Summary Document

Topic: Comparative Immunogenicity Trials of Novel Candidate COVID-19 Vaccines in a Seropositive Population

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Disclaimer: This document provides a summary of key points from the literature, guidelines or other documents from experts on the subject matter, including from national and multilateral organizations and authorities. This document does not aim to be exhaustive. Due to the rapidly evolving situation, this summary document may not include latest evidence and updates are likely. New versions will be issued when significant new information becomes available. Its purpose is to support organizations and institutions involved in the development of COVID-19 vaccines. It is the responsibility of each vaccine developer to review available evidence, take into account relevant guidance and recommendations, and to seek scientific advice from regulatory agencies as appropriate.

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Overview:

The seroprevalence of SARS-CoV-2 is approaching 100% in most settings worldwide, either through vaccination, infection, or both (hybrid immunity). Thus, all future COVID-19 vaccines will largely serve to boost pre-existing immune responses. In this Summary Document (SD), we therefore discuss cross-platform comparisons of COVID-19 vaccine-induced immune responses in a predominantly seropositive population and possible design features of a Phase 3 clinical trial.

The rapidly changing SARS-CoV-2 environment must be considered when designing Phase 3 comparative immunogenicity trials for new COVID-19 vaccines. SARS-CoV-2 is currently transitioning from a pandemic to endemic phase and from original to Omicron strain, with subsequent waves caused by Omicron-related variants not unlikely. In addition, trial settings are nearing universal seropositivity. As a result, future trial populations will largely include primed individuals, with rapidly increasing hybrid immunity. This SD addresses the current regulatory guidance for new COVID-19 vaccine development and discusses 'comparative immunogenicity' versus 'immuno-bridging' considering the rapid transition to universal seropositivity and hybrid immunity. Factors which require consideration include:

i. The constancy assumption
ii. The surrogate endpoint
iii. The protection equation
iv. Platform differences
v. The efficacy of the comparator vaccine
vi. The effect of baseline titres on immune responses

A comparative immunogenicity trial should be considered in the context of vaccines developed to boost pre-existing immunity. Given the lack of a well-established, broadly applicable correlate of protection (CoP) for COVID-19, the emphasis will be on the totality of immune responses, with a provision of post marketing effectiveness data as confirmatory evidence of clinical benefit.

This SD discusses Phase 3 **comparative immunogenicity studies** for the clinical development of novel candidate COVID-19 vaccines in a SARS-CoV-2 seropositive environment. This SD is structured into the following two parts:

- **Part A** provides the background for comparative immunogenicity studies and discusses this approach to support authorisation of novel COVID-19 vaccines. It briefly addresses the current regulatory guidance for new COVID-19 vaccine development and discusses 'comparative immunogenicity' versus 'immuno-bridging' considering the rapid transition to universal seropositivity and hybrid immunity.
- **Part B** provides considerations for a pragmatic clinical development approach and discusses key design features, including key trial entry criteria and immunogenicity objectives and endpoints, in Phase 3 clinical development trials in a seropositive population.

PART A: BACKGROUND

Introduction: The seroprevalence of SARS-CoV-2 is approaching 100% in most settings worldwide, either through vaccination, infection, or both (hybrid immunity). Thus, all future COVID-19 vaccines will largely serve to boost pre-existing immune responses. In this SD, we therefore discuss cross-platform comparisons of COVID-19 vaccine-induced immune responses in a seropositive population and possible design features of a Phase 3 clinical trial.

Clinical disease endpoint trials are the gold standard for the authorisation of vaccines. When such efficacy trials (placebo or active-controlled) are no longer practical to conduct, other approaches can be considered for licensure of novel COVID-19 vaccines. While regulatory authorities have issued guidance on immuno-bridging, these now require adaptation to the current, near-universal, seropositive environment.

Immuno-bridging means inferring the clinical efficacy of a comparator vaccine, as estimated in a controlled trial, to a candidate vaccine by means of the vaccine-induced immune responses, when the setting of the head-to-head immuno-bridging trial reliably represents the setting of the efficacy trial of the comparator vaccine (i.e., the constancy assumption). Vaccine efficacy (VE) of the novel candidate vaccine is inferred when non-inferior or superior immune responses of the candidate vaccine are demonstrated relative to a licensed comparator vaccine for which efficacy or effectiveness in preventing a specific disease outcome has been established, providing the constancy assumption applies.

