4 Variant vaccine “boost” arm samples against variant strain

3 Variant vaccine “boost” arm samples against parent strain

- **Primary analysis**
  - nAb GMT ❹ vs. ❺
  - The lower bound of the 95% CI around the GMT ratio ≥0.67
- **Secondary Analysis**
  - nAb GMT ❹ vs. ❻
- Other secondary analysis
  - Comparing seroconversion rates :
    - ❺ vs. ❻
    - ❸ vs. ❹

Or if optional arm included

- nAb GMT ❹ vs. ❶
- The lower bound of the 95% CI around the GMT ratio >1

- Present reverse cumulative distribution

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- If ICP specific to vaccine construct, vaccine as above with just the variant vaccine. The percentage of subjects that achieve titres at or above the ICP (i.e. the seroprotection rate) against the variant strain (i.e. ❹) should be determined. Lower bounds of the 95% CI to be agreed with CHMP

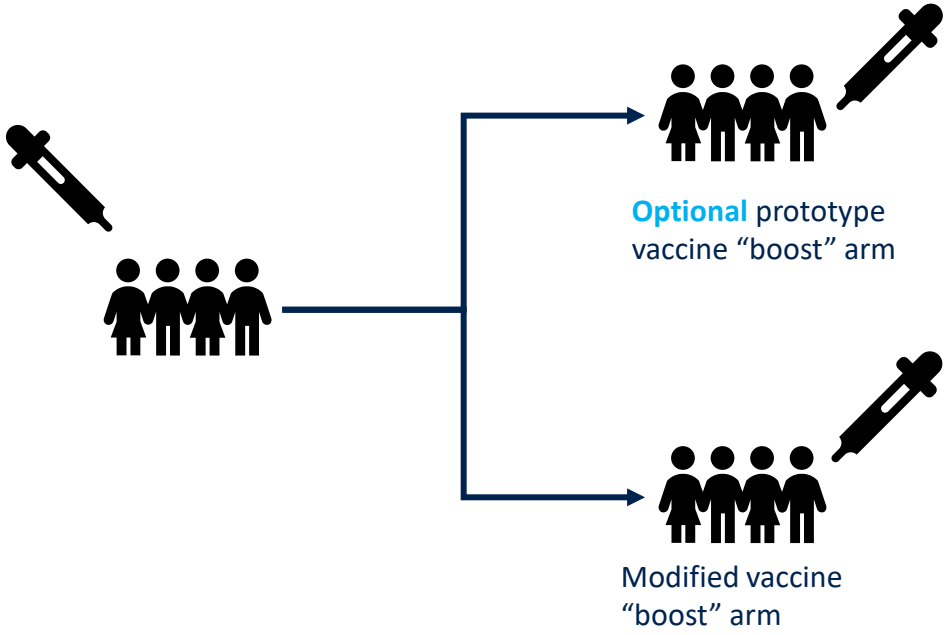
Subjects previously vaccinated against SARS-CoV-2 i.e., “booster” strategy

Inclusion criteria

Previously vaccinated with prototype vaccine primary series

Vaccination

Single dose “boost” vaccination



Neutralizing antibody titres

5 **Previous CT samples** against prototype (original) strain

2 Prototype vaccine “boost” arm samples against variant strain

4 Modified vaccine “boost” arm samples against variant strain

- **Primary analysis**
  - nAb seroresponse rate and GMTs for ❹ vs. ❺
  - non-inferiority margins of -10% for seroresponse rates and 1.5-fold for GMTs

Or if optional arm included

- ❹ vs. ❷

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ACCESS Guideline clinical considerations

- Guidance is less specific than the EU or US guidelines re the comparisons to be made – key differences highlighted

- **If *in vitro* assays from sera of subjects vaccinated with the current vaccine have shown that cross-reactivity with the new variant is not sufficient, a comparative study of the two vaccines may not be in the best interest of trial subjects,** a stand-alone immunogenicity and reactogenicity study would be appropriate
- Include both vaccine-naïve **and subjects already vaccinated** with the current vaccine version; depending on vaccine coverage, the latter may be the focus of the study.
- **Ideally include > 65 years old** <<*note "ideally"*>>.

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ACCESS Guideline other clinical considerations

- Other considerations
  - For a vaccine using a **viral vector, antibodies against the viral vector should be measured**. Enrolling subjects previously vaccinated within the pivotal trial might provide within-subjects **evaluation of the kinetics of antibodies against the viral vector** and their potential impact on the immune response to repeated vaccinations.
  - Consider additional studies e.g., **homologous vs. heterologous prime-boost regimen**, either of the same vaccine (current and new vaccine versions) or mixing with a vaccine from another platform.
  - **Data on concomitant vaccination e.g., with flu vaccine** (safety including reactogenicity, and immunogenicity) with either the original or the variant vaccine are welcome.
- Since an updated vaccine variant will build on a previously authorised parent version with established quality, safety and efficacy; from a public health perspective, **it may be justifiable to roll out the new vaccine candidate already in parallel with the previous version in absence of clinical immunogenicity and safety data while these studies are ongoing**. Such approach, only based on non-clinical data, will have to be discussed with Regulatory Authorities.
- For COVID-19 vaccines which are not yet authorised where an update to the SARS-CoV2 strain is considered, some considerations of this document may apply.
- Multivalent
  - Combination of a new sequence with the current sequence in the new vaccine version (i.e., generation of a bi- or multivalent vaccines) may necessitate additional immunogenicity studies to define the appropriate dose for each sequence and to investigate whether the addition of a second (or subsequent) sequence(s) does not result in an inferior immune response to vaccines with a single sequence. For example, competition at an mRNA level may occur and hamper immunogenicity.
  - The reactogenicity of the combination should be evaluated, for example in comparison to the single sequence vaccine.

WHO Guideline clinical considerations

- **If the prototype vaccine efficacy result was less than 60%, a stricter non-inferiority margin should be used**. This is to reduce the risk of listing/approving a modified vaccine with a lower vaccine efficacy than stipulated in the WHO "Consideration for evaluation of COVID19 vaccines," version November 2020.
- Data from booster studies in which the **prototype vaccine and modified vaccine** COVID-19 vaccine are administered to people who previously received the prototype COVID-19 vaccine **should be provided**
- Provide plan to gather effectiveness data on the variant COVID-19 vaccine

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ACCESS Guideline Clinical considerations

