WHO ad hoc consultation
COVID Vaccines
Methodological approaches to assess variants effect on vaccine efficacy, effectiveness and impact

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Report
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IT IS CRITICAL TO CONTINUE GENERATING RANDOMIZED EVIDENCE AS RANDOMIZED TRIALS ARE THE MOST RELIABLE METHOD FOR ASSESSING THE EFFICACY AND SAFETY OF VACCINES

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Preface

Since the start of the COVID-19 pandemic, WHO has received several reports of public health events possibly due to variants of SARS-CoV-2. WHO has an existing mechanism for tracking and evaluating variants of the virus that causes COVID-19. WHO is now expanding that mechanism to provide guidance to developers/manufacturers and countries on changes that may be needed for vaccines and how reformulated vaccines may be evaluated. WHO routinely assesses if variants of SARS-CoV-2 result in changes in transmissibility, clinical presentation and severity, or if they impact on countermeasures, including diagnostics, therapeutics and vaccines. It’s critical that countries continue to report emerging variants to WHO, to assure there is a globally coordinated mechanism to monitor their impact and advise countries and vaccine developers accordingly. To serve these objectives there is a need to continue designing and conducting new trials and studies and advance the systems for close monitoring of the vaccines impact on overall epidemiology and virus transmission and disease severity, severe disease and death so vaccines can have maximum effect. This consultation is being organized bearing in mind the emerging evidence and the WHO Members States requests for the prompt establishment of a global framework for vaccines evaluation. WHO held a consultation to discuss the methodological approaches that could be used to assess the impact of variants on vaccine effectiveness, and to discuss how modified vaccines targeting new variants of concern could best be evaluated.

Objectives of the ad-hoc consultation

- To outline current WHO efforts to set up a mechanism to provide guidance to developers/manufacturers and countries, and to coordinate changes that may be needed for vaccines.
- To discuss the most robust methodological approaches to assess – during vaccine roll-out - if a circulating new COVID variant – considered of public health relevance - has an impact on vaccine effect.
- To deliberate on the research approaches that could be considered when assessing vaccines that have been adjusted to address vaccine efficacy issues with new variants.

The workshop was introduced by Drs Soumya Swaminathan (Chief Scientist, WHO) and Michael J Ryan (Executive Director of the Health Emergencies Programme, WHO) and was chaired by Philip Krause (Chairperson of the WHO COVID vaccines Expert Group). Workshop sessions covered the generation of randomized evidence during COVID-19 vaccine rollout, conducting observational studies during vaccine deployment, and research to support an evaluation of the efficacy and effectiveness of new vaccines against variants. After each session, a group of panel members were invited to provide comments. An agenda including the names of panel members is provided in Annex 1. This report is a summary of presentations and panel discussions. It does not necessarily reflect the views of the organizers, participants or panel members.
EXECUTIVE SUMMARY

During 2020, a number of vaccines against SARS-CoV-2 were developed, evaluated and authorized at unprecedented speed. Multiple vaccines are being rolled out globally and are seen as pivotal to COVID-19 control. Authorized COVID-19 vaccines are highly efficacious. However, SARS-CoV-2 is prone to mutation and multiple variant strains have been identified. There is concerning evidence that some of these variants may be defined as variants of concern because they may affect the severity of disease, transmissibility, and/or the virus-neutralizing ability of host immune responses. Loss of vaccine efficacy against these variants could have major implications for public health control efforts.

WHO must play a central role in coordinating activities to identify the need for vaccines against new SARS-CoV-2 variants and the sequences that are most appropriate for global use. WHO’s is establishing a risk assessment framework for SARS-CoV-2 variants. An effective response to new variants will depend on continuing collaboration and sharing of sequence data, as well as virus and serological samples, particularly those with associated clinical information. The approach used to identify strains for influenza vaccines provides a model of which a COVID-19 response could be based. High variability is also a feature of influenza virus. Global surveillance systems have been put in place to monitor circulating strains of seasonal influenza, to inform twice-yearly updating of influenza vaccines in the southern and northern hemispheres. These systems are also used to assess influenza vaccine effectiveness. These influenza systems could offer important lessons for COVID-19, and provide an infrastructure that could be adapted for SARS-CoV-2 surveillance and assessment of COVID-19 vaccine effectiveness.

Placebo-controlled randomized clinical trials generate the most reliable evidence on efficacy. However, as vaccines become more widely available, such trials can be considered challenging. Nonetheless, in settings where vaccine supplies are still limited and important evidence gaps remain, they may still be justified. Randomized trials with active comparators (authorized vaccines) can provide valuable data on efficacy and effectiveness, though they have limitations in evaluating efficacy against variants, which may escape immunity from the active comparator previously shown to be effective. In some settings, randomization can be embedded within delivery programmes. Randomization during vaccine rollout programmes provide an opportunity to include randomization and generate comparative data. Multifactorial designs can be used to generate data on more than one research question (for example, relating to vaccine type as well as dosing schedule).
Observational studies are a complementary source of data on vaccine effects in the context of circulating new COVID-19 variants. They have the drawback that lack of randomization introduces a significant risk of bias. Case-control approaches can mitigate these biases, particularly test-negative designs, which are often used in influenza surveillance systems to assess vaccine effectiveness. Retrospective matching across multiple parameters using large data sets may also offer a way to gain insights into vaccine effectiveness. None of the approaches can fully address the issues associated with bias and confounding and therefore results can be difficult to interpret.