Within-platform immuno-bridging: Early in 2021, regulatory guidance (WHO, EMA, FDA, ACCESS) proposed immuno-bridging as an acceptable approach for licensure of variant of concern (VOC)-strain adapted monovalent COVID-19 vaccines if the modified vaccine is manufactured using the same platform and process ('within-platform') as the authorised prototype vaccine (1–4). The guidance presumed that within-platform immuno-bridging trials would include seronegative populations. With the expectation that the Omicron VOC would replace the Delta VOC and that the development of an Omicron vaccine would primarily be to boost and broaden pre-existing immune responses, CEPI discussed within-platform immuno-bridging in a predominantly seropositive population in a previous SD (5).

Cross-platform immuno-bridging: Later in 2021, the MHRA published a consensus among ACCESS Consortium members providing additional considerations for 'cross-platform' immuno-bridging as an acceptable approach for authorising novel COVID-19 vaccines (6). The guidance however preceded the Omicron wave and assumed that cross-platform immuno-bridging trials would include seronegative populations. Several developers were able to perform cross-platform immuno-bridging trials in seronegative populations, including SK Bioscience, Biological E, and Valneva (7–9); however, the window of opportunity to perform such trials is closing fast. This SD therefore discusses cross-platform comparative immunogenicity trials in a predominantly seropositive population.

Designing comparative immunogenicity trials: Several factors should be considered when designing Phase 3 comparative immunogenicity trials for authorising new COVID-19 vaccines. Factors which require consideration include:

vii. The constancy assumption
viii. The surrogate endpoint
ix. The protection equation
x. Platform differences
xi. The efficacy of the comparator vaccine
xii. The effect of baseline titres on immune responses

i) **The constancy assumption**: A requirement for inferring VE by means of an immuno-bridging trial is that the effect of the licensed comparator vaccine (immunogenicity, VE, and their relationship), as estimated in its placebo-controlled trial, reliably represents its true effect in the setting of the immuno-bridging trial (10). This is referred to as the constancy assumption. The effect of the comparator vaccine as a two-dose primary vaccination regimen against ancestral strains in a seronegative population will almost certainly be different from its effect as a single dose booster against, for example, the Omicron VOC. In addition, a different relationship between VE and antibody responses between the two settings cannot be excluded. Therefore, for currently licensed comparator vaccines, the assumption of constancy between the (seronegative) settings of initial efficacy trials and the (seropositive) settings of new comparative immunogenicity trials, does not apply. This implies that immuno-bridging for new COVID-19 vaccines would be impossible in the current environment; rather, a comparative immunogenicity trial should be considered in the context of vaccines developed to boost pre-existing immunity.

ii) **The surrogate endpoint:** When immuno-bridging is not possible, authorisation based on an adequate and well-controlled comparative immunogenicity trial, which demonstrates the vaccine's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, can be considered (see section below on lessons from seasonal influenza vaccines). The absence of an established, broadly applicable CoP against COVID-19 that is reasonably likely to predict clinical benefit, has precluded defining seroprotection rates and clinically meaningful seroconversion or seroresponse rates (SRR) as success criteria (endpoints) in clinical trials. In the absence of a CoP that is applicable across vaccine platforms and SARS-CoV-2 variants, immuno-bridging cannot be used to quantitatively estimate the actual VE of a novel vaccine. The ecological study by Khoury et al., which demonstrated a correlation between the average magnitude of vaccine-induced neutralising antibody levels and protection against symptomatic disease across different seronegative trial populations and vaccine platforms, is often cited as one that validates the use of anti-SARS-CoV-2 antibodies as a CoP (11). Such ecological studies; however, are indicative rather than conclusive in terms of correlation at the individual level. The demonstration of an association between vaccine-induced neutralising (and binding) antibody levels and VE in preventing COVID-19 in these ecological trials has however justified the use of neutralising, and potentially binding, antibody levels as immunological markers for novel COVID-19 vaccines (12).