- If regimen is prime-boost, utilise subjects that have received the current vaccine version and randomise to the prime-boost regimen or one single injection to investigate the potential for cross-priming and whether one single injection is sufficient to elicit the same magnitude of response against the new variant as the prime-boost regimen. It may be possible to include this type of design as a sub-study or extension study to the ongoing follow-up of the pivotal trial
- Short-term data, up to 2 months depending on the vaccine regimen (e.g., up to 1 month after the second dose in a prime-boost regimen with a dosing interval of 4 weeks);
- Determine binding antibodies, neutralising antibodies and T-cell response (at least an Elispot assay). Responses should be measured against the current and new targets; The same assay should preferably be used with a change in the target analyte.
- In the absence of known CoP, comparison of sera from individuals vaccinated with prototype vaccine from the same platform should be undertaken. Demonstration of comparable titres **may not assure similar level of protection** as the correlation of antibody titres to effectiveness is not established. **Compare to a panel of sera from convalescent patients** infected with the new variant. Use standardised reference material e.g., WHO (NIBSC) International Standard and Reference Panel for anti-SARS-CoV-2 antibody. <<*important reference to WHO IS*>>
- **Immuno data of around 300 per arm** would provide for an acceptable level of precision for antibody data; for example, assuming a standard deviation on the log scale of about 1.25, 300 subjects would give precision of about 15% for geometric mean titres (e.g., if the point estimate was 100, the 95% CI would go from about 87 to 115). <<*explicit statement re the subject numbers needed*>>
- Comparing neutralising antibody titres raised against the variant after administration of the updated vaccine with those raised against the initial strain after administration of the current vaccine, adequate justification for the choice of the non-inferiority margin and the design of the study (head-to-head or a comparison to sera from previously immunised individuals) is expected. **Regulatory authorities will look at the totality of evidence presented at the time of approval** <<*subtle statement re totality of data in case the non-inferiority margin is missed)*

Safety data requirements

- Data collected during immunogenicity trials (28 days after vaccination?) should be sufficient
- Should include solicited local and systemic adverse events assessed daily for at least 7 days after each study vaccination
- Serious and other unsolicited adverse events (WHO guidance indicates - for the duration of the study)
- Additional safety may be required if safety signal arises from clinical studies

- ACCESS
  - **Specific immune power calculation** - The number of subjects exposed should inform reactogenicity e.g., around 300 per cohort (e.g., 300 vaccine-naïve subjects or 300 subjects already vaccinated with the current vaccine version) would achieve a precision of about ±5% in the estimate of reactogenicity based on the 95% confidence interval (CI).
  - It may be justifiable to **roll out the new vaccine candidate already in parallel with the previous version** in absence of clinical immunogenicity and safety data while these studies are ongoing.
  - **Updated Risk Management Plan** (including country-specific Annex/Addendum) would be required to ensure that adverse events can be appropriately captured for both the variant and prototype vaccine versions.
  - **Traceability** of the brand and batch, distinguishing suspected ADRs with new and old formulations and collecting quality information on immunisation and medical history need to be a key focus of the updated RMP

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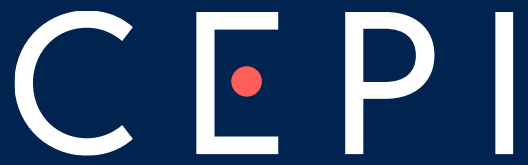
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Break

Part 2:

Use Cases &
Panel Discussions

Vaccine Clinical Development Plan- Approaches in the context of products with EUA

Anh Wartel, MD
Deputy Director General, CARE Unit,
International Vaccine Institute (IVI)

COVAX Workshop

SARS-CoV-2 Variants

Vaccine Clinical Development Plan

Approaches in the context of products with EUA

Anh Wartel, MD
Deputy Director General, CARE Unit, IVI
25th March, 2021

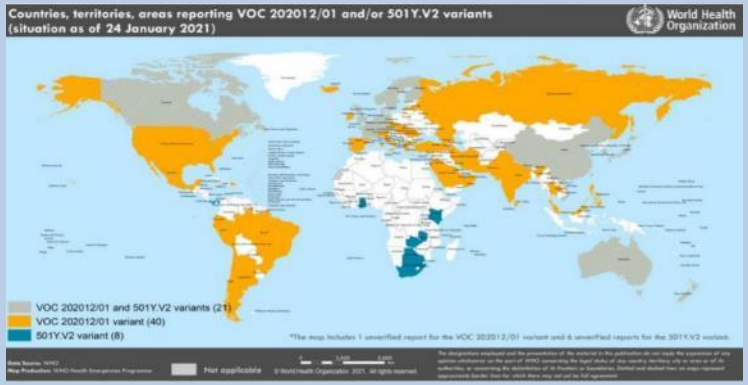
International Vaccine Institute

Background

- 310 vaccine candidates are being tested, as of mid-March 2021[1]
- 81 in clinical testing (i.e., 27 in phase I; 25 in phase I/II; 6 in phase II; ***18 in phase III***; and 5 in phase IV)
- At least ***13 in use***

- More than 447 million doses have been administered – Enough to vaccinate **2.9%** of the Global Population[2]

- SARS-CoV-2 variants have emerged since Q3, 2020: **UK** (B.1.1.7), **South Africa** (B.1.351), and **Brazil** (P1)[3]



- Concerns of variants: increased transmission; increased morbidity and mortality; **immune escape with reinfection risk and loss of efficacy**

Sources: 1) https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/; 2) https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/#global (Accessed on March 22, 2021); 3) https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update47-sars-cov-2-variants.pdf?sfvrsn=f2180835_4 (Accessed on March 25, 2021) ; 4) https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-march-2021 (Accessed on March 25, 2021)

Regulatory Update as of March 17, 2021

	Manufacturer	Name of Vaccine	NRA of Record	Platform
1.	Pfizer BIONTECH	BNT162b2/COMIRNATY Tozinameran (INN)	EMA	Nucleoside modified mNRA
2.	AstraZeneca Oxford	AZD1222	Core – EMA Non-COVAX	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
3.	SK BIO AstraZeneca Oxford	AZD1222	MFDS KOREA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
4.	Serum Institute of India	Covishield (ChAdOx1_nCoV-19)	DCGI	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.
5.	Sinopharm / BIBP	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	NMPA	Inactivated, produced in Vero cells
6.	sinovac	SARS-CoV-2 Vaccine (Vero Cell), Inactivated	NMPA	Inactivated, produced in Vero cells
7.	moderna	mRNA-1273	EMA	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)
8.	Janssen	Ad26.COV2.S	EMA	Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein
9.	The Gamaleya National Center	Sputnik V	Russian NRA	Human Adenovirus Vector-based Covid-19 vaccine
10.	康希诺生物 CanSinoBIO	Ad5-nCoV	NMPA	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)
11.	NOVAVAX		EMA	No pre-submission meeting yet.
12.	Vector State Research Centre of Virology and Biotechnology	EpiVacCorona	Russian NRA	Peptide antigen
13.	Zhifei Longcom, China	Recombinant Novel Coronavirus Vaccine (CHO Cell)	NMPA	Recombinant protein subunit
14.	IMBCAMS, China	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	NMPA	Inactivated
15.	Sinopharm / WIBP	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	NMPA	Inactivated, produced in Vero cells

- 15 vaccines are approved for emergency use by regulatory agencies and vaccines rollout programs on ongoing.

- **Vaccine efficacy** has been **documented** with various vaccine platforms in several countries, including those with the circulating variants.

- **In vitro immunogenicity data** are available against several **variants of concern**.

