2021 WHO Product Development for Vaccines Advisory Committee (PDVAC) Virtual Consultation: WHO mechanisms to support manufacture of and Access to mRNA Vaccines in Low- and Middle-Income Countries

5 November 2021

Closed meeting

Participants:

PDVAC: Isabelle Bekeredjian-Ding, Sophie Biernaux, Alejandro Cravioto (SAGE chair, ex-officio member), Sinead Delany-Moretlwe, Gagandeep (Cherry) Kang, David Kaslow (PDVAC chair), Ruth Karron, Jerome Kim, Claudio Lanata, Raman Rao, Gustavo Santos, Yiming Shao, Kavita Singh, Marian Wentworth, Beno Nyam Yakubu, Gerd Zettlmeissl.

Apologies: Peter Smith

WHO: Moredreck Chibi, Martin Friede, Birgitte Giersing, Lindiwe Makubalo, Caroline Marshall, Analia Porras, Erin Sparrow

Executive Summary:

Rationale for the meeting:

The COVID-19 pandemic has again highlighted that populations in regions without vaccine manufacturing capacity are last-in-line to receive vaccines in times of need. Today, only 4% of Africa's population is fully vaccinated. To address this stark and persistent inequity, WHO has initiated the establishment of technology-transfer hubs in regions that currently have no or limited vaccine manufacturing capacity. These hubs will be funded and mandated to establish new-generation vaccine manufacturing technologies, and to then transfer these technologies to existing and new manufacturers in LMICs (i.e., spokes). The first of these hubs, in South Africa, will establish and transfer mRNA vaccine technology. This investment will empower countries to drive their own R&D agendas, thereby shifting the dialogue on global R&D priority setting, resulting in greater diversity of candidates in the pipeline that are truly built 'ground up', based on the realities and priorities of countries' needs.

In June of 2021, PDVAC expanded its remit to support the COVAX manufacturing task force, including the evaluation of expressions of interest related to selection of regional hubs for vaccine manufacture and priority platform manufacturing technologies for technology transfer. PDVAC communicates its recommendation to WHO. PDVAC also provides, in the context of the Immunization Agenda 2030 (IA2030), and specifically strategic priority area 7 on Research and Innovation, reviews of the outputs, workplans, and reports from the SP7 working group (WG) consultations on defining country and regional priorities. PDVAC will work closely with the SP7 WG to develop an integrated strategy on research and development priorities and targets for R&D in immunization, across all three levels (country, regional, global).

PDVAC will further expand in 2022 and will seek to recruit regional representatives who play a key vaccine-related technical, strategic and/or programmatic role. In particular, PDVAC is seeking to define a mechanism to partner with regions to define R&D priorities through a truly global approach, for example to collectively identify priority vaccine targets for the mRNA platform.

The intended aims of this PDVAC session were to:

- Review the workstreams related to the WHO hubs and spokes to date, and anticipated future activities;
- Understand the role