iii) **The protection equation:** Protection against COVID-19 is dependent on an interplay between different immunological markers (13). The relationship between vaccine-induced immune responses and protection can conceptually be represented by an equation that considers all relevant immune parameters in a weighted fashion: P = f (Ab, nAb, CD4, CD8, B, innate). This concept implies that immuno-bridging or comparative immunogenicity based on antibodies alone provides an imprecise and partial measure of the vaccine's overall clinical effect and may explain why protection against severe disease can be maintained despite loss of neutralising activity. Additional markers that could have a clinical impact must be considered when cross-platform comparisons are made, especially when prevention of severe COVID-19 is the public health priority. The residual 'unknown' in the protection equation has resulted in a greater emphasis being placed on the **totality of the immunogenicity data** included in the submission, as well as on a post-marketing trial to confirm the vaccine's benefit on clinical disease.

iv) **Platform differences:** The protection equation differs between vaccine platforms, as for example CD8 T cells may contribute more to the efficacy of adenoviral and mRNA than protein-based vaccines, including adjuvanted subunit and nanoparticle vaccines. The complex, composite nature of protection, as captured in the equation, is further illustrated by (i) the early onset of protection against symptomatic COVID-19 (i.e., 10 days after the first vaccine dose despite an average incubation time of 5-7 days), as observed in the pivotal efficacy trials for mRNA and Ad26.CoV.2S vaccines and suggesting a protective effect of vaccine-induced innate immune responses, (ii) the finding that protective threshold levels for neutralising antibodies appear to differ between mRNA-1273 and ChAdOx-1 vaccines, and (iii) the 50% efficacy of mRNA-1273 in the absence of detectable neutralising antibodies in the mRNA-1273-specific CoP analyses. In addition, cell-mediated immunity (CMI) is thought to play an important role in protection against severe COVID-19; however, assessment of CMI responses is hampered by the lack of validated assays.

v) **The efficacy of the comparator vaccine**: The lack of robust clinical efficacy data for vaccines used as a booster against circulating VOC strains, complicates the choice of the comparator vaccines. Effectiveness data from the UK Health Security Agency (translated from odds ratios obtained from the test-negative case-control design) show rapid waning of effectiveness of Pfizer's BNT162b2 vaccine, including against hospitalisation with the currently dominant Omicron VOC to ~75% 10-14 weeks following booster vaccination (14). This is comparable to US data

which showed waning effectiveness of mRNA vaccine boosters (3rd dose), against COVID-19-associated hospitalisations due to Omicron, to 78% among those boosted at least four months previously (15). Effectiveness against emergency care visits due to Omicron declined to 66% and 31% among those vaccinated 4-5 months and ≥5 months previously, respectively. Data from case-control observational studies should be interpreted with caution, and the potential impact of incidental COVID-19 amongst COVID-associated hospitalisations should be considered. Robust effectiveness data for ChAdOx-1 as a booster are lacking altogether.

vi) **Baseline seropositivity:** Baseline titres should be considered in the design of pivotal immunogenicity studies when developing novel COVID-19 vaccines to boost existing immune responses in seropositive individuals as i) the baseline may have an important effect on vaccine-induced immune responses, and ii) it is a covariable that can almost certainly not be used in an analysis of covariance. Therefore, the statistical comparisons should be a function of the baseline titres. If done this way, it is possible, for example, that the test vaccine is adequate for certain ranges of baseline titre but fails for other ranges.

Lessons from seasonal influenza vaccines - comparative immunogenicity trials: In the clinical development of novel seasonal influenza vaccines, the accelerated approval pathway can be used to support an FDA Biologics License Application (16). Such approvals are based on adequate and well-controlled comparative immunogenicity trials demonstrating the vaccine's effect on the surrogate endpoint of anti-hemagglutinin (HA) antibodies (Ab), which is reasonably likely to predict a clinical benefit. In addition, non-inferiority (NI) of the vaccine's induced anti-HA-Ab responses against those of a licensed comparator must be demonstrated. Approval under this pathway is subject to adequate and well-controlled confirmatory post-marketing studies being conducted to confirm the vaccine's clinical benefit. The accelerated approval regulatory mechanism was used to license the trivalent inactivated influenza vaccines Fluarix® (GlaxoSmithKline Biologicals) in 2005, FluLaval® (ID Biomedical Corporation of Quebec) in 2006, Afluria® (bioCSL) in 2007, Agriflu® in 2009 (Novartis), and Fluad® in 2015 (Novartis). Post-licensure studies have verified the clinical benefit of these vaccines (17). A recent example of a cross-platform comparative immunogenicity trial carried out under the accelerated approval pathway is the head-to-head comparison of Novavax' Matrix-M-adjuvanted nanoparticle influenza vaccine and Sanofi's quadrivalent seasonal influenza vaccine Fluzone (18). In comparative immunogenicity trials for novel seasonal influenza vaccines, geometric mean titres (GMTs) and clinically meaningful seroconversion rates are assessed against the surrogate endpoint of anti-HA antibody titres.