- There is a need to generate **additional clinical data** for EUA vaccines, **in the context of variants.**

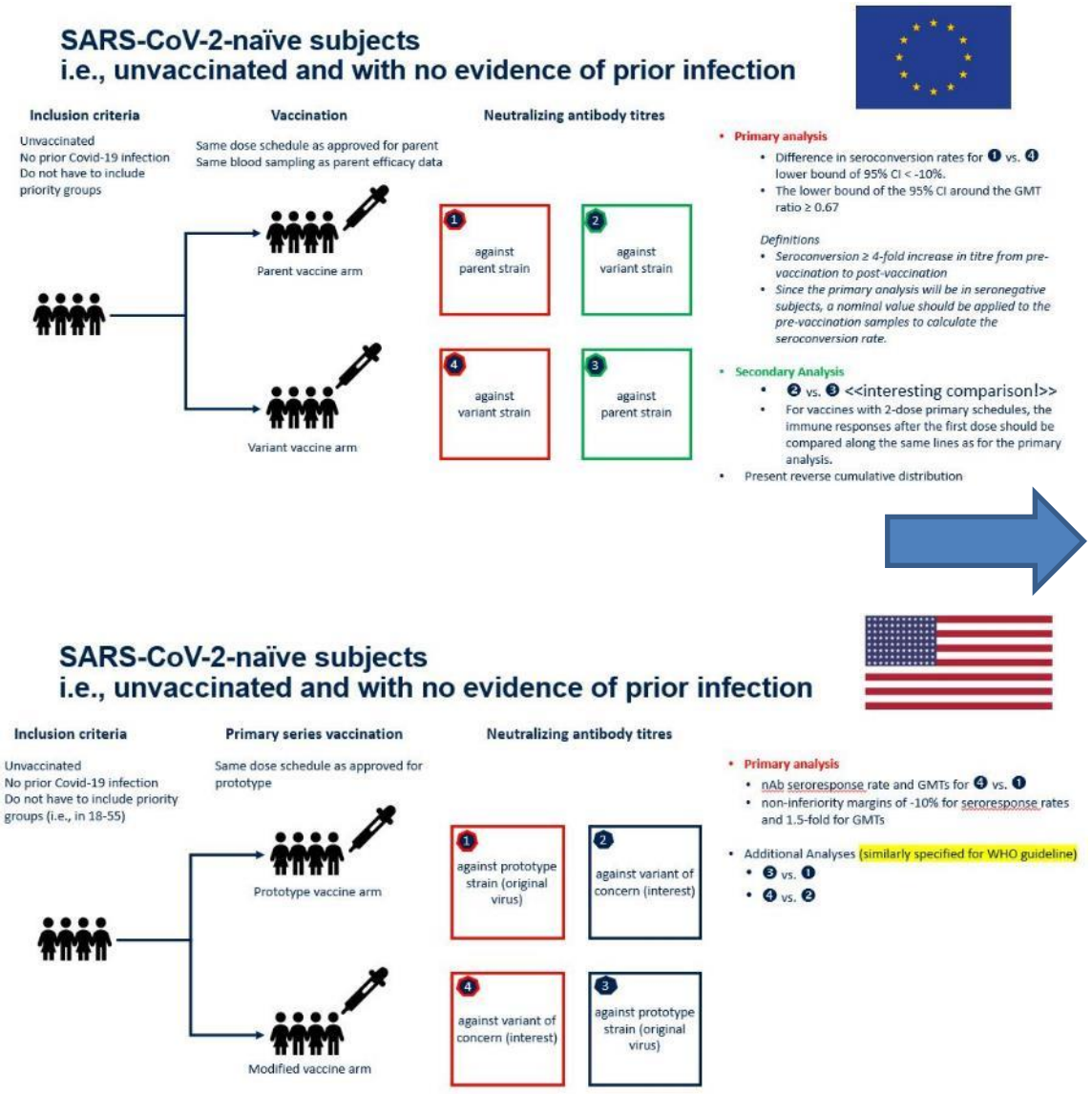
Source: 31st WHO Regulatory Update on COVID-19. 19th March 2021

Setting the scene - scenario we are focusing on…

- In terms of vaccine development stage and scientific knowledge, we have made **great progress**.
- **Several EUA vaccines** based on vaccine efficacy endpoints, with a satisfactory safety profile after regulatory review are approved.
- Data suggest a **strong correlation between humoral immune response and vaccine efficacy** with growing **acceptance by regulators**.
- Then **emergence of variants** is worrisome as well as its **implications on clinical development plans** for the **EUA vaccines**.
- **Available guidelines from EMA/US FDA/ACCESSS/WHO** helps in the design of additional studies in the post-authorization stage for vaccine developers – **Immune bridging based on non-inferiority studies** is encouraged.

Scenario	Vaccine type	SARS-CoV-2	Vaccine against original strain authorized?	Pivotal clinical trial ?	Comparator vaccine ?
1-2)	'adapted'	'variant' strain	yes	Immune bridging based on NI	'prototype' vaccine against original SARS-CoV-2 strain **(within platform)**

In light of EMA and US FDA regulatory guidance, additional considerations for discussion – Baseline and Immune Response Assessment



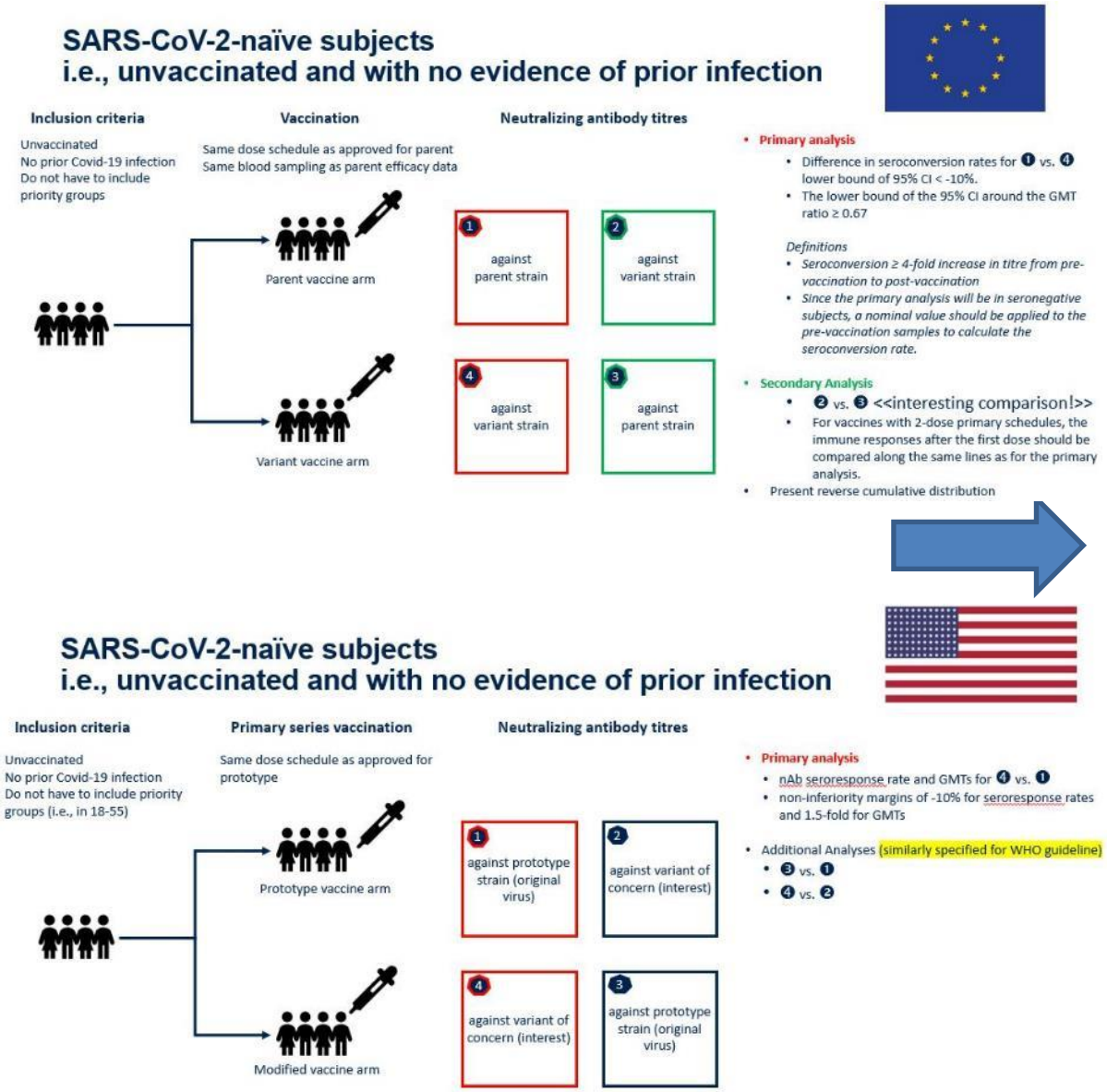
- **Countries** of choice for clinical trials **and study population for immunogenicity data comparisons** are **important.**