For both randomized and observational studies, sieve analysis provides an important methodology for assessing efficacy against viral variants. In effect, this approach filters out data on individual variants so that the effects of vaccination on each can be independently assessed. A deeper understanding of specific correlates of protection would facilitate immunological bridging studies. However, they may not be needed to evaluate modified vaccines, if it can be demonstrated that the immune responses they generate against variants are similar to those generated against the original strain.

To address the threat of new variants, new vaccines may be needed, or existing platforms could be modified. For modified vaccines, a key question is the type of evidence that will be required to support authorization. Clinical outcome trials may not be necessary when prototype vaccines were already shown to be effective, enabling rapid reaction in this case. As a general principle, immunological bridging studies, assessing whether modified vaccines generate similar responses to original vaccines, will provide the best trade-off between speed and confidence. Harmonized approaches across regulatory agencies will also help to expedite the development of vaccines targeting important new variants.

Although the influenza model provides a conceptual and practical framework that could be applied to COVID-19, important questions remain. One key issue relates to the criteria that would be used to decide on a COVID-19 vaccine switch, given current uncertainties about the types and levels of immune responses that are most meaningful for protection.
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1. **WHO must play a role in coordinating activities to identify the need for vaccines against new SARS-CoV-2 variants and the sequences that are most appropriate for global use.**

   Continuing global collaboration and sharing of sequence data, virus samples and serum samples, which have been so important in the successful response to COVID-19, were seen to be essential. While there is a need to establish approaches to deal with the immediate threat posed by SARS-CoV-2 variants of concern, efforts must also be made to establish a sustainable long-term platform for monitoring and responding to COVID-19 globally.

2. **As vaccines are deployed, it will be essential to gather data on their performance against evolving variants.** Placebo-controlled randomized clinical trials generate the most reliable evidence on efficacy. However, as vaccines become more widely available, such trials can be considered challenging. Observational studies are a complementary source of data on vaccine effects in the context of circulating new COVID-19 variants. They have the drawback that lack of randomization introduces a significant risk of bias. Animal studies would also be important for gaining a deeper understanding of the impact of variants on disease processes and on natural and vaccine-induced immune responses.

3. **Regulatory alignment at global level is important.** Regulatory authorities are working to identify appropriate regulatory pathways for vaccines targeting new variants and efforts to coordinate approaches globally.

4. **In addition, alongside open communication among multiple global professional communities, it is essential that public communication is also prioritized to raise awareness of key challenges and ongoing activities, and to build and maintain public confidence in COVID-19 vaccination.**
Introduction

Vaccines will be central to COVID-19 control. Following identification of SARS-CoV-2, several effective vaccines have been developed, tested and authorized at remarkable speed. They are being rolled out in multiple countries and mechanisms such as COVAX have been established to ensure wider access to vaccine supplies.

SARS-CoV-2 is an RNA virus and hence prone to mutation. Multiple variants have been identified by genome sequencing. Variants of particular concern are those that enhance transmissibility, cause more severe disease, or affect virus neutralization. Such variants could have significant implications for therapies, diagnostics and, in particular, vaccines.

Given this threat, there is a need to track the evolution of SARS-CoV-2, to understand the biological significance of newly identified variants, and to use this new knowledge to inform vaccine development to ensure that vaccines continue to provide effective protection.

Not all variants are equally important from the disease control perspective, some will be defined as variants of concern, and few are likely to influence vaccine efficacy. The decision-making framework incorporates a delicate balancing act – as well as a rapid response to ensure that new variants are targeted before they become a major global problem, there is also a need for high confidence that efforts are being directed against variants posing the greatest potential threat.

The response to new variants may include modification of existing vaccine platforms or development of new vaccines. At some point, bivalent or multivalent vaccines may be needed. A key challenge will be to determine the kinds of evidence required to evaluate modified or new COVID-19 vaccines, as well as the regulatory processes that will ensure timely access to safe and efficacious products.

Although SARS-CoV-2 is not simply a different form of influenza, the two viruses have several features in common, including rapid evolution and variation in the key surface structures targeted by the immune system. An extensive global system has been put in place to track influenza strains so that vaccines can be updated annually to match circulating virus strains. There are opportunities to learn from and adapt these mechanisms in order to ensure an agile response to SARS-CoV-2 evolution.
Context

**WHO is developing a risk assessment framework** in response to the emergence of SARS-CoV-2 variants of concern. The framework is important for clarifying what decisions need to be made, and what evidence is needed to make those decisions, in order to respond effectively to such variants.

The framework includes multiple aspects spanning monitoring, assessment of the impact of variants, and coordinated responses to those of most concern.

