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Workshop Report

COVAX Manufacturing and Clinical Development SWAT Teams Workshop on “*Multivalent COVID vaccines to help address emergence of variants: CMC and clinical implications*”

April 14th, 2021

Meeting report prepared by
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Executive summary

On 14th April 2021, the COVAX Manufacturing and Clinical Development & Operations SWAT Teams co-hosted a workshop on “Multivalent COVID vaccines to help address emergence of variants: Chemistry, Manufacturing, and Controls (CMC) and clinical implications.” The main aim was to cover CMC and clinical themes related to vaccine candidates that comprise multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

Key points from the manufacturing case studies included:

- The successful expansion of Gardasil® human papilloma virus (HPV) type coverage to Gardasil®9 leveraged a platform manufacturing process that enables manufacturing of multiple serotypes with the same equipment train, an integrated control strategy that relies on process and analytical control to ensure consistency and quality, a flexible supply chain to meet changing demand, and a life cycle management approach to respond reactively and proactively to changes.
- To remain effective, the composition of seasonal influenza vaccines must be reviewed and updated for each season to include the haemagglutinin (HA) antigens expressed by the most current circulating influenza wild-type viruses.
- Seasonal influenza challenges include requirement for year-round surveillance, increasing number of candidate vaccine viruses (CVVs), legislation increasingly a barrier to access and use of CVVs, tight manufacturing timelines, annual update of licenses is labour and time intensive, and risk of vaccine mismatch due to evolving viruses.

Key points from the clinical case studies included:

- Clinical development of multivalent vaccines potentially becoming available towards the end of the year must be seen in the context of the emerging epidemiology and current vaccine roll out as well as previous priming with either vaccination or natural infection.
- Potential interference/immunodominance among antigens of multivalent vaccines as well as original antigenic sin post previous exposure is plausible and should be considered when deciding on, designing, and testing multivalent vaccines. Antigen design and choice of vaccine platform may mitigate this risk.
- Takeda has developed a bivalent norovirus vaccine candidate, TAK-214, with lessons learned on selection of antigens and adjuvants and imbalanced formulation, assessment of immunogenicity and choice of assays, selection of endpoints in efficacy trials, as well as emerging epidemiology.
- The high-dose quadrivalent influenza vaccine was licensed via an immunobridging approach. No additional efficacy trial was required given the proven clinical benefits of the high-dose trivalent vaccine.
- Moderna’s vision for variant vaccines is a multivalent, boost indication for all comers (previously vaccinated and immune-naïves) to close the immunological gap that may lead to reduced efficacy of prototype vaccines, address epidemiology in different geographies, and be a stepping-stone to a multivalent primary series vaccine resilient to continued evolution.
- Harmonisation of endpoints used for immunologic non-inferiority assessment and standardisation of respective definitions would be preferable (geometric mean titre [GMT], seroconversion rate, seroresponse rate).

Other general key points included:

- A globally coordinated response is essential for identifying variants of concern (VOC), their impact on vaccines, and the need for modifications to vaccine composition.

- Regulatory alignment to assess modifications to monovalent SARS-CoV-2 vaccines with established efficacy is largely achieved, but detailed guidance on multivalent vaccines is not yet provided.
- Specifications for multivalent vaccines must be based on characteristics of vaccine lots demonstrated to be safe and effective in clinical studies.
- Dose ranging studies characterising neutralising antibody and cell-mediated immunity can be as important for setting CMC specifications as they are to determine the target clinical dose for Phase 3.
- Clinical development programs will vary for proposed multivalent vaccines and approval strategies should specifically address multivalent vaccines based on an authorised platform with clear demonstration of efficacy based on a clinical disease endpoint versus multivalent vaccines based on platforms which are not yet authorised.

The slideset from the meeting can be found on the COVAX Epi Hub:

<https://epi.tghn.org/covax-overview/clinical-science/> and a recording to the session can be found [here](#).