- Baseline and Immune Response Assessment
  - **EUA vaccine** (prototype vaccine) used as a **comparator** should be provided by the manufacturer.
  - Given the deployment of **National Immunization program and variants circulation**, baseline profile of the subjects enrolled may differ compared to the previous studies with the prototype vaccine. (i.e., **harder to find seronegative subjects** and **meet** the primary analysis with the **four-fold rise** definition).

⇒ Immunogenicity data comparison may be difficult since the **prototype** and **adapted vaccines populations don't match**.

- In case it is **unethical** to use prototype vaccine in clinical trial due to poor protection from variants and, therefore, a **historical control** is needed.

In light of EMA and US FDA regulatory guidance, additional considerations for discussion – Immunobridging assays



- Characterization: regulatory accepted, qualified immunological assays conducted under GCLP, and for clinical samples collected from EUA prototype vaccine comparator, and new variant vaccine-vaccinated participants

- Readout: *relative* immunogenicity to an appropriate control standard (e.g., NIBSC International Standard)

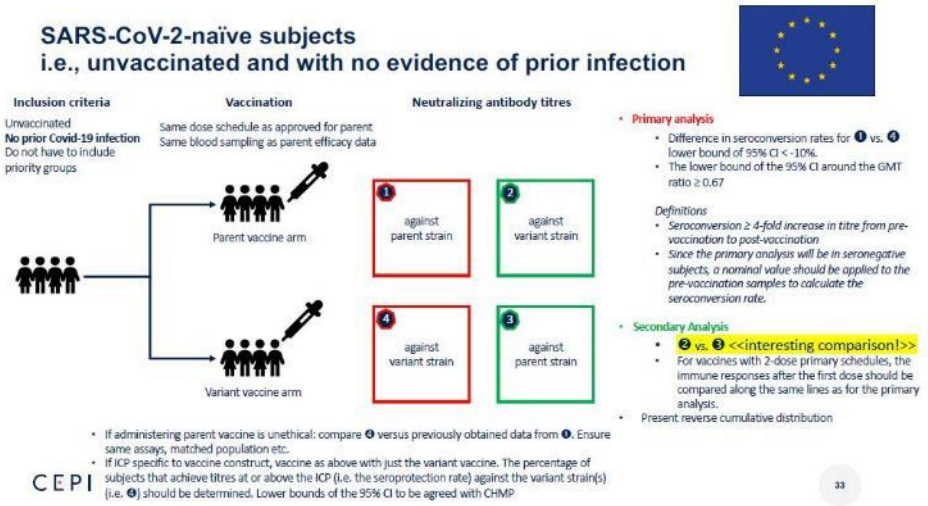
- Clinical relevance: demonstrated **clinical association** of **prototype vaccine immune bridging** readout to **vaccine efficacy** with one or more EUA prototype vaccine preferably including the same precedented prototype vaccine class; if feasible/available, clinical association of variant vaccine Immunobridging readout to variant strain.

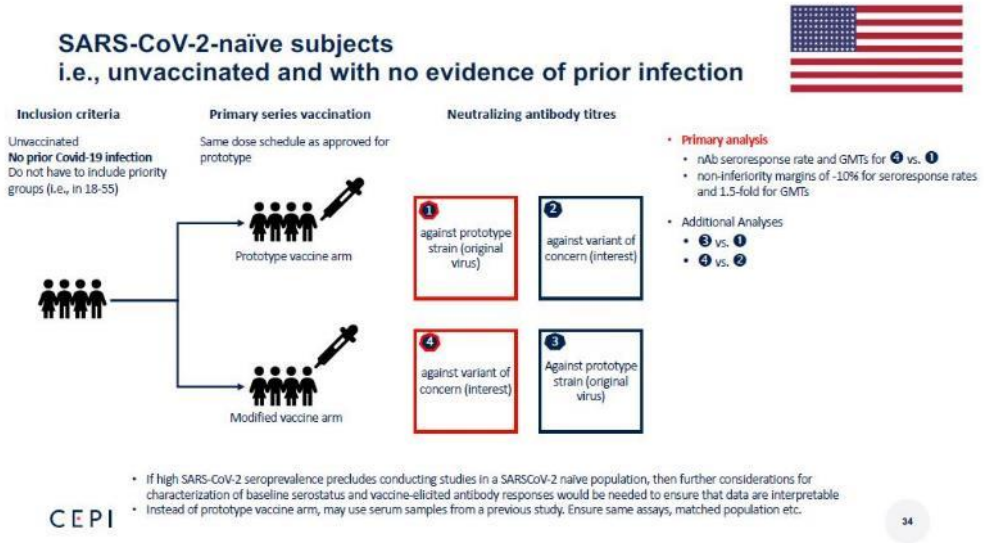
For example, robust evidence that neutralizing antibody (NAb) response to the variant strain:

- parallels the neutralization levels induced by the "prototype" vaccine to the prototype strain,
- matches or surpasses the neutralization levels observed among individuals infected with the variant strain

=> **Suggestive evidence** from **four** different COVID-19 platforms (mRNA, adenovirus, subunit adjuvanted and inactivated virus) supports a **relative NAb response** as a candidate **immunobridging assay**.

