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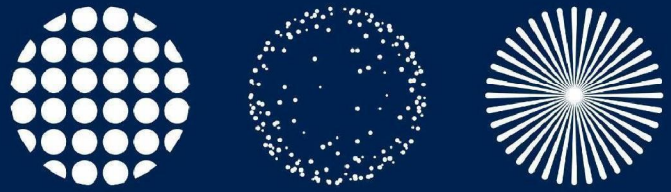
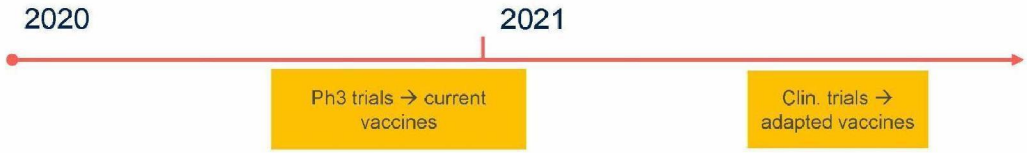
Clinical Development Aspects Regarding Vaccine Adaptations to New Variants

5.1.2e

18th February 2021



The pandemic has evolved since its beginning: Implications for clinical development



	2020	2021
Population immunity	Vast majority immune-naïve	Increasing proportion seropositive – either through natural infection or vaccination
Match: vaccine strain → circulating SARS-CoV-2 strain	Almost perfect (exceptions…)	Increasingly suboptimal - with new variants emerging / replacing original D614G strain
Vaccination coverage	Vaccines not licensed / not available	Vaccines increasingly rolled out – in particular in high risk groups
Vaccine efficacy	Established based on large conventional placebo-controlled vaccine efficacy trials	Placebo-controlled trials increasingly difficult in certain countries / populations → alternative approaches
Correlate of Protection (CoP)	Absent	Emerging evidence pointing at nAbs → hope for CoP established based on various sources of evidence, including breakthrough cases from Ph3 VE trials

COVID-19 Vaccines Against New Strains: Options

I. Address new variants with **currently approved vaccines:** Mix & Match, prolonged dosing intervals, …

II. Vaccine adapation against new variants

a) Based on **approved 'prototype' vaccines** (against original strain)

b) Licensure of **new vaccines ('wave 2')** against new strains without approved 'prototype' / without availability of evidence supporting vaccine efficacy of the 'prototype'

III. Monovalent versus **bi-/multivalent vaccines**

I. Available COVID-19 Vaccines: "Mix & Ma

1. **Improve immune response**
   a) Breadth of IR
   b) Duration
2. **Address practical / operational aspects** ('interchangeability' of vaccines)

Concepts:

- **Heterologous primary immunization:** A - B
- **Heterologous boosting:** A – A B

Questions:

- Appropriate priming?
- Relevant platform combinations?

3 – 12 wks months - >1 yr

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II. Vaccine Adaptation Against New Strains

- **a) Approved 'prototype'** *versus* **b) New ('wave 2') vaccines**
  - a) 'Protoype': immunologic bridging (NI)
  - b) New vaccine: immunologic bridging (NI) – followed by confirmatory clinical efficacy?

- **Dosing regimen** (most vaccines based on 2 doses for PI in immune-naïves):
  - Primary series versus single booster:
    - Immune response post natural infection
    - Immune response post vaccination with 'original' vaccine
  - Will we differentiate between primed / naïve (or do we need one general regimen)?
  - Dose sparing
  - Different platform preferable for 'boost' against new strain (heterologous boost)?

Immune Bridging / Immunologic Non-Inferiority

- **"Vaccine immune response is reasonably likely to predict protection against COVID-19"**
  [*Development and Licensure of Vaccines to Prevent COVID-19*, FDA Guidance Document]
- Neutralising antibodies (?)
- NI based e.g. on GMTs, NI margin to be aligned (alternative: GMT threshold?)
- GMTs in seronegatives versus seropositives
- Separately for the original strain and the new strain (NI may differ based on original versus new strain assays)
- Validated assays, international standards…
- Followed by confirmatory vaccine efficacy or effectiveness study?
- What if GMT for new vaccine is outside NI margin but vaccine efficacy exceeds WHO / NRA criteria for vaccine efficacy (primary endpoint ≥50%, lower bound >30%)?
- What will be the comparator vaccine?
  - Same product ('original' vaccine)
  - Same / similar platform (e.g. subunit and WIV)
  - Alternative (across) platform?