Agenda

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10 min	Introductions, meeting overview and rules	Ajoy Chakrabarti, BMGF
15 min	Current thinking: regulatory expectations for variant vaccines	Dean Smith & Catherine Njue, Health Canada
Manufacturing case studies		
20min	Multi-filo vaccine design based on an MVA platform	Hubertus Hochrein, Bavarian Nordic
20 min	Challenges of developing a multivalent vaccine for the global market: Gardasil®9	Paula Annunziato & Dicky Abraham, Merck
20 min	Introducing new flu strain and challenges with multivalent vaccines	Beverly Taylor, Seqirus
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Clinical case studies		
10 min	Introduction	Jakob Cramer, CEPI
10 min	Immunological perspectives	Arnaud Didierlaurent, University of Geneva
15 min	Takeda bivalent norovirus vaccine	Jim Sherwood, Takeda
15 min	Sanofi TIV to QIV influenza vaccine	Kevin Yin and Sandrine Samson, Sanofi
20 min	Moderna COVID-19 vaccines	Darin Edwards, Brett Leav, and Carla Vinals, Moderna
Concluding Remarks and Wrap-up		
10 min	WHO support to regulatory preparedness	David Wood, WHO
10 min	Meeting close and discussion	Jakob Cramer, CEPI

Introduction

Dr Ajoy Chakrabarti from the Gates Foundation welcomed participants and set the context for the workshop.

Addressing SARS-CoV-2 variants will impact development activities related to COVID-19 vaccines for the foreseeable future. Previous workshops have discussed introduction of a modified or new vaccine to address variants; however, this workshop focused specifically on multivalent vaccines and lessons learned by others when developing such vaccines. This joint workshop covered three major Chemistry, Manufacturing, and Controls (CMC) themes for vaccine candidates that comprise multiple SARS-CoV-2 variants, including impact on potency assays and setting release specifications, impact on formulation and stability, and difference between multiple drug substances (DS) that are blended together versus multiple antigens in a single DS. Clinical themes included risk of immunological interference, how to benchmark the response to the new antigen against the response of the prototype vaccine antigen, and safety.

Current thinking: regulatory expectations for variant vaccines

Dr Dean Smith and Dr Catherine Njue, Health Canada, gave an overview of current regulatory thinking on multivalent vaccines and requirements for nimble regulation during a pandemic.

Summary points included:

- CMC characterisation and quality control (QC) for vaccine antigens in a multivalent vaccine is the same as that for monovalent vaccines, with the additional consideration of antigen interference in the QC assays.
- Options include single antigen DS requiring blending, multiple antigens in a single DS, and VOC adapted antigen design. Each are associated with different advantages and disadvantages.
- Specifications for multivalent vaccines must be based on characteristics of vaccine lots demonstrated to be safe and effective in clinical studies or through clinical experience.
- Dose ranging studies characterising neutralising antibody and cell-mediated immunity can be as important for setting specifications as they are to determine the target clinical dose in Phase 3.
- There is potential complexity with release/end of shelf-life specifications with multivalent vaccines and differing rates of potency decline between multiple antigens.
- Clinical development programs will vary for proposed multivalent vaccines, and a distinction should be made between multivalent vaccines based on an authorised platform with clear demonstration of efficacy based on a clinical disease endpoint versus multivalent vaccines based on platforms which are not yet authorised.
- For COVID-19 vaccines which have already been authorised, the generation of a bi- or multivalent vaccine will likely necessitate additional immunogenicity studies to define the appropriate dose for each sequence.
- Studies will also be needed to investigate whether the addition of any further sequence does not result in an inferior immune response to vaccines with a single sequence, and reactogenicity will need to be evaluated.
- Clinical development plans for multivalent vaccines based on platforms which are not yet authorised will depend on the stage of development including available data on immunogenicity, safety, and efficacy. Early discussions with regulatory agencies are needed.