In light of EMA and US FDA regulatory guidance, additional considerations for discussion – Lab assays and variants availability





- According to US FDA, for variant vaccines using the same platform as used for EU approval, that **immunobridging** should be **acceptable** to approve variant/adapted vaccines comparing prototype neut Abs in a prototype neut assay to variant neut Abs in a variant neut assay.
- On one hand, it is encouraged to include the **International standard (IS)** as a benchmark.

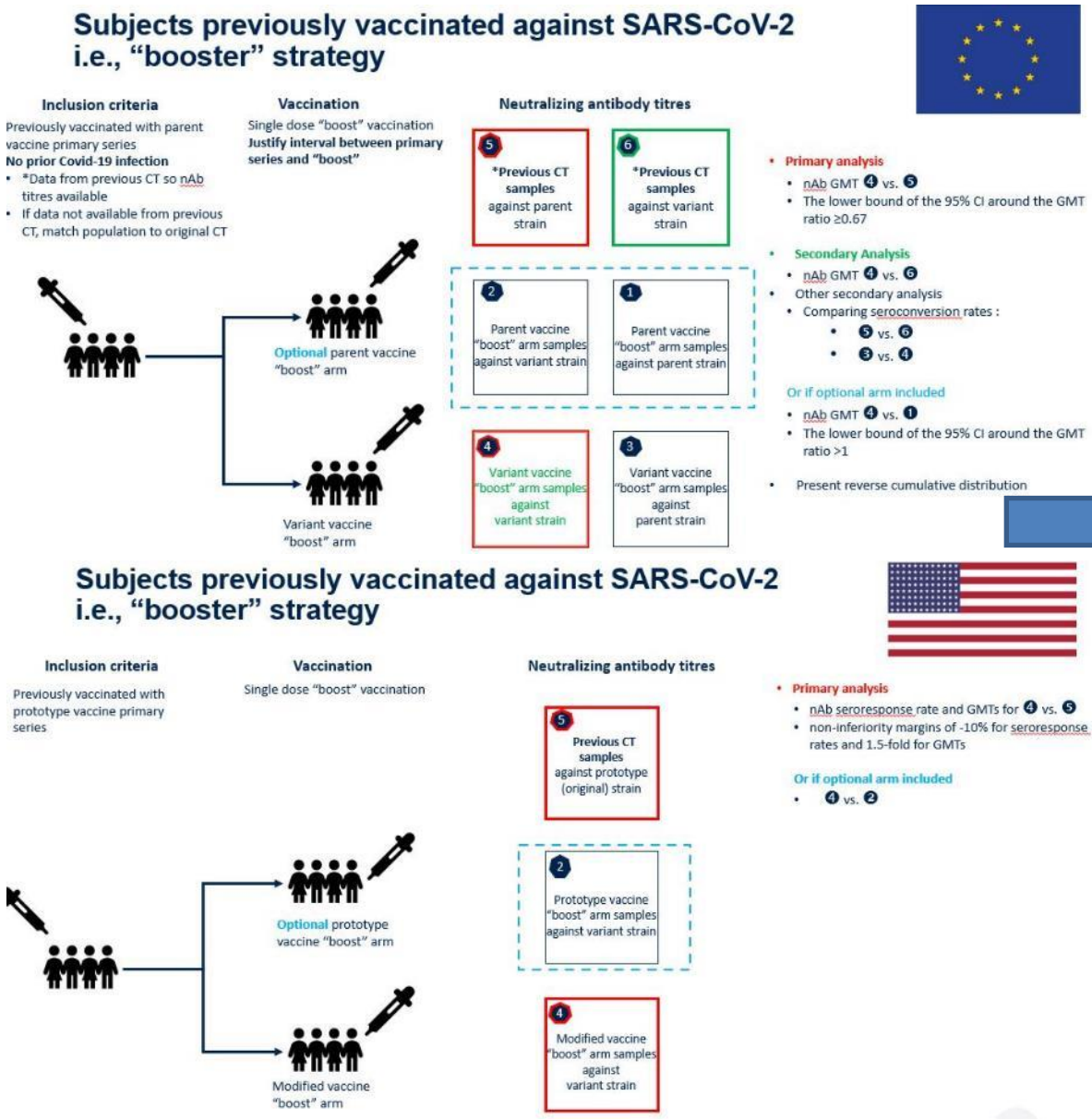
- However,

  - The CoV-2 prototype and variant NAb assays are not the same - will **be challenging to show NI for the variant**.
  - South Africa is reporting data and mentioning **differences** between viruses in cell culture.
  - An IS for each variant should solve this issue, but it will take some time.

- **Assay's characteristics** may have **an impact** on the readout of clinical sample testing (e.g., low or high titers with the adapted vaccine compared to the titers elicited with the prototype vaccine).

- For now, it would be good to get a **landscape of circulating variants of concern,** particularly **sequence-confirmation** of which variant did **infect** for the IS effort.

In light of EMA and US FDA regulatory guidance, considerations to be taken – Immune correlate of protection is known



- In **both scenarios** (i.e., SARS-CoV-2 naïve subjects and previously SARS-COV-2 vaccinated subjects),

- if **ICP is specific** to a vaccine construct, vaccine should be as above with just the variant vaccine. The percentage of subjects that achieve **titers at or above** the ICP (i.e., seroprotection rate) against the variant strain should be **determined**.

Furthermore, the **LB of 95% CI** should be **agreed** with CHMP in EU.

- **US FDA guidance**, **GMTs NI margin** require is **1.5 -fold increase.**

In light of ACCESS Guideline Clinical Considerations

- All guidelines (EMA/US FDA/ACCESS) recommend the collection of the **same safety data** (i.e., solicited local and systemic adverse events for at least 7 days post injection as well as serious and other unsolicited adverse events) during the immunogenicity trials with **short-term data** up to **2 months** depending on the vaccine regimen.
- Although the ACCESS guideline is less specific compared to EMA and US FDA guidance, there is recommendation on the clinical data **sample size for adapted vaccine**:
    - Immunogenicity bridging data: **300 subjects per arm**
    - Safety bridging data while accumulating the safety data from the prototype vaccine: **300 exposed subjects** (i.e., 300 vaccine-naïve subjects or 300 already vaccinated with the prototype vaccine) would achieve a precision of about **5%** in the estimate of **reactogenicity based on the 95% CI.**

⇒ <u>The clinical database may be sufficient if prototype data is considered.</u>

In light of ACCESS Guideline Clinical Considerations – Cont'ed

- Interestingly, from a public health perspective it may be **justifiable to roll out** the **adapted vaccine** candidate in **parallel** with the previous prototype vaccine:
  - in the **absence** of clinical safety and immunogenicity data,
  - as an **adapted vaccine** candidate will **build** on previously authorized prototype vaccine with **established quality, safety, immunogenicity, and efficacy,**
  - but such approach will have **to be discussed** with **Regulatory Authorities.**

⇒ <u>Engagement of developers with regulators is critical and urgent.</u>

Summary – Key takeaways

- **Guidelines from EMA/US FDA/ACCESS/WHO** have been issued early in the process and are **helpful** for vaccines developers.