Summary and conclusions: The rapidly changing SARS-CoV-2 environment must be considered when designing Phase 3 comparative immunogenicity trials for new COVID-19 vaccines. SARS-CoV-2 is currently transitioning from a pandemic to endemic phase and from original to Omicron strain, with subsequent waves caused by Omicron-offspring not unlikely. In addition, trial settings are nearing universal seropositivity. As a result, future trial populations will largely include primed individuals, with rapidly increasing hybrid immunity. This unique, watershed moment in SARS-CoV-2 epidemiology *currently* precludes immuno-bridging but should VE of vaccines when used as a booster be demonstrated in a randomised, controlled, clinical trial, immuno-bridging may again be possible in the future. A comparative immunogenicity trial can be considered when immuno-bridging is not possible, and the totality of immune responses should be emphasised given the lack of a CoP for COVID-19. PART B discusses key design features and considerations for such an approach.

PART B: A PRAGMATIC WAY FORWARD - CONSIDERATIONS

Introduction: The WHO is in the process of developing a framework to define data requirements for authorisation of novel COVID vaccines. The framework foresees i) scenarios in which novel COVID-19 vaccines can be authorised using non-inferior or superior comparative immunogenicity data, and ii) scenarios that may require clinical efficacy trials. However, an early draft of the framework does not explicitly address serostatus of the trial population or the use of novel COVID-19 vaccines as a booster vaccination.

Any pivotal Phase 3 clinical trial should consider the current transitioning of SARS-CoV-2 from a pandemic to endemic phase. This significantly complicates pivotal trial design. Vaccine developers and regulatory authorities must also consider the rapid transition to universal seropositivity and hybrid immunity, conferred by vaccination and single or multiple SARS-CoV-2 infections. Uncertainties are not limited to regulatory requirements and SARS-CoV-2 epidemiology, but also include uncertainties regarding i) the VE or effectiveness of comparator vaccines when given as a booster vaccination, ii) future COVID-19 vaccine composition, iii) the antigenic signature of subsequent VOCs, and iv) future COVID-19 vaccine policy and implementation post-licensure.

A booster dose of a vaccine based on the original strain represents the current standard of care for protection against COVID-19 caused by currently circulating VOC (Omicron). This provides a unique, but likely short-lived, window of opportunity for comparing a novel VOC-adapted (e.g., Omicron) vaccine to one based on the original strain. New VOC (e.g., Omicron) vaccines are expected to induce superior neutralising antibody titres to Omicron, and likely to subsequent Omicron-related circulating strains, compared to the original strain-based vaccine that they are seeking to replace.

It remains unclear whether authorisation of new COVID-19 vaccines based on comparative immunogenicity data will require an "adequate and well-controlled confirmatory post-marketing study to verify the vaccine's clinical benefit", in line with the FDA's accelerated approval pathway for novel seasonal influenza vaccines. If a post-licensure trial is required following approval of new COVID-19 vaccines based on the totality of the immunogenicity data, vaccine developers may want to *instead* consider a Phase 3 comparative immunogenicity trial as a fully powered, nested, sub-study in a case-driven efficacy trial. A combined comparative immunogenicity and efficacy trial may bring an upside for future immuno-bridging trials (e.g., for strain adaptation), preparing the novel vaccine for use as a comparator vaccine with demonstrated VE in a predominantly primed population.