Additional discussion points included:

- *Which vaccines are considered as the comparator for non-inferiority studies?*
 - Choice of comparator in a non-inferiority study is very important and should be discussed with the regulator during the design of the study.
 - The current thinking is that the immune response induced by a multivalent vaccine be compared to the immune response induced for example by the prototype vaccine against the virus upon which the prototype vaccine was based. With bivalent vaccines for example, two comparisons would have to be carried out, one against each sequence.
- *What are examples of possible margins for non-inferiority in the case of COVID vaccines?*
 - Margins of 10% for seroresponse and 0.67 for GMT are typically used; however, other margins are possible if they can be justified depending on the situation.
- *Is it appropriate to conduct a variant study in parallel with a Phase 3 study for the prototype vaccine so approval for both can be submitted simultaneously?*
 - This is dependent on what data are available. It is important that some efficacy data (i.e., interim analyses) are available for the prototype vaccine first before proceeding to assess immunogenicity for a multivalent vaccine.

Manufacturing case studies

Multi-filo vaccine design based on a MVA platform

Dr Hubertus Hochrein, Bavarian Nordic, discussed a multivalent single vector vaccine based on the MVA platform which has been developed for filoviruses.

The speaker's summary points included:

- MVA-BN[®]-filo is a multivalent vaccine designed to protect against Marburg, Ebola Zaire, and Sudan viruses, as well as smallpox.
- MVA-BN[®]-filo encodes for the major protective antigen glycoprotein of all filoviruses and for the conserved nucleoprotein known to induce T cell responses.
- MVA-BN[®]-filo demonstrates that the MVA platform could be the basis for multivalent vaccines.
- MVA-BN[®]-filo induced immune responses to the incorporated transgenes covering the lethal filoviruses.
- Synergy was achieved with another single vector multivalent vaccine (FPV-multifilo) in protecting against Ebola virus (EBOV) challenge in non-human primates (NHP).
- MVA-BN[®]-filo demonstrated strong synergy with monovalent adenoviruses in protecting NHP against EBOV challenge.
- In combination with monovalent adenoviruses, MVA-BN[®]-filo synergistically induced strong (antibodies and T cells) and durable immune responses in various clinical trials.

Additional discussion points included:

- *What approach has been used for polycistronic immunogens?*
 - Polycistronic immunogens have not been used for the described filovirus vaccine; however, they have been used in other MVA constructs, for example for a respiratory syncytial virus vaccine. There, the sequences of the nucleoprotein and the matrix protein incorporated as T cell targets have been separated by an 2A-peptide. Large sequences encoding for structural components are better expressed by individual promoters. With a wide variety of different promoters and insertion sites at hand, an individual promoter driven response is preferable to a multicistronic response.

- *Is there evidence that the inclusion of nucleocapsid protein provides additional benefit?*
 - The immune response to all the inserts including the nucleoprotein could be measured, which includes T cell responses. It has been observed in various animal studies that those T cell responses form part of the protection following MVA vaccination. In experimental settings with only little antibody induction, likely T cell mediated immune protection could be observed. It is difficult to determine what part the immune response to the nucleoprotein plays in the overall protective response in filo virus infection, but for other viral infection models the addition of T cell targets resulted in improved protection.

Challenges of developing a multivalent vaccine for the global market: Gardasil®9

Dr Paula Annunziato and Dr Dicky Abraham, Merck, discussed the challenges of developing a multivalent HPV vaccine for the global market.

Key points included:

- Gardasil®9 expanded on coverage against the oncogenic HPV types moving from targeting the causes of about 70% to 90% of cervical cancers around the world. The development of Gardasil®9 was based on the quadrivalent Gardasil vaccine. Gardasil®9 was licensed based on demonstrating comparable immunogenicity to the original four Gardasil types and then showing clinical efficacy against cervical dysplasia caused by the five new oncogenic types.
- The successful expansion of Gardasil® HPV type coverage to Gardasil®9 leveraged:
 - A platform manufacturing process that enables manufacturing of multiple serotypes with the same equipment train.
 - An integrated control strategy that relies on process and analytical control to ensure consistency and quality.
 - A flexible supply chain to meet changing demand.
 - A life cycle management approach to respond reactively and proactively to changes.