- For vaccine developers that have prototype vaccine and have demonstrated efficacy, **immune bridging based on NI** is recommended by regulators – immunogenicity assumptions will **drive the size** of the trial.

- Generation of additional safety data should be **discussed with regulators**.

- Further clarity is needed – **what assays** are needed?; How to **interpret the NI** of immune response using **different assays** and potentially testing prototype and adapted vaccines in different populations?

More Considerations

- Wherever these new variant vaccines are tested and deployed, one must consider the following:

  - **pharmacovigilance** must be **strengthened** to assess the safety of these adapted vaccines;

  - **surveillance of emerging variants** under immune pressure is **crucial**; and

  - virus **sieve analysis** of breakthrough infections should be put in place.

- With sequences and characteristics of the vaccines, can we reeducate the immune response system? Are there any l**essons learnt** from **flu vaccine?...**

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Panel Discussion: Products with or without EUA, Full Registration

Moderated By:

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Discussion Panel Members – Variant vaccines adapted from prototype vaccine which already achieved authorization

Panel Members

- **Gustavo Mendes Lima Santos,** ANVISA (Brazil)
- **Phil Krause**, US FDA
- **Marco Cavaleri,** EMA

Speakers joining the panel:

- **Anh Wartel**, IVI
- **Sylvie Briand**, WHO
- **David Wood,** Independent Consultant
- **Adam Hacker**, CEPI

Potential Discussion Questions

1. **Reacting quickly to new variant strains:** Can you please share a few thoughts on (absence of) validated assays and (lack of) international standards for new variant strains regarding immunobridging trials?

2. **Without a quantitative CoP but with international standards in place** – could there be a pathway forward to authorize future COVID-19 vaccines adapted to new variant strains based on immunogenicity only (without immunobridging, e.g. influenza)?

3. **NI in seronegatives:** It will be increasingly difficult to recruit populations seronegative to both the original and the variant strain. Could this be reflected by using appropriately defined seroconversion rates (SCR) rather than seroresponse rates (SRR)?

4. **For 2-dose vaccines**, immunobridging will be assessed post 2nd dose. What are your thoughts regarding immunobriding post 1st dose in seropositives (to possibly establish single dose regimen in previously vaccinated / infected persons)?

Pathways for Approval of COVID-19 Vaccines Based on SARS-CoV-2 Variant Strains

Jorge Flores, MD

Margaret Toher, PhD

David Kaslow, MD

Center for Vaccine Innovation and Access (CVIA)

Mar 25 2021

Pathways for Approval of COVID-19 Vaccines Based on SARS-CoV-2 Variant Strains

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Pathways for approval of COVID-19 vaccines based on variant SARS-CoV-2 strains

Alignment on nomenclature used in this presentation

- **Prototype vaccine:** vaccine based in the original SARS-CoV-2 virus
- **Adapted vaccine:** vaccine against variant strain (based on the prototype vaccine)
- **Approval:** Emergency Use approval (EUA), Emergency Use Listing (EUL), Conditional Marketing Authorization (CMA)

Approval of adapted COVID-19 vaccines based on prototype vaccines not already approved

Framing the *Problem*

- Current regulatory guidance for adapted vaccines do not explicitly address manufacturers **without** an existing approved prototype vaccine
- Such manufacturers are considering parallel development of prototype and adapted vaccines; their prototype vaccine candidates fall into one of two classes:
  - Those with an approved **precedented** vaccine (e.g., mRNA, adenovirus, inactivated virus)
  - **Novel vaccines**, without existing approved prototype made by other manufacturer (e.g., recombinant subunit, DNA)
- Large placebo-controlled clinical efficacy trials have rapidly become infeasible to conduct

Framing the *Solution(s)*

- Given that current regulatory guidance provides an immunobridging pathway to approval for adapted vaccines for manufacturers with approved prototype vaccines, under what conditions and by what clinical design might immunobridging studies be an acceptable pathway for approval of adapted vaccines from manufacturers without an approved prototype vaccine
  - if adapted vaccine is based on a **precedented** class?
  - if adapted vaccine is based on a **novel** class?
- When immunobridging is not an acceptable pathway for approval, then what alternative clinical efficacy trials might feasibly be conducted?

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Three simplifying assumptions for a new adapted vaccine based on precedented prototype vaccine class

- ***Efficacy:***

  Approval of adapted vaccines based on immunogenicity bridge to an existing approved prototype vaccine by another manufacturer
  - *Immunobridging has been used to bridge immunogenicity to efficacy through use of another manufacturer's approved vaccine (e.g., meningococcocal and pneumococcal vaccines)*
  - *Data from testing COVID-19 vaccines from diverse platforms indicates a strong correlation between the vaccine induction of neutralizing antibodies and clinical efficacy*

- **Safety:**

  Robust combined prototype and adapted vaccines safety databases submitted for approval review
  - *Safety can also be bridged between an adapted vaccine and its prototype vaccine manufactured in the same platform*

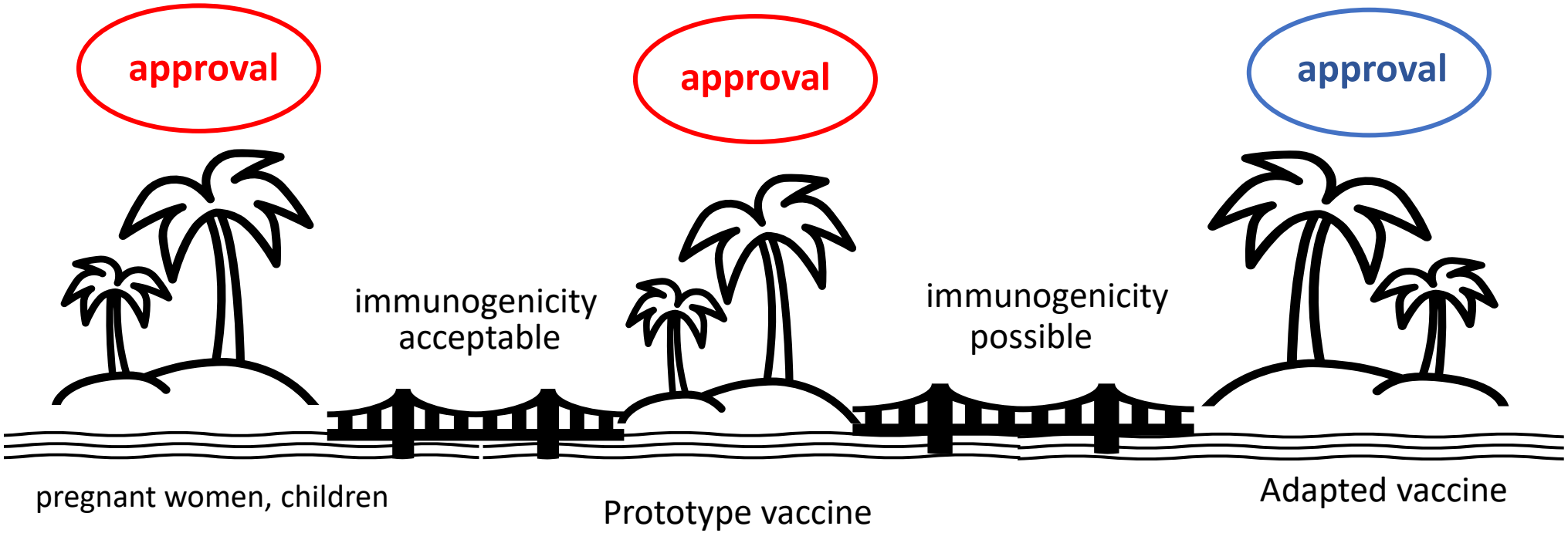
- **Post-approval commitments:**

  Conduct and report during initial post-approval introduction
  - clinical endpoint data (effectiveness)
  - additional safety data through active and passive surveillance (pharmacovigilance)