A key principle is to draw upon existing infrastructure and systems wherever possible, including that established for influenza, the R&D Blueprint for coordinating research in response to emerging infectious disease threats, global laboratory networks, existing partnerships, and established regulatory procedures (such as prequalification and emergency use listing). The short-term goal is to ensure a coordinated, rapid and effective response to new variants of concern, while the long-term aim is to establish a sustainable approach for COVID-19 and other infectious disease challenges.

The current workshop builds on discussions held on COVID-19 R&D priorities in January 2021. This had highlighted key issues relating to the evolution of SARS-CoV-2 and the implications of new variants for vaccines, therapeutics and diagnostics.

The January meeting also had stressed the critical importance of rapid and open sharing of sequence data, virus specimens and serum samples. It also highlighted the importance of integrating work on animal models to understand the biological significance of new variants.

Key priorities included global surveillance, with extensive sequencing and sequence information deposited into a readily accessible global database and samples made available through a global biobank (virtual or physical), sera collection, analysis and biobanking, risk assessment for vaccine, therapeutic and diagnostic development, and development of guidance to stakeholders such as countries, researchers and manufacturers. Such activities needed to be globally coordinated and underpinned by strong public communication.
It is critical to continue generating randomized evidence as randomized trials are the most reliable method for assessing the efficacy and safety of vaccines.

Placebo-controlled RCTs are the most informative designs and can be considered ethical in settings where standard of care does not yet include access to a COVID vaccine.

Additional safe and effective COVID-19 vaccines are needed in a timely manner to adequately address the pandemic on an international scale. Randomized clinical trials provide reliable & interpretable results regarding whether vaccines are safe & provide worthwhile efficacy. RCTs using placebo controls have enhanced efficiency & interpretability. Using clinical endpoints provides increased reliability. Assessments of durability of effects and safety are of key importance. Creative approaches are needed to obtain substantive insights about the influence of viral variants on efficacy, including for experimental vaccines. When randomization against placebo controls is not possible, use of Active Controls might enable a reliable evaluation of efficacy and safety, though with limitations when the active control may also be less effective against new variants. This could be run as a non-inferiority trial, with a non-inferiority margin chosen that reflects the uncertainty surrounding the efficacy of the comparator in that particular setting. Moreover, ‘Sieve analysis’ enables the impact of variants to be assessed within an RCT design, where variants with different clinical impact are circulating. The three overarching objectives of Virus Sieve Analysis include: (i) To develop direct insights from placebo-controlled RCTs about whether viral variants are meaningfully influential regarding the efficacy of an experimental vaccine; (ii) to develop a biomarker of the virus (e.g., neutralizing antibody titer from a pseudovirus or live virus assay) that predicts how well a vaccine (or vaccines) prevents an endpoint with that specific virus and, gleaning insights useful for optimizing strain selection in the formulation of future versions of vaccines and; (iii) to develop insights into molecular mechanisms of protection. The sieve analogy highlights the fact that natural defense mechanisms filter out virus to some degree and the vaccine acts a further filter in those in the active arm of a trial. By characterizing cases of disease, sieve analysis can be used to compare how well these two layers filter out specific viral variants – providing data on the protective efficacy of a vaccine against specific variants. Sieve studies can also be used to identify biomarkers that predict the degree of viral protection and to shed light on molecular mechanisms of protection. Sieve analyses can also provide a way to explore this strain specificity.

Identification of specific correlates of protection would be valuable, to inform new vaccine development and provide surrogate endpoints for randomized trials.

However, it is possible that immune correlates of protection could vary by vaccine type, by strain and also by clinical endpoint (e.g. asymptomatic infection, mild disease, severe disease). It is also possible to integrate evaluations of new COVID variants into immune correlates analyses of placebo controlled RCTs, in order to increase confidence in immune correlates as they are developed. The caveat to consider is that the immune correlates...
correlates could differ by viral strain, e.g. the antibody threshold predictive of high vaccine efficacy may differ by strain, therefore the immune correlates analyses should include assessment of strain-dependency.

**Valuable randomized evidence could be obtained by randomization of treatment within existing clinical practice.**

This was illustrated using an example from breast cancer screening in the UK, where mammography is routinely offered to women aged 50–70, a total of seven mammograms. There have been concerns that screening is leading to overdiagnosis of clinically unimportant issues, but some advocates have argued for additional screening.

To address uncertainties regarding the effects of breast screening programmes, the AgeX trial is evaluating the addition of an eighth screen, either before age 50 or after age 70. The trial is embedded in the NHS Breast Screening Programme, with 4.5 million women randomized to receive (or not) an extra breast screening invitation. Using existing infrastructure makes the trial highly cost-effective to run despite its enormous size. AgeX was launched in 2010 and finished recruiting in 2020. It is inevitably a long-term trial as it will be assessing clinical outcomes.

**There are advantages in incorporating large, simple, streamlined randomised trials into COVID vaccine rollout programs to get appropriately reliable evidence on efficacy.**

For COVID vaccines randomization could be integrated in the deployment plans with large numbers of participants being randomised in the context of national vaccination programme. Such randomization approach can address some uncertainties with relatively little additional investment.