Additional discussion points included:

- *Was the possibility of licensure of the nine valent vaccine based on comparative immunogenicity to the four valent vaccine considered?*
 - Licensure of the original four types included in Gardasil®9 was based on immunogenicity. To demonstrate that the additional types conferred benefit in terms of efficacy, clinical efficacy of the new types against cervical dysplasia had to be demonstrated.
- *How long does it take to complete one batch of Gardasil®9 and how many production lines are needed to allow for vaccine production?*
 - The number of lines needed to allow for vaccine production is based on supply and demand. At the start, one production line was used to manufacture all nine types; however, this has since increased due to global demand. A typical drug substance lot can be manufactured in under 10 days if done sequentially.

Introducing new flu strain and challenges with multivalent vaccines

Dr Beverly Taylor, Seqirus, provided an overview on seasonal influenza and challenges with multivalent vaccines.

Main points included:

- To remain effective, the composition of seasonal influenza vaccines must be reviewed and updated for each season to include the HA antigens expressed by the most current circulating influenza wild-type viruses.
- This is a lengthy and complex process and requires extensive and ongoing collaboration between all stakeholders.
- A review of recent global surveillance data informs the vaccine virus recommendations made by the World Health Organisation.
- The vaccine virus recommendations, provided in February for the northern hemisphere and in September for the southern hemisphere, provide a guide to national public health authorities and vaccine manufacturers for the development and production of multivalent influenza vaccines for the upcoming influenza season.
- It is the responsibility of each national regulatory authority to approve the composition and formulation of the vaccines used in that country.
- Influenza vaccine virus recommendations are dynamic, with several CVVs being considered for each season.
- Most National Influenza Centres supply influenza viruses as part of the WHO Global Influenza Surveillance and Response System, however there is a lack of legal clarity if the viruses can be used for vaccine manufacturing and research.
- It is neither feasible nor efficient to start bilateral negotiations with all CVV provider countries prior to confirmation of recommended viruses. Once the vaccine recommendation is made, there is limited time for manufacturers to conclude bilateral negotiations in time for the manufacturing campaign.
- Nagoya Protocol (NP) or National Access and Benefit (ABS) Legislation differs in each country and is often only available in the local language which poses challenges with interpretation of requirements.
- It is not always clear which viruses may be considered as “like” viruses to the recommended virus and could be used as an alternative in manufacturing.
- Several cases of delays in influenza virus sharing due to implementation of the NP/ABS legislation have already been experienced.
- Seasonal influenza challenges include requirement of year-round surveillance monitoring, increasing complexity of virus clades/sub-clades results in more CVVs to consider, NP/ABS legislation is increasingly a barrier to the access and use of CVVs, manufacturing timelines are tight with any delays impacting vaccine supply, annual update of licenses is labour and time intensive, and there is a risk of vaccine mismatch due to evolving viruses.

Clinical case studies

Introduction

Dr Jakob Cramer, Coalition for Epidemic Preparedness Innovations, introduced this section of the workshop and set the scene for the presentation of clinical case studies related to the development of multivalent vaccines.

Summary points included:

- Clinical development of multivalent vaccines potentially becoming available towards the end of the year must be seen in the context of the emerging epidemiology and current vaccine roll out as well as previous priming with either vaccination or natural infection.
- Particular consideration should be given to Wave 2 vaccine candidates that have not yet entered advanced stage clinical development.

- The coordination of ‘strain change’ by WHO is a difficult and complex matter but of relevance with regards to planning and timing the clinical development of multivalent and monovalent adapted vaccines. Many manufacturers are advancing modified vaccines based upon VOC B.1.351 without awaiting WHO guidance.
- The seropositivity rate is increasing significantly in countries with vaccine roll out but also through natural infection, and currently primary objectives have been assessed based on seronegative subjects in clinical vaccine efficacy trials. This needs consideration when planning clinical trials for the development of adapted monovalent or multivalent vaccines including the assessment of appropriate immunisation schedules (e.g., two doses for priming versus single dose for boosting).
- Challenges related to the establishment of non-inferiority for polio vaccines and how they might apply to COVID-19 vaccines include:
 - The non-inferiority assessment and sample size will depend on the immune readout being used for the non-inferiority assessment. Seroresponse rate may be easier to achieve than seroconversion rate.
 - The immune response to a homologous virus type assay will likely be superior to a heterologous assay.
 - Serotype-specific differences in immune response can lead to imbalanced antigen concentrations in the vaccine.
- The ACCESS group of regulators have included a few statements on multivalent vaccines in their regulatory guidance. In terms of immunological non-inferiority, there is, however, no consensus approach with the Food and Drug Administration requesting comparisons based on the seroresponse rate (and GMTs) while the European Medicines Agency requests seroconversion rate (and GMTs).
- Harmonisation of endpoints used for immunologic non-inferiority assessment and standardisation of respective definitions would be preferable (GMT, seroconversion rate, seroresponse rate).