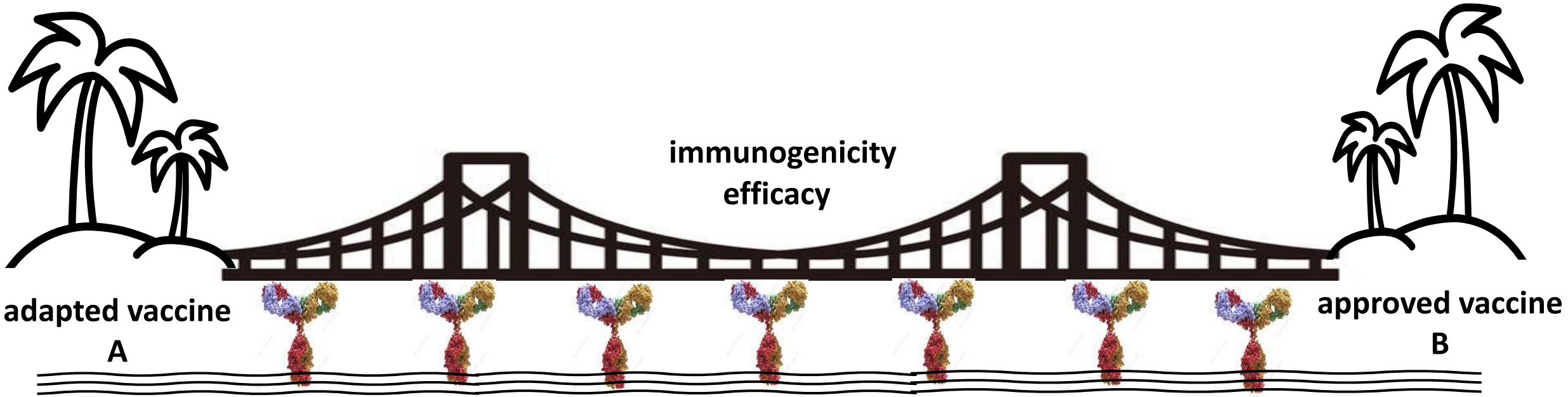
Expedited approval of adapted vaccines

for vaccines already approved for emergency use

(as discussed in the previous presentation)



Approval of adapted vaccines when a prototype vaccine has not yet been approved



Early clinical development of adapted vaccines

Objectives:

- Prove safety
- Bridge immunogenicity to prototype vaccine (if available)
- Bridge immunogenicity to approved adapted vaccine from different developer*

Endpoints:

- Safety (reactogenicity, AEs, SAEs)
- Neutralization of parental and variant strains

Study arms:

- Adapted vaccine
- Prototype vaccine from same developer and/or
- Approved prototype vaccine from different developer*

~ 300 subjects per arm

Analysis:

- Non-inferiority of seroresponse rates and GMT

**** Possible for vaccines using similar platforms***

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Advanced development of adapted vaccines

Try to exploit the potential for **immunobridging** as much as possible

- to a previously approved adapted vaccine manufactured with the same / similar / equivalent platform
- to a previously approved adapted vaccine manufactured with different platform

When no immunobridging is possible (different antigens, different platforms, different mechanisms of action) clinical efficacy will have to be proven

Advanced development of an adapted vaccine when a prototype vaccine is in development

When adapted vaccine in the same class is approved

	Phase 3
Purpose	Bridge to approved adapted vaccine from a different manufacturer
Objectives	IMMUNOBRIDGING
	SAFETY
Arms	2 arms: adapted vaccine, approved adapted vaccine
Key Comparisons	NAb non-approved vs approed adapted vaccine
Approximate size/arm	2-3K

When no approved adapted vaccine is available to bridge or the vaccines belong to different classes

	Phase 3
Purpose	Direct Demonstration of Vaccine Efficacy
Objectives	CLINICAL EFFICACY
	SAFETY
Arms	2 arms: adapted vacccine, prototype vaccine
Key Comparisons	Covid-19 Attack rates adapted vaccine vs comparator
Approximate size/arm	20-30K

Sequential immunobridging
Adapted vaccine to approved prototype vaccine of a different class

Platform A = Prototype and adapted subunit vaccines

Platform B = Approved prototype recombinant Adeno vaccine

		N subjects	
Step 1	Vaccine	Safety population	Immunogenicity subcohort
arm 1	Platform A prototype vaccine	3000	300
arm 2	Platform B approved prototype vaccine	3000	300
Step 2			
arm 3	Platform A adapted vaccine	3000	300

** Immunogenicity endpoints: Neutralizing antibody to Prototype and variant viruses

Analytical approach

	comparison	endpoint	design	Criterion 1	Criterion 2	
STEP 1	arm 1 vs arm 2	NAb to original strain	Non-Inferiority	GMT 0.67-1.5X*	S-response rate (-10%)*	If criteria met go to step 2
STEP 2	arm 2 vs arm 3	Nab to variant	Non-Inferiority	GMT 0.67-1.5X*	S-response rate (-10%)*	if critria met, submit for approval

The More Challenging Path to approved for Variant Vaccines Whose Prototypes are not yet Approved

More straightforward pathway
(EU approved for prototype)

- EU approved prototype
- same manufacturer
- monovalent
- same platform
- same formulation
- no new adjuvant
- similar construct
- same route
- same schedule
- different sequence

- prototype not approved
- different manufacturer
- bivalent - polyvalent
- different platform
- different formulation
- different adjuvant
- different construct
- different route
- different schedule
- different sequence

Examples:

- Biosimilars *("identical" but manufactured by a different developer)*
- "Similar" platforms *(e.g., new Ad vector)*
- New inactivation method
- New adjuvant
- Additional doses
- Intranasal administration
- Mixed with initial vaccine (bivalent)

If two or more variables are introduced at the same time – can immunogenicity bridging be applied?

If two or more differences are introduced concurrently – will immunobridging still be acceptable?

