ICMRA COVID-19 Vaccine development: Future steps Workshop

Thursday 24 June 2021

Co-chairs: Dr Yasuhiro Fujiwara (Chief Executive, PMDA, Japan) and Dr June Raine (Chief Executive, MHRA, UK)

1. Welcome and objectives of the workshop

Following on from the 10 February 2021 ICMRA workshop on COVID-19 vaccine variants, the objective of this workshop was to brainstorm among regulators about the development of second-generation vaccines and booster doses, with a particular focus on immunobridging, the design and use of controlled trials (placebo or other controls), and correlates of immunity.

The co-chairs highlighted the importance of a well-coordinated and convergent global response to evaluating existing vaccines and developing modified and new vaccines in the face of SARS-CoV-2 variants of concern. This was reinforced by the timely publication of 'SARS-CoV-2 Variants and Vaccines' in *The New England Journal of Medicine**.

2. Summary outcomes of WHO meetings on correlates of protection/immunity and vaccine development with the challenge of SARS-CoV-2 variants

- Sylvie Briand, Global Infectious Hazards Preparedness Department, WHO
- David Wood, Regulation and Prequalification Department, WHO

WHO underlined the complexity of measuring vaccine efficacy unless the goal of what is being measured is clear, e.g. reduction of severity and mortality or reduction of transmission? It is difficult to compare studies which used different endpoints. Regulatory requirements need to be streamlined.
WHO currently estimates vaccine protection against the four variants of concern at approximately 50% or more protection, based on neutralising antibodies. In addition, there is still intense transmission in some but not all regions and significant disparities in vaccination access and coverage. The complex global context increases the difficulty to have a unique response. The disparity in sequencing capacity is also posing difficulties for surveillance and decision making.
As part of creating a framework for assessment of vaccine effectiveness, WHO has established the Technical Advisory Group on COVID-19 Vaccine Composition (TAG CO-VAC). It begins work in July and will provide a reference to advise on methods to assess variants of concern, interpretation of the effect of these variants, and recommend any necessary adaptations to the COVID-19 vaccines platforms.
This complements the work of the COVAX Regulatory Advisory Group (COVAX RAG), which brings together representatives of regulatory agencies covering all WHO regions, including Argentina, Australia, Brazil, Canada, Europe (EMA & EDQM), Ghana, Japan, Singapore and USA.
For the WHO, the global priorities for regulators and regulatory convergence are:

- Evaluation of post-approval changes/modifications/extension of indications to approved vaccines with established efficacy;
- Guidance on evaluation of second-generation vaccines that are in development (including reliance strategies); and
- Responding to real-world scenarios e.g., pharmacovigilance if heterologous ('mix-and-match') immunization schedules are used, and alignment on requests from regulators to industry on pharmacovigilance studies and data collection.

Key questions include whether correlates of protection will be the same across all vaccine platforms, and the design and analysis of clinical studies (including for booster doses) to define correlates of protection, e.g. non-inferiority vs superiority, selection of comparator and end points.

3. Clinical trial designs for COVID-19 vaccines

- Yasuhiro Fujiwara, PMDA
- June Raine, and Lisa Campbell, Clinical Trials Unit, MHRA, UK

Clinical trials for COVID-19 vaccines are increasing difficult to conduct in some countries and regions, especially the ability to include placebo control arms, as more people are vaccinated. Alternative designs are needed, for example non-inferiority trial designs, but there remain open questions including selection of active comparators, levels of correlates of protection and immunogenicity, clinical endpoints (and objectives, such as prevention of serious disease or of transmission), follow-up and duration of protection, etc.
It was proposed that 'platform' study designs (using several investigation drugs with single active comparator) to evaluate efficacy could be suitable. The importance of agreed terminology and definitions is key to ensuring acceptance of trial designs, and their results.
These questions could be addressed through the creation of an ICMRA Clinical Trials Working Group that would seek to promote international trials, and to build consensus among regulators on master protocols and designs, particularly in the context of health emergencies. Such a workstream could complement WHO efforts promoting better use of scarce resources. It was proposed to engage with the WHO R&D Blueprint programme on lessons learned concerning the uptake of WHO Master Protocols, and early-stage engagement with researchers and industry.
The existing ICMRA framework for regulatory authorities' involvement in management of global health crises will be reviewed to ensure that experience from the COVID-19 pandemic are considered for future preparedness planning.

4. Discussion

- Marion Gruber, Office of Vaccines Research and Review, CBER, FDA, US
- Marco Cavaleri, Biological Health Threats and Vaccines Strategy task force, EMA, EU

The brainstorming session was intended to promote exchange of views and to identify key issues where convergence among regulators is important, i.e. authorisation of second-generation vaccines and alternative approaches to demonstrate vaccine efficacy.
Factors to consider in clinical trial designs to determining the effectiveness of second-generation COVID-19 vaccines includes the epidemiology and trajectory of the pandemic across countries and regions, including whether there is high or low prevalence of SARS-CoV-2, as well as vaccine availability, vaccination coverage, etc. Furthermore, it should be recognized that data to support the authorization of 2nd generation vaccines may depend on whether the vaccine will be used for primary series vaccination or for booster vaccination based on primary series vaccination with a different vaccine.
There was convergence on the key issue that regulators need to reach alignment in, namely appropriate study designs to demonstrate the effectiveness of 2nd generation COVID-19 vaccines and the need to generate robust data for authorisation. Approaches to authorization of 2nd generation vaccines may include placebo controlled clinical disease

endpoint trials provided they can still be ethically performed. Alternative approaches may include relative clinical disease endpoint efficacy studies and possibly human challenge trials.

There was consensus that immunogenicity bridging studies may be needed if an assessment of effectiveness of 2nd generation COVID-19 vaccines in clinical endpoint efficacy studies are no longer feasible. These could be designed as non-inferiority immunogenicity studies if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or superiority designs if the comparator vaccine has demonstrated modest efficacy. The selection of immune markers to predict effectiveness (e.g. neutralizing antibody titre using WHO certified reference standard), identification of meaningful endpoints and statistical criteria, choice of appropriate vaccine comparators (e.g. platform) and population comparator groups (e.g. matched by age, gender, prior vaccination status) were also highlighted as critical factors to agree upon.

Other challenges for regulators included defining approaches to demonstrate effectiveness for 2nd generation vaccines that will be solely developed as booster vaccines, e.g. administered as heterologous boost following a primary series with another vaccine (potentially comparing the immunogenicity of booster responses induced by the 2nd generation vaccine to the homologous boost afforded by the primary series vaccines), and practical aspects of interpreting trial data with different dosing regimens or second-dose intervals. Sharing the responses to sponsors with other regulators would help building global convergence.

5. Next steps

In addition to recognition of the complexity and challenges, international regulators moved towards consensus on key issues where convergence is highly needed. The importance of the role of WHO, especially the new TAG-CO-VAC, was highlighted.

Questions around study designs need to be further explored including from the practical aspects. It was proposed to create a new forum through setting up an ICMRA Clinical Trials Working Group.

An ICMRA follow-up workshop will be organised after the summer to focus on development and approval of second-generation vaccines.

***DOI: 10.1056/NEJMsr2105280, 23 June 2021**

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