If properly designed, with due attention to local constraints and local record systems, large, simple, streamlined trials can be conducted conveniently and at low cost without materially interfering with the urgent process of efficient rollout. Studies involving randomization during deployment can provide data even as vaccine roll-out is beginning (when observational studies, which work best when vaccine uptake is in a moderate range, neither too low nor too high, can be particularly challenging), retaining the important aspect of randomization, minimizing the biases that can make interpretation of observational data challenging.

Within existing programmes, participants could be randomized to receive different vaccine products or vaccination schedules at different intervals, with the need for very little change in routine practice. Electronic health records could provide a way to follow up participants, although the nature of follow up would depend on local context. Genotyping of breakthrough cases could provide important data on the efficacy of particular vaccines against variants of concern. If current vaccines are suspected to be somewhat less effective against new
Randomized comparative immunogenicity studies can provide additional information on alternative immunization schedules

For example, in the United Kingdom, the so-called “COM-COV study” is assessing the impact of combining doses of different COVID-19 vaccines. The study will include several vaccines (AstraZeneca/Oxford ChAdOx1 and Pfizer/BioNTech BNT162b2), with contrasting platform technologies (chimpanzee adenovirus vector versus mRNA and lipid nanoparticle). Being able to combine vaccines would create more flexibility for vaccination programmes, and there is also some evidence that heterologous vaccination generates more potent immune responses.

COM-COV is a comparative immunogenicity study, so will deliver results within months, in time to inform the national vaccine programme. The study is assessing all four combinations of the two vaccines, and is also comparing four-week and 12-week intervals between first and second doses. It has the potential to incorporate other vaccines. It is being run as a non-inferiority trial, comparing anti-spike protein antibody levels. Multiple other antigenicity assays are being run, and systems serology and mucosal immunity is being explored in a subset of participants. COM-COV also provides a potential platform for exploring other questions, such as different approaches for booster vaccinations.

Additional considerations when considering randomized designs

A global mechanism coordinated by WHO is needed. It is important to root the discussions in the global context and needs. Despite the efforts of mechanisms such as COVAX, access to vaccines remains unequal globally. Efficacy and safety data are also needed in different regional contexts and, with important uncertainties surrounding the efficacy of some of the existing vaccines against current variants of concern, collecting robust data during initial rollouts could generate vital data to inform decision-making on future introductions and on vaccine modifications. Although COVID-19 is a public health emergency and there is a drive to respond rapidly, it was argued that there were also important opportunities to collect randomized evidence of local relevance.

An important step is to identify specific priority public health goals. Those may include to save lives or to reduce infection, which could inform the design of randomized studies integrated within vaccination programmes. Given that the uncertainties around some important public health questions remain, deploying vaccines that turn out to have limited efficacy could have significant implications for future public trust. Although not ideal, this does provide opportunities for randomized deployment targeting particular priority groups, such as healthcare workers.
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or older people, and would facilitate high-value placebo-controlled randomized evidence being generated. Using suitably simple, streamlined methods, large-scale randomisation can accompany rollout, yielding results that are far more reliable than would be possible with any non-randomised stepwise approach. Countries are likely to vary in their capacity to carry out such studies, but they would be feasible in some with sufficient planning, coordination and global support. For example, mobile phone apps could be used to collect data on symptoms and hospital surveillance used to identify cases of severe disease. In the context of new variants, superspreading events, clusters of infections and breakthrough cases following vaccination would warrant special attention and investigation.

It is critical to continue working towards the identification of correlates of risk and surrogates of protection, which will facilitate the conduct of bridging studies, for example among younger populations. Although neutralizing antibodies appear to be correlated with protection, other immune mechanisms may also be important, and protection may be possible without neutralizing antibodies. Nevertheless, it was underlined that specific immune correlates of protection might not be needed for modified vaccines targeting new variants, if it can be shown that the responses generated by a new vaccine to a new variant are similar to those generated by the original vaccine to the original virus.

Other methodological approaches are being proposed but there is a need to discuss their relevance and appropriateness in the context of COVID vaccines. Cluster randomized trials were suggested as a possible alternative to randomization of individual participants. However, it was noted that cluster size needed to be small to maintain power and the study must include a large number of clusters, and cluster randomized trials may not be appropriate when anticipated relative effect sizes are expected to be small. Stepped wedge designs are a form of cluster randomized trial, in which variation in the speed of a rollout geographically naturally creates intervention and control areas. However, stepped wedge trials were felt not to be a desirable design option for evaluation for COVID vaccines as they are difficult to organize, and because differences in the timing of intervention introduction in the context of an evolving epidemic add further complexity to the interpretation of any results. A quasi-experimental approach called regression continuity design was noted. When arbitrary cut-offs exist for an intervention, such as age or geographic area, it may be possible to compare outcomes in individuals close to but either side of cut-off thresholds or boundaries. Opportunities may also exist to evaluate the potential of vaccines for post-exposure prophylaxis, where interventions are used to prevent infection in those known to be exposed to an infectious case. The efficacy of different vaccines could be compared for different variants.

Generation of robust evidence rapidly was deemed critical, to get ahead of the virus as it evolves and to prevent the spread of variants of concern. Randomized controlled trials are likely to become increasingly difficult as
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Vaccine supplies may increase and other approaches will need to be considered. One important function of RCTs will be to identify correlates of protection, which could facilitate more rapid studies than those focusing on clinical outcomes.

**Observational studies are a complementary source of data on vaccine effects in the context of circulating new COVID-19 variants**

**Addressing uncertainties around vaccine efficacy against new COVID variants during deployment.**

As noted above uncertainties around some important public health questions remain and deploying vaccines that turn out to have limited efficacy could have significant implications for future public trust. For example, South Africa is considering an approach to address uncertainties regarding the efficacy of the AstraZeneca/Oxford vaccine against the 501Y.V2 (or B.1.351) variant. South Africa has experienced a severe second wave of COVID-19 believed to have been driven by the 501Y.V2 variant. Genomic surveillance indicates that it had become the dominant strain in South Africa by mid-January 2021, and has spread to more than 30 countries by early February 2021.

The 501Y.V2 variant has a selective advantage, potentially linked to higher transmissibility or immune evasion. South Africa had originally planned to rollout the AstraZeneca/Oxford vaccine, but question marks have been raised about its effectiveness against 501Y.V2. Laboratory assays suggest that several COVID-19 vaccines, including the AstraZeneca/Oxford vaccine, are less able to neutralize 501Y.V2. Clinical data are extremely scarce. The single-dose Johnson & Johnson vaccine retains efficacy of 57% against moderate/severe disease and 85% against hospitalization and severe disease caused by 501.Y.V2. No comparable data exist for the AstraZeneca/Oxford vaccine, but a small study suggests efficacy of just 22% against mild to moderate disease, an outcome of less clear public health significance.

South Africa has received supplies of the AstraZeneca/Oxford vaccine, but has chosen initially to roll out the Johnson & Johnson vaccine. One possibility being considered is to use the AstraZeneca/Oxford vaccine in a two-step approach, collecting data on hospitalization in the first 100,000 people in higher risk groups and comparing outcomes with historical data from placebo arms of past trials run in South Africa. A wider rollout would be dependent on the measure of protective efficacy identified in the first phase (and relevant data generated in other countries).
Building on the influenza surveillance experience in the Region of the Americas.

A surveillance infrastructure established for influenza and other respiratory infections in Latin America and the Caribbean is being extended to COVID-19, and could be used to assess COVID-19 vaccine effectiveness.

With support from PAHO and the several Member States, capacity has been built in the Latin America and the Caribbean region for respiratory virus surveillance, culminating in the launch of the Severe Acute Respiratory Infections Network for the Americas (SARInet). This is based on sentinel surveillance for severe acute infections and influenza-like illnesses. In 2020, it was extended to include COVID-19, with 21 countries using SARInet to monitor COVID-19.

This infrastructure has also been used to investigate the effectiveness of influenza vaccines through the REVELAC-i initiative. A total of 13 countries in the region supply SARI date to enable annual pooled analysis of vaccine effectiveness in children and older adults. The data also enable the effectiveness of single doses and full two-dose series to be assessed, as well as effectiveness against particular strains. Data feed into the Global Influenza Vaccine Effectiveness (GIVE) report.

As well as integrating surveillance, a proposal has been formulated to evaluate COVID-19 vaccination using the REVELAC-i methodology. This would make use of a case-negative case-control design, which attempts to address some of the potential biases associated with non-randomized studies. Vaccination effectiveness is assessed by collecting data on swabbed patients presenting at sentinel sites, who will be a mixture of vaccinated and unvaccinated individuals. The ‘test-negative’ cases provide the controls for the ‘test-positive’ cases, on the assumption that those seeking help for symptoms are a reasonably homogenous group. This approach may enable the impact of factors such as age, sex, type of vaccine, dosing schedules, variants and severity of illness on COVID-19 vaccine effectiveness to be determined through adaptation of an existing regional network.

Using a retrospective cohort design to assess COVID vaccine effects during roll-out

The experience in Israel was used to describe some of the methodological challenges associated with analysis of real-world data to assess vaccine effectiveness. Israel rapidly established a vaccination programme and by mid-February 2021 40% of its population of 9 million had received at least one dose of COVID-19 vaccine. Vaccine effectiveness is being explored using data collected by Clalit Health Services, a non-profit payer-provider that provides a full range of services to more than half the population of Israel and has a comprehensive digital health platform.
To emulate an RCT, data analyses are addressing multiple challenges posed by the lack of randomization. These include the likelihood that vaccinated and non-vaccinated people differ, as socioeconomic status impacts on the likelihood both of being vaccinated and of being infected. In addition, risks and infection rates change over time as more people are vaccinated and circulating strains evolve, but differently for different groups.

Studies can be designed using a retrospective cohort approach, covering either all members (vaccinated versus unvaccinated) or adopting a test-negative design. Matching is then carried out, for individual characteristics but also to control for key confounders over time. Although it can be difficult to determine whether all potential confounders have been considered, reassurance can come from comparing disease trends with those seen in RCTs. For example, no differences in outcomes between cases and controls should be seen in the first ten days or so after vaccination, before a protective response has been generated in vaccine recipients.