1. prototype not approved
2. bivalent - polyvalent
3. different platform
4. different formulation
5. different adjuvant
6. different construct/core sequence
7. different route
8. different schedule
9. different strain sequence
10. different manufacturer

If Immunobridging is not allowable, what clinical studies need to be conducted for new adapted vaccines

- Comparator clinical efficacy trial with a variant-matched approved adapted vaccine (non-inferiority / superiority)

  it will be challenging to identify an approved adapted vaccine comparator

- Comparator efficacy trial with an approved prototype vaccine

  This will be required if there is evidence that the epidemics is mixed, included continuing circulation of the prototype strains

  A placebo-controlled study could potentially be justified if the variant has "taken over" the epidemics.

- Effectiveness study

  Would the regulators / country authorities allow the conduct of a circumscribed effectiveness study (e.g., a stepped-wedge designed trial)? before and towards approved

Notes:

1) The studies above would have to be properly powered to meet the original efficacy expectations from WHO, FDA, EMA, etc.

2) For efficacy evaluations the adapted vaccine under test does not necessarily have to share features with the comparator vaccine (i.e., different platform, adjuvant, are OK)

PATH

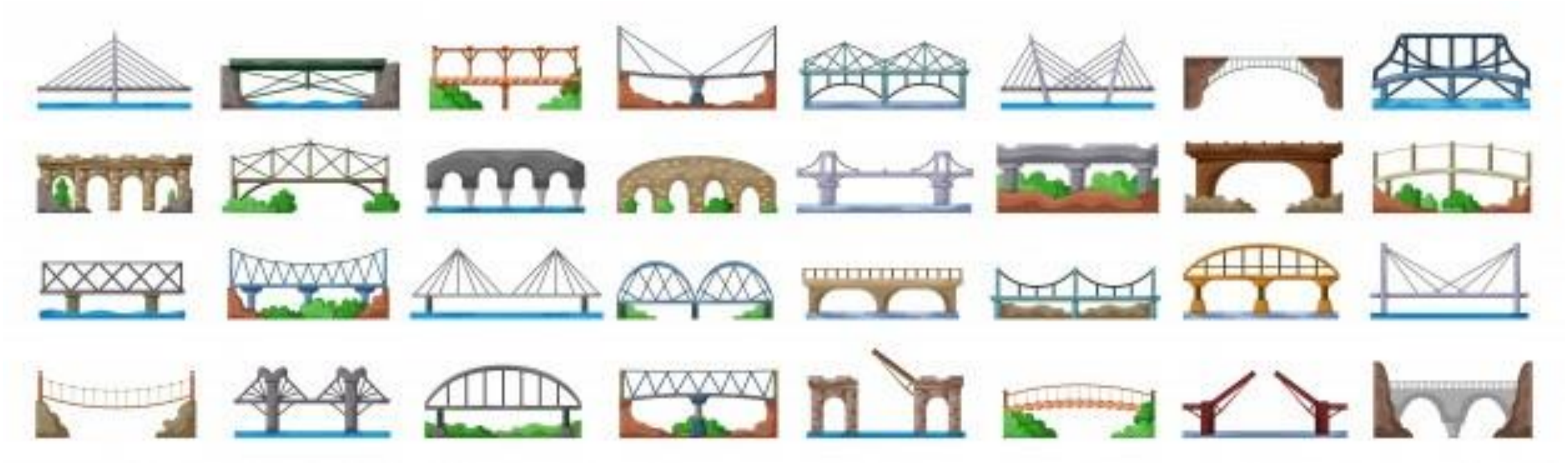
Summary: key takeaways

- **Immunobridging (IB):** a potential expedited pathway for new adapted vaccines from manufacturers without existing approved prototype vaccines, particularly when adapted vaccine based on precedented class of approved prototype vaccine is available
- Likelihood of acceptance depends on difference between new adapted vaccine candidate to approved prototype vaccine providing immunobridging (platform, adjuvant, etc.)
- Sufficiently large safety database will be needed
- Post-approval pharmacovigilance and effectiveness studies shall be initiated at introduction
- If immunobridging is not acceptable and
  - An approved adapted vaccine is available as a comparator, then non-inferiority efficacy studies may be the next best alternative; however, the study size may be infeasible
  - No approved vaccine is available with demonstrated efficacy against the variant(s) of concern, then clinical efficacy trial design will depend on the circulating strains and efficacy of the available approved prototype comparatorv; in rare instances, a placebo-controlled trial might be feasible to conduct

Additional research needed to inform decisions re. immunobridging vs clinical efficacy trial

- Further characterize the Immune response to variant strains.
- Develop standard reagents (antibodies and virus panels) and validate assays
- Continue work on Correlates of Protection
- Refine preclinical challenge models
  - Passive transmission of human antibodies
  - Cross-protection studies
- Develop CHIM
- Strengthen natural history studies:
  - Breadth and evolution of the immune response
  - Emergence of sequence variants at the individual level
- Response to vaccination among previously infected subjects
  - With the original virus
  - With variant vaccines

Thanks!



Jorge Flores, Margaret Toher and David Kaslow

Panel Discussion: Products in Development Without Path to Efficacy / EUA

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Discussion Panel Members: Pathway for variant vaccines for which no prototype vaccine has been authorizied

Panel Members

- **Gustavo Mendes Lima Santos,** ANVISA (Brazil)
- **Phil Krause**, US FDA
- **Marco Cavaleri,** EMA

Speakers joining the panel:

- **Jorge Flores**, CVIA
- **David Kaslow,** CVIA
- **Sylvie Briand**, WHO
- **David Wood,** Independent Consultant
- **Adam Hacker**, CEPI

Potential Discussion Questions

1. **Platform pairings?:** An immuno-bridge "across vaccine platforms" is a challenging request. Are there certain platforms more amenable to such comparisons (e.g., sub-unit to inactivated? vector to RNA?)

2. **Safety database?:** Studies have been very large for initial efficacy studies driven by the need to accumulate sufficient cases rapidly. Presuming a licensure pathway is found acceptable based on immunogenicity, is 3000 vaccine-exposed subjects a reasonable target for an adult indication with a known vaccine platform?

3. **Comparator vaccine?:** There are real and practical challenges to acquiring sufficient quantity of comparator vaccine for head-to-head studies. If the 'appropriate' comparator is not accessible, are there design consideration a sponsor can propose to mitigate concerns (e.g., superiority success criteria)

4. **Beyond antibodies?:** What additional immunologic characterization is minimally expected in phase 3 if the phase 1 and 2 studies have extensively characterized the product if cross-platform comparisons are entertained?

5. **Back neutralization?:** What are implications of lower neutralizing antibodies from the variant vaccine against the prototype virus in comparison with prototype vaccine against prototype virus, presume response are well above HCS panel titers?

Wrap Up & Next Steps

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Closing remarks

- Thank you all for your participation and engagement today
- Workshop report distributed shortly to summarize today's conversation
- We will continue to share resources at the website here: https://epi.tghn.org/covax-overview/clinical-science/
- Please consider sharing your thoughts and suggestions on this and/or future workshop in our Discussion Forum https://epi.tghn.org/community/groups/group/cwsg/
- Next workshops:
  - COVAX Maternal Immunisations WG: 13th April 2021
  - COVAX CMC/Clin Dev SWAT teams: 14th April 2021 (multivalent COVID-19 vaccines)
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines

Clinical Development & Operations SWAT Team