A head-to-head comparison between a VOC-adapted (e.g., Omicron) vaccine and an original strain-based vaccine is expected to provide superior protection to COVID-19 relative to original strain-based comparator vaccines, and rapid demonstration of clinical VE of the candidate vaccine is not hypothetical in the event of rapidly waning protection against COVID-19 conferred by original strain-based vaccines. This would be especially pertinent if subsequent waves of infections are caused by strains that are genetically related to Omicron with incremental antigenic change. This is plausible given viral evolution and viral fitness in primed individuals. By March 2022, BA.2 rather than BA.1 has become the predominant Omicron lineage in several countries. BA.1 and BA.2 have some genetic differences which may make them antigenically distinct, and reinfection with BA.2 following infection with BA.1 has been documented (19).

Trial design: Acknowledging that regulatory requirements may differ depending on trial design, we discuss a fully powered comparative immunogenicity study aimed at boosting pre-existing immunity conferred by vaccination, infection, or both. The trial can be conducted as a stand-alone Phase 3 clinical trial or as a fully powered (nested) immunogenicity study in a randomised, active-controlled efficacy trial aimed at showing (comparative) VE against COVID-19. This allows vaccine developers to propose a stand-alone comparative immunogenicity trial, or propose the concept of a nested sub-study, depending on their own assessment of the requirements and aforementioned uncertainties. The clinical efficacy part of the trial is beyond the scope of this SD. For information on active-controlled efficacy studies for COVID-19 vaccines, see the publication "*COVID-19 vaccine trials: The use of active controls and non-inferiority studies*" by Fleming et al (10).

A head-to-head immunogenicity comparison between original strain-based vaccines and VOC-based vaccines is supported by the WHO's TAG-CO-VAC, that continues to encourage COVID-19 vaccine developers to generate data on the effects of current and variant-specific COVID-19 vaccines so that they can be considered as part of a broad decision-making framework (18).

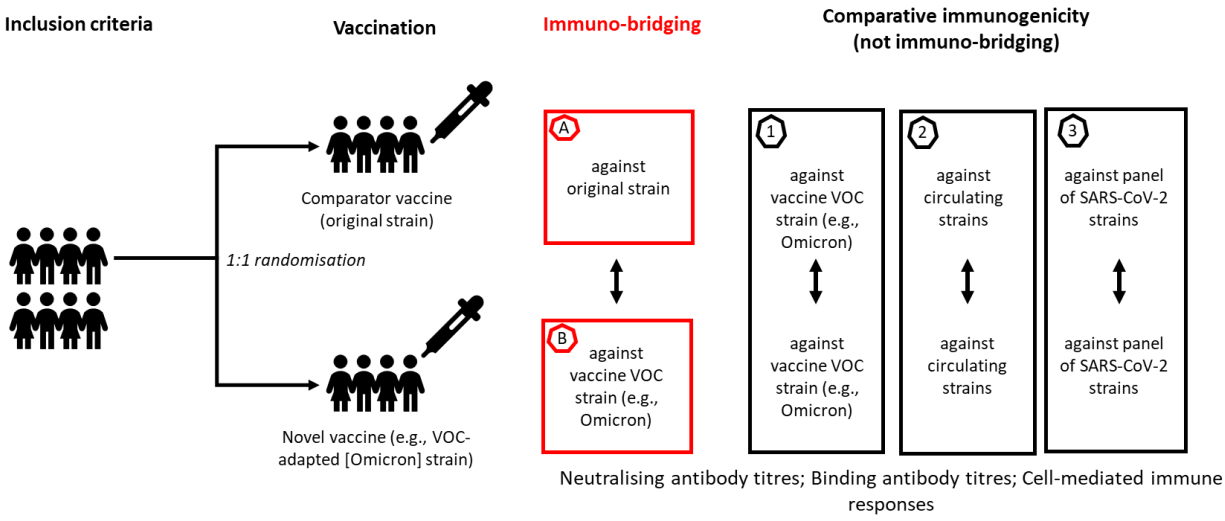
Key entry criteria:

- **Age group (e.g., adults aged 18 and older)**: Adequate representation of vulnerable individuals (e.g., older adults; those with underlying health conditions) is strongly encouraged; randomisation should be stratified by age group (younger adults /older adults).
- **Baseline COVID-19 vaccination status:** Enrolment may occur irrespective of prior COVID-19 vaccination. Vaccine history is usually reliable and easy to obtain. Randomisation should be stratified by self-reported vaccine history (yes/no), and the latter verified based on vaccine records. A minimum three-month interval between the study vaccine and last COVID-19 vaccine dose is suggested. It is acknowledged that developers may prefer a degree of homogeneity with respect to prior vaccinations.
- **Prior COVID-19 diagnosis:** Enrolment should occur irrespective of prior history of COVID-19 clinical disease or PCR-confirmed SARS-CoV-2 infection. Self-reported absence of prior COVID-19 does not exclude prior SARS-CoV-2 infection, as the majority of infections (irrespective of the VOC) are asymptomatic. Therefore, self-reported history is unreliable for distinguishing those with and without prior COVID-19. In case of self-reported COVID-19, a minimum three-month interval between the study vaccine and most recent PCR-confirmed COVID-19 episode is suggested.
- **Baseline serostatus**. Enrolment of subjects irrespective of baseline serostatus should be considered. In most countries, the proportion of seronegative individuals is now well below 5%. Anti-S-Ab seropositivity can result from vaccination or natural SARS-CoV-2 infection.

Randomisation:

- **Single-dose booster comparison:** The randomised comparison of a single booster dose of a licensed original strain-based vaccine and novel (e.g., VOC [Omicron]-based) vaccine can be considered ethical in a primed population irrespective of vaccination history. The provision of an original strain-based booster dose in vaccinated individuals is the (current) standard-of-care response to Omicron and is supported by effectiveness data. The administration of a single vaccine dose in unvaccinated seropositive individuals is supported by a wealth of single-dose immunogenicity data in unvaccinated individuals with a history of COVID-19.
- **Randomisation ratio:** A ratio of 1:1 is recommended.
- **Stratification**: Randomisation stratified by self-reported vaccine history (yes/no) should be considered.

Figure 1: Trial schematic.



Immunogenicity objectives:

- **Key immunogenicity objectives**: The novel (e.g., VOC [Omicron]-based) vaccine, developed to potentially replace vaccines based on the original strain, is designed to enhance efficacy against COVID-19 caused by

current (Omicron) and future (Omicron-offspring?) circulating VOC. The association of vaccine-induced antibody responses with VE justifies a co-primary or dual primary objective of demonstrating NI or superiority of antibody responses induced by the novel (e.g., VOC [Omicron]-based) vaccine booster against the VOC-strain contained in the vaccine (Omicron) (Box 1) and circulating strains not-contained in the vaccine (Box 2), compared to a booster of the original strain-based vaccine.

- **Breadth of immune responses**: A heterologous spike antigen booster with a VOC (Omicron) vaccine is expected to increase the breadth of immune responses and enhance cross-reactivity. Comparing cross-reactive immune responses induced by the novel (e.g., VOC [Omicron]-based) vaccine booster against a panel of SARS-CoV strains (e.g., original, Beta, Delta) to those induced by a booster with the Original-based comparator vaccine will test the *concept* of enhanced cross-reactive immunity conferred by the heterologous spike boost. Measurement of cross-reactivity against SARS-CoV-1 would test for pan-Sarbeco protection.
- **NOTE on immuno-bridging!** Immuno-bridging seems redundant when the effect of the licensed comparator vaccine, as estimated in its placebo-controlled trial, does not represent its true effect in the seropositive setting of the comparative immunogenicity trial (i.e., the constancy assumption does not apply). For illustrative purposes and to contrast with other immunogenicity comparisons, the classic immuno-bridging comparison is depicted in the Trial Schematic by the comparison between the red Boxes A and B (i.e., demonstrating NI of immune responses of the novel (e.g., VOC [Omicron]-based) vaccine to the VOC [Omicron] strain compared to the immune responses of the prototype vaccine to ancestral strain).

Immunogenicity endpoints:

- **Neutralising antibodies:** GMTs and SRR are traditionally co-primary endpoints for comparing the range and distribution of responses; GMTs are the most useful measure for the upper end of the range of responses whilst SRRs provide insight into the lower end of the range (i.e., non-responders). In seropositive populations, the geometric mean fold rise (GMFR) should be considered as a secondary endpoint. The lack of a CoP precludes defining clinically meaningful seroprotection, seroconversion, and seroresponse rates. A four-fold increase is often considered the default for SRRs, but baseline titres in the seropositive population further complicate defining a clinically meaningful rise. As an alternative to SRR, reverse cumulative distribution curves (RCDCs) may be considered (as a secondary endpoint?) as they provide a measure for the whole range of seroresponses and thereby facilitate an 'all-in-one' comparison of all possible fold-rises by means of rank tests. RCDCs appear particularly informative in instances where a broadly applicable protective antibody threshold or CoP have not yet been established.
- **Binding antibodies**: The immune analyses for neutralising antibodies as described above can also be conducted for IgG binding antibodies. The corresponding endpoints are GMTs, GMFR, and RCDCs (or SRR) of anti-SARS-CoV-2 binding (IgG) antibodies as measured by validated ELISAs.
- **Cell-mediated immune responses:** Given the protection equation, additional markers that might have a clinical impact must be considered when making cross-platform comparisons, especially since the public health goal of COVID-19 vaccination prioritises protection against severe disease and death. CMI plays an important role in protection against progression to severe disease. The residual 'unknown' in the protection equation places a greater emphasis on the totality of the data included in the submission, as well as on an adequate well-controlled post-marketing trial to confirm the vaccine's benefit on clinical disease. The inclusion of additional CMI analyses can minimise the risk of wrongly accepting or rejecting candidate vaccines. Descriptive comparative data which focus on CD4 and or CD8 T cell frequencies and phenotypes (e.g., Th1/2, Tfh), as well as antibody profiling, should be considered as exploratory endpoints to support the data package (e.g., functional profiling through 'systems serology' approaches and avidity analyses, meeting pre-defined standards developed on a case-by-case basis). RCDCs can also be used to plot cellular immune responses as illustrated in the publication by Shinde et al (18). Rank testing of RCDCs for the proportion of polyfunctional T cells can also be considered. Evaluation of specificity and breadth of T cell cross-reactivity against a panel of original and VOC peptides not contained in the vaccine will help understand protection against VOC.

Statistical considerations:

- **Primary analysis set:** A primary analysis which includes all subjects irrespective of baseline serostatus should not be a concern when there is near universal seropositivity. Whilst it may be intuitive to restrict the primary

analysis of a boosting trial to anti-S-Ab seropositive individuals, this is unpractical (e.g., seroreversion and label claims). In addition, it would be unjust to exclude individuals who have been vaccinated but seroreverted or never responded with measurable antibody titres. A sensitivity analysis eliminating baseline seronegative individuals should be performed to complete the data package.

- **Subset analyses**: If randomisation is stratified by vaccination history (yes/no), sensitivity analyses can be conducted by stratum to assess the vaccine's effects in individuals with or without history of vaccination. To assess immunogenicity in individuals with COVID-19 as documented by anti-N-Ab seropositivity, further sensitivity analyses can be performed comparing subjects anti-N-Ab seropositive to those anti-N-Ab seronegative at baseline. Sensitivity analyses by prime-boost platform history (e.g., full homologous prime-boost mRNA or adenovector series; adenovector prime and mRNA-boost) should also be considered.
- **Not vaccinated and anti-S-Ab negative and anti-N-Ab negative**: This subset is likely very small and too small for meaningful analyses but would identify individuals that might benefit from a full primary vaccination regimen.
- **Age:** Age should be considered a co-variable due to immuno-senescence and age being a key risk factor of severe COVID-19.
- **Baseline titres:** The effect of baseline titres (pre-existing immunity) on vaccine-induced immune responses should be assessed.
- **Non-inferiority:** The conventional statistical success criterion for NI comparison to a COVID-19 vaccine with established efficacy in the setting of the trial, is that the lower bound of the appropriately alpha-adjusted confidence interval is >0.67 using GMT and >10% for SRR as co-primary endpoints. Widening of NI margins decreases precision and increases the uncertainty inherent in cross-platform immuno-bridging in the absence of an established surrogate endpoint that accurately predicts protection in the individual. The WHO framework which remains under development, currently includes scenario-based NI versus superiority requirements.
- **Superiority**: A superiority design might be preferable when the comparator vaccine has demonstrated moderate (rather than high) efficacy as the downward margin for error is smaller, putting more emphasis on the *unknown* components of the equation. When comparing VOC-adapted (e.g., Omicron) vaccine boosters to vaccine boosters based on the original strain, superiority of immune responses to Omicron or subsequent circulating VOC is not hypothetical and therefore may be less of a concern.

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