**The need to remain aware of the intrinsic methodological challenges of observational designs**

There are methodological challenges associated with the estimation of vaccine effectiveness from observational studies. Moreover, vaccine effectiveness can be defined in several ways, to reflect protection against infection, clinical disease, transmission, or clinical disease in those affected (the usual primary outcome measure in phase III trials). Variant-specific vaccine effectiveness can be determined by stratified/sieve analysis incorporated into either clinical trials or observational studies following rollout. Sieve analysis in the RV144 HIV vaccine trial, for example, was used to show that protection was strongly associated with a limited number of HIV genotypes.

Prospective cohort studies provide a measure of vaccine effectiveness based on a risk ratio comparing transmission rates in vaccinated and unvaccinated groups. Case-control designs aims to control for the confounders likely to introduce bias into simple prospective cohort approaches. The case-control approach can be applied prospectively, integrated into an ongoing surveillance programme, or retrospectively, using electronic health records. Test-negative studies are a type of case-control design in which controls are drawn only from those testing negative, thus controlling for differences in care-seeking behaviour.

**Important considerations in the design and interpretation of results from observational studies**

All observational studies are afflicted by biases, which can only be partially mitigated. However, biases are most important when small effects are anticipated. If the variants of concern are considered likely to have large effects on vaccine efficacy, biases will be less of an issue. Stratifying analyses by viral sequence or performing sieve
analyses can reduce the risk of bias in observational studies designed to determine relative efficacy against different strains.

**Adequately matching cases and controls during a dynamically evolving epidemic is challenging.** This remains the case even when prospective approaches can be used to match for time and place. However, with COVID-19 surveillance already integrated into the Latin America and Caribbean network, embedding of COVID-19 vaccine effectiveness studies some argued that this may be feasible.

**The is a large body of experience among the influenza community.** This community had been using sequence data to examine the impact of genetic variants on vaccine effectiveness for more than 15 years. It was possible to obtain clade-specific data, and even examine the impact of single amino acid changes, using a test-negative approach. The approach is dependent on sequencing of all viruses and having a random or representative population sample, which could be challenging for COVID-19 in some settings. It can provide information relatively rapidly, sufficient to inform the choice of strains for seasonal flu vaccines in the northern and southern hemisphere. The system is reliant on there being virus in circulation and good vaccine coverage.

**A note of caution was sounded.** The assumption is that SARS-CoV-2 will continue to behave like influenza, showing high levels of year-on-year variability. Another possibility is that SARS-CoV-2 is adapting to a new host and will become more genetically stable over time.

To date, variants have been found to affect transmission rather than disease severity. Nevertheless, it would be wise to assume that new COVID variants will continue to appear. Even so, changing vaccine formulations is challenging and should only be considered when absolutely essential and as part of a globally coordinated effort.

**Evaluation of efficacy and effectiveness of modified or new vaccines against new COVID variants**

**A range of issues that need to be taken into consideration by the developers of modified or new vaccines.**

These include the choice between adaptation of existing vaccines or development of new vaccines, the potential for bivalent or multivalent vaccines, and the choice of dosing strategy. The potential advantages (or disadvantages) of mixing vaccine platforms, during a primary series or for booster doses, will add further complexity. Notably, the environment for product development is now very different from 2020. Increasing numbers of people are seropositive, due to natural infection or vaccination, multiple new variants are appearing,
placebo-controlled trials are increasingly difficult, and there is the possibility of more specific correlates of protection being identified in the near future.

The activities of the WHO Working Group on COVID-19 Animal Models could support efforts to understand the impact of new variants and support vaccine development.

Extensive global efforts have been made to coordinate the development of animal models for COVID-19. Multiple small and large animal models have been developed, each with its own advantages and disadvantages, emphasizing the importance of the ‘portfolio’ approach. Results from animal studies have been highly consistent with those from phase I and II trials.

Animal models can be used to provide insights into the mechanisms of disease, as well as how virus variants affect natural and vaccine-driven immunity. Animal models therefore have a key role to play in understanding the biological impacts of variants and identifying the need for vaccine reformulation.

Regulatory authorities are working to identify appropriate regulatory pathways for vaccines targeting new variants and efforts to coordinate approaches globally.

Discussions between WHO, the EMA, FDA and Health Canada have identified a set of shared principles to guide future activities, with details to be agreed following further discussions. Inputs from manufacturers are also due to be considered. The principles are based on the assumptions that vaccines are targeting the viral spike protein, that specific immune markers predictive of protection have not yet been identified but neutralizing antibodies are a major component of the protection response generated by a vaccine, that clinical efficacy studies are not feasible, and that variant vaccines are made by the same manufacturer using the same process as the original vaccine that was demonstrated to have clinical efficacy.

Under these circumstances, regulatory authorities will accept inferred efficacy based on non-inferiority clinical immunogenicity studies comparing immune responses of a modified vaccine to variant strains to those induced by the original vaccine to the original strain. Immunologic data from booster studies on previously immunized participants will be required for both the original and modified vaccine. Multiple other key issues have yet to be discussed, including the criteria for introducing modified vaccines, post-authorization studies and multivalent vaccines.

Where it is not possible to make modified vaccines, new vaccines will likely need to follow the same evaluation paradigm regardless of potential issues posed by variants, and thus be evaluated in randomized controlled clinical endpoint trials.
The experience with the strain selection process for influenza virus vaccines will be adapted for COVID-19.

Trivalent or quadrivalent influenza vaccines are updated twice a year in readiness for flu seasons in the northern and southern hemispheres. Choice of strains included depends on data from the WHO Global Influenza Surveillance and Response System (GISRS), covering more than 100 countries.

The GISRS network is responsible for genetic and antigenic analysis of virus samples, with rapid and open sharing of samples and sequence data. Serological studies are used to determine the likely protection that existing vaccines will offer against new circulating viruses. Serological, sequence and drug resistance data all feed into choice of vaccine strains. A strain change is recommended only when marked antigenic changes are observed, as well as sequence changes at key sites in the haemagglutinin gene and poor recognition of variant virus by sera from vaccine recipients; suitability of strains for production platforms must also be considered. In terms of COVID-19, a similar kind of systematic risk assessment will be organized to determine the need for deployment of an updated vaccine, covering such issues as antigen change, association with outbreaks, geographic spread and fitness data. However, for SARS-CoV-2, it is not yet clear what level of antigenic change should be considered clinically meaningfully, or how antigenic change should be routinely assessed.

How to further refine and develop global regulatory alignment on how to assess and authorize modified or new COVID vaccines

So far vaccine development had relied on sharing of sequence information, and that novel platform technologies provided opportunities to rapidly modify vaccine products. If a range of vaccine products become required, this could exacerbate supply issues. Multivalent vaccines could be one long-term approach, but it was considered too early to be considering their use at present.

The influenza surveillance system has provided an infrastructure that could be built upon for monitoring of COVID-19, with capacity building at sites that required it. Representative or random SARS-CoV-2 samples were seen as important, and the importance of antigenic as well as genetic data was emphasized, as well as virus isolates with associated patient data. A high priority is to obtain as much information as possible about new variants in ongoing phase III trials, to support clade-specific or variant-specific efficacy analyses. Other important questions to address include potential interactions with flu vaccines, the impacts of repeat vaccination, and the potential for vaccine-enhanced disease (which has not been detected to date).
The importance of maintaining close alignment between clinical development and regulatory oversight was highlighted, as well the need for a coordinated global approach to regulatory approvals to expedite the development and introduction of new vaccines. Simple, clear and adaptable guidance is required in order to provide the flexibility to respond to a highly dynamic situation. Internationally agreed quality, safety and efficacy criteria and harmonized processes will provide a global framework to support effective risk assessments and evidence-based decision-making.

**Conclusions**

A coordinated global approach is critical. The workshop highlighted the important role WHO must play in coordinating activities to identify the need for vaccines against new SARS-CoV-2 variants and the sequences that are most appropriate for global use.

The approach used to identify strains for influenza vaccines provides a model on which COVID-19 response will be based. An effective response to new variants will depend on continuing collaboration and sharing of sequence data, as well as virus and serological samples, particularly those with associated clinical information. In terms of the information required to support future decision-making, neutralization may not be an ideal indicator of vaccine effectiveness, but it may nonetheless provide an indication of the need for a modified vaccine and an initial method for evaluating such a vaccine. More information is needed on the neutralization threshold that is clinically meaningful. Although it would be valuable to have more precise correlates of protection, these may not be needed for decision-making about modified vaccines based on known effective vaccines. In terms of clinical data, it was generally agreed that useful data could come from multiple sources, including trials and observational studies.

The influenza model illustrates how observational approaches can yield valuable and actionable insights. For both approaches, sieve analysis provides a key methodology for assessing the impact of variants of concern.

Randomized studies will always provide the most reliable results, by addressing systematic differences between those who get vaccinated versus those who do not and are thus preferred where feasible. Despite the greater availability of vaccines, trials could be considered in settings where vaccine supply is limited or where there are uncertainties that need to be addressed using more reliable and interpretable results. Placebo-controlled trials are most informative and could be considered when supply is limited. However, active controlled trials are also a valuable source of data. With planning and preparatory work, randomized studies can be embedded in routine
vaccine delivery services and deliver valuable robust data, using immunological and/or clinical endpoints. Factorial designs can be used to address multiple questions simultaneously. If trials are kept simple, very large trials may be feasible. Post-exposure prophylaxis studies may offer an efficient way to assess changing vaccine efficacy against variants.

As COVID-19 vaccines become widely used outside trial settings, observational data offer new opportunities to explore efficacy and safety, with the caveat that the lack of randomization introduces a significant risk of bias. Test-negative study designs, as used for flu, offer one approach for minimizing this risk. Cohort studies using electronic health records can be used to generate data on vaccine effectiveness, requiring sophisticated matching to mitigate the risk of bias.

A coordinated global approach is also required to identify and characterize variants of concern, including impacts on transmissibility, immune responses and vaccine efficacy, and to advise on their implications for vaccine development and deployment. Animal model studies have a critical role to play in understanding mechanisms of disease and natural and acquired immunity.

For variants, initial studies could explore issues such as the feasibility of obtaining protective immune responses against specific variants and the safety of boosting. Dialogue between developers and regulators is important for determining the most appropriate ways to assess variant-targeting vaccines.

A harmonized approach across regulatory agencies is essential to ensure that new product development is expedited to address the urgent public health threat posed by new variants while also assuring the safety and efficacy of new products.

While systems are needed in order to respond to the immediate challenge of novel SARS-CoV-2 variants, there is also a need to consider the sustainability of such systems and how they might be adapted for other emerging infectious threats. Finally, all activities should be underpinned by transparency and strong public communication.
## Appendix 1 – Agenda

Chairperson – Philip Krause

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speakers</th>
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<tbody>
<tr>
<td>13:00 – 13:05</td>
<td>Welcoming remarks</td>
<td>Drs Soumya Swaminathan and Michael J Ryan</td>
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<tr>
<td>13:05 – 13:10</td>
<td>Objectives of the meeting</td>
<td>Philip Krause</td>
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### PLENARY SESSION - SETTING THE SCENE

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
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<tbody>
<tr>
<td>13:10 - 13:20</td>
<td>Outline of WHO integrated risk evaluation framework and the decision-making process for changes to vaccine composition</td>
<td>Sylvie Briand</td>
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<tr>
<td>13:20 - 13:30</td>
<td>New COVID-19 variants and research priorities</td>
<td>David Heyman</td>
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### GENERATING RANDOMIZED EVIDENCE DURING COVID VACCINES ROLL-OUT

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
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<tbody>
<tr>
<td>13:45 - 14:00</td>
<td>Randomize trial on alternating vaccine doses study in the United Kingdom</td>
<td>Mathew Snape</td>
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<tr>
<td>14:00 - 14:15</td>
<td>Randomising millions in routine breast screening clinics – the AgeX trial</td>
<td>Valerie Beral</td>
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<tr>
<td>14:15 – 14:30</td>
<td>Randomising hundreds of thousands during vaccine deployment</td>
<td>Richard Peto</td>
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<tr>
<td>14:30 – 15:15</td>
<td>What are the benefits and challenges of generating randomized evidence during vaccine deployment?</td>
<td>Plenary discussion</td>
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<td>Panel Members: Jerome Singh, Elizabeth Halloran, Peter Figueroa, Cheryl Cohen, Samba Sow, Susan Ellenberg</td>
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### CONDUCTING OBSERVATIONAL STUDIES DURING VACCINE DEPLOYMENT

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<th>Time</th>
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<th>Speakers</th>
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<tbody>
<tr>
<td>15:15 – 15:30</td>
<td>Considerations for evaluation of COVID vaccines during deployment in South Africa</td>
<td>Helen Rees</td>
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<tr>
<td>15:30 – 15:45</td>
<td>Using seasonal influenza vaccine effectiveness surveillance platforms to evaluate COVID vaccines efficacy</td>
<td>Alba Maria Ropero</td>
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## Methodological approaches to assess variants effect on efficacy, effectiveness and impact

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>15:45 – 16:00</td>
<td>Cohort studies during deployment to assess vaccine effects: the experience in Israel</td>
<td>Ran Balicer</td>
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<tr>
<td>16:00 – 16:15</td>
<td>Possible estimation of variant-specific vaccine effectiveness from observational studies</td>
<td>Ira Longini</td>
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<tr>
<td>16:15 – 16:45</td>
<td>In which context can observational studies contribute to evaluate vaccine effect against variants and, what are the considerations for interpreting the results? Panel Members: Peter Smith, Rakesh Agarwal, Tom Fleming, Richard Peto, Martha von Horoch, Danuta Skowronska, Manoj Murhekar</td>
<td>Plenary discussion</td>
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### RESEARCH TO SUPPORT EVALUATION OF EFFICACY AND EFFECTIVENESS OF NEW VACCINES AGAINST VARIANTS

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<tbody>
<tr>
<td>16:45 – 17:00</td>
<td>Clinical development aspects regarding vaccines modifications</td>
<td>Jakob Crammer</td>
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<tr>
<td>17:00 – 17:15</td>
<td>Animal studies to assess modified vaccines’ efficacy against variants: immunization response and challenge data</td>
<td>César Muñoz-Fontela</td>
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<tr>
<td>17:15 – 17:30</td>
<td>Clinical data to support use of COVID-19 vaccines against SARS-COV-2 variants</td>
<td>Marion Gruber</td>
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<tr>
<td>17:30 – 17:45</td>
<td>Using the influenza experience to assess vaccine effectiveness</td>
<td>Kanta Subbarao</td>
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<tr>
<td>17:45 – 18:15</td>
<td>What are the research requirements to support vaccine evaluation after a strain change, if needed? Panel Members: Mike Levine, Alicia Fry, Sheena Sullivan, Moji Adeyeye, Rogerio Gaspar</td>
<td>Plenary discussion</td>
</tr>
<tr>
<td>18:15 – 18:30</td>
<td>Conclusions and next steps</td>
<td>Chairperson</td>
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<tr>
<td>18:30</td>
<td>End of meeting</td>
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