Immunological perspectives

Dr Arnaud Didierlaurent, University of Geneva, discussed immunological considerations for multivalent vaccines.

Summary points included:

- Potential interference/immunodominance among antigens of multivalent vaccines is plausible (i.e., risk of original antigenic sin in those previously infected/vaccinated) and should be considered when deciding on or designing multivalent vaccine.
- Antigen design (i.e., rational antigen design to favour cross-reactive antibody response) and choice of vaccine platform (i.e., different vaccine platform for booster) may mitigate this risk.
- The inclusion of a large amount of sequence to generate a broad vaccine is not always preferable and may risk immunological overload or interference.
- Implications for study design/read-outs of multivalent vaccines include:
 - The potential for increased reactogenicity in primed individuals (previously infected or vaccinated); if two doses are needed should be assessed.
 - It is important to compare each monovalent vaccine versus multivalent vaccine.
 - It is critical to also assess primed individuals in clinical studies as the response in naïve individuals may not be representative.
 - It is critical to have validated antibody cross-neutralisation tests to assess established strains.
- However, reasons to be optimistic include:

- The quality of antibodies (e.g., breadth) increases with time, and boosting several months after the first vaccine/infection is beneficial.
- In contrast to neutralising antibodies, T cell responses in convalescent or vaccinated individuals are not substantially affected by variant mutations, thus can support affinity maturation and improve B cell fitness.
- There is emerging evidence that previous infection with some variants elicit “fitter B cells” that may be recalled by vaccination.

Takeda bivalent norovirus vaccine

Dr Jim Sherwood, Takeda, discussed lessons learned in the development of multivalent bi-component Norovirus vaccine.

Summary points included:

- Norovirus is highly infectious and responsible for widespread human disease.
- Takeda has developed a bivalent norovirus vaccine candidate, TAK-214.
- Factors considered for selection of antigens and formulation for TAK-214 include epidemiology (e.g., strain variation, incidence of different genotypes/strains by age group), serological cross-reactivity, possible interference/competition of antigens, and selection of dose and regimen.
- Emergent strains emphasise the importance of surveillance over time. Regional emergence of new viral variants (e.g., GII.17) does not necessarily lead to global circulation and establishment requiring vaccine adaptation as new variants may disappear again.
- Noroviruses were non-cultivable until recently, and a neutralisation assay using this system is still under development. A correlate of protection has been proposed but has yet to be confirmed.
- Noroviruses bind to human cells through attachment with histo-blood group antigens (HBGA) and a blocking assay for this binding has been developed. Takeda is currently in the process of validating an HBGA blocking assay for use in late Phase 2/3 development even though this is not a direct measurement of neutralisation.
- Dose selection may require multiple study arms testing different strain-specific antigen concentrations, balanced / imbalanced formulations as well as different adjuvants stratified by age groups. Appropriate trial design such as factorial design should be considered.
- The selection of vaccine efficacy endpoints (accounting for different vaccine-contained and non-vaccine-contained viral strains) depends on the population. A “standard approach” was used to assess efficacy against vaccines components. Other options, including “all noro” as the primary endpoint and co-primary endpoints, were considered. Endpoints with a co-pathogen were excluded. In terms of cross-protection, efficacy against non-vaccine genotypes was included as an exploratory endpoint.

Sanofi trivalent to quadrivalent influenza vaccine

Dr Kevin Yin, Sanofi, discussed high dose influenza vaccine and the development of the quadrivalent from trivalent vaccine.

Key points included:

- Valency increase for influenza vaccines is not new.
- Licensure of influenza vaccines is based on antibody response. The HA inhibition titre (e.g., seroconversion) is a ‘proxy’ of correlation.

- High-dose vaccines (i.e., four times the antigen of standard dose unadjuvanted vaccine) are newer influenza vaccines for use in adults 65 years of age and older. A fast-track licensure path based on immune response allowed for early access of high-dose trivalent vaccines.
- The high-dose trivalent vaccine was demonstrated to outperform the standard dose unadjuvanted trivalent vaccines, which is supported by numerous efficacy and effectiveness studies.
- Based on demonstration of the non-inferior immunogenicity of high-dose quadrivalent (IIV4-HD) versus high-dose trivalent (IIV3-HD), efficacy/effectiveness data of IIV3-HD was inferred to IIV4-HD. This approach has been recognised by authorities and IIV4-HD is now licensed in the USA, Europe, and four other countries.
- IIV4-HD was licensed via an immunobridging approach. No additional efficacy trial is required given the proven clinical benefits of IIV3-HD.

Moderna COVID-19 vaccines

Dr Darin Edwards and Dr Brett Leav, Moderna, discussed multivalent variant mRNA COVID vaccines.

Key points included:

- Moderna has experience with multi-component mRNA products.
- Prior to emergence of VOCs, mRNA-1273 clinical development plan was testing a third vaccination of mRNA-1273, should annual boosters be required to maintain protective titres. Moderna is also now advancing strain-matched vaccines for boost and prime against VOCs.
- The B.1.351 (South Africa) strain was the first to show reduction in neutralisation, and Moderna is currently advancing a B.1.351-matched variant as a booster vaccine.
- The vision for variant vaccines is a multivalent (cocktail of lipid nanoparticles containing mRNA), boost indication for all comers to close the immunological gap that may lead to reduced efficacy of prototype vaccines, address epidemiology in different geographies, and be a stepping-stone to a multivalent primary series vaccine resilient to continued evolution.
- Experience with multi-component mRNA vaccines to date shows no interference.
- Numerous planned non-clinical studies are in progress at present including murine, hamster, and NHP studies.
- Data from a murine study shows that a multivalent approach appears most effective in broadening the immune response as a primary vaccination series demonstrating a balanced immune response in naïve mice.
- mRNA-1273.351 is an effective third dose booster in a mouse model. Further studies are ongoing in mice, hamsters, and NHP to evaluate boosting with monovalent and multivalent mRNA vaccines.
- Clinical trials are underway with either the monovalent variant vaccine designated 351 and the multivalent vaccine combining the 351 variant with the prototype 1273 Wuhan strain.
- Key considerations for immunobridging include difference in binding/neutralisation assays against parent and variant strain, comparison of surrogate endpoints across strains of varying morbidity and mortality, and differences in absolute levels of neutralising antibody. Setting criteria for booster indication based on the immune response to a booster dose of vaccine in naturally infected subjects or defining a fold increase versus baseline would allow for harmonisation and booster indication for all comers with history of vaccination or infection.

Concluding remarks and wrap-up

WHO support to regulatory preparedness

Dr David Wood, WHO, discussed WHO support to regulatory preparedness.

Summary points included:

- A globally coordinated response is essential for identifying VOC, their impact on vaccines, and any modifications to vaccine composition.
- Regulatory alignment to assess modifications to SARS CoV-2 vaccines with established efficacy is largely achieved, but detailed guidance on multivalent vaccines not yet provided.
- Further regulatory guidance is being developed.
- Careful messaging is essential so as not to disturb public trust in COVID-19 vaccines.

Meeting close and discussion

Dr Jakob Cramer thanked attendees for their participation in the workshop and outlined the next steps as follows:

- Resources will be shared at the following website (<https://epi.tghn.org/covax-overview/>) and a workshop report will be distributed.
- Workshop attendees are invited to join post-workshop discussions on the [COVAX hub](#).
- Other COVAX workshops to be held include:
 - April 28th Vaccine Safety Workshop: COVID 19 Vaccines Risk Management Planning: Stakeholders Experiences and Perspectives
 - May 20th COVAX Clinical Development and Operations Workshop.