Access to comparator vaccine?

Clinical Vaccine Efficacy: WHO Guidance for PQ

- At least 50% vaccine efficacy against COVID-19 (regardless of severity); mild symptomatic, moderate, and severe disease; hospitalizations and death. Lower bound of alpha-adjusted CI >30%
- A lower bound ≤30% but >0% may be acceptable for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.
- For non-inferiority comparison based on efficacy to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of alpha-adjusted CI around the primary relative efficacy point estimate is >-10%.

[Considerations for the Evaluation of COVID-19 Vaccines. WHO 25th November 2020]

Primary Endpoint Definitions in Current Phase 3 VE Trials

Objective: To evaluate VE against confirmed COVID-19 as compared to placebo.

	Moderna	Pfizer/BNT	Novavax	J&J	Oxford/AZ
Primary Endpoint	Prevention of first occurrence of protocol-defined symptomatic COVID-19 **regardless of disease severity**	Efficacy against (first) confirmed symptomatic COVID-19 **regardless of disease severity**	Prevention of first case of symptomatic COVID-19 **regardless of disease severity** – defined for the primary efficacy endpoint as: • Positive RT-PCR AND • Mild COVID-19 OR • Moderate COVID-19 OR • Severe COVID-19	Prevention of first occurrence of **moderate to severe/critical COVID-19** defined as: • Positive RT-PCR or other NAAT AND • Moderate COVID-19 (**Any ≥1** of: RR>20/min, abnormal SpO2 > 93%, pneumonia, DVT, or dyspnoea **OR Any ≥2** of: fever, chills/rigors, cough, malaise, headache, myalgia, gastrointestinal symptoms, anosmia/ageusia, or limb rashes) OR • Severe/critical COVID-19	Prevention of first case of symptomatic COVID-19 **regardless of disease severity**
Baseline status	PCR & anti-N-ab negative at baseline	no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection	SARS-CoV-2 negative at baseline	SARS-CoV-2 negative at baseline	Not seropositive at baseline

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Moving Forward: VE Based on Clinical Endpoints?

- **Randomised controlled trial design challenging**:
  - Placebo-controlled:
    - Inclusion of high-risk groups ⇒ increasingly difficult
    - Lower risk of exposure & mortality ⇒ fewer events → larger samples size and / or longer F/U
  - Active comparator:
    - Clinical superiority compared to partially effective vaccines
    - Clinical non-inferiority compared to vaccine with 'established' VE

    However, can an adapted vaccine be compared against an 'original' vaccine (with new strain dominating)?
- VE trial **primarily based on clinical endpoints** *versus* **confirmatory following immunologic NI**?
  - At least 50% VE: Relax lower bound?
- **Primary endpoint** (with large proportions being seropositive / imperfect match of vaccine / circulating strains):
  - Is it still appropriate / feasible to assess VE against COVID-19 **regardless of severity in seronegatives**?
  - **De-risk** with additional dual primary endpoints (e.g. true moderate-severe, BoD)?

Vaccine Safety

- Safety database of n=3,000 exposed or less (e.g. for emergency approval)?
  → can developers leverage on evidence available (from large Ph3 trials) for 'original' vaccine?
  - … same product
  - … data from comparable platforms
- Anti-vector immunity
- Antigenic sin re boost with adapted vaccine / multiple circulating SARS-CoV-2 variants
  - VMED
- Feasibility of long-term safety F/U
- Vaccine adaptation based on variation (same product) → both monovalent vaccines used in parallel in case 'original' and new strain co-circulate: how to track vaccine-specific safety events post licensure?

Main Points for Consideration

I. **'Mix & Match'** (heterologous priming / heterologous boosting)

II. **Vaccine adaptation** *versus* **new vaccine**

III. **Monovalent** *versus* **multivalent**

- Establishing VE: based on **clinical** or **immunologic** endpoints
- Safety database: **leverage on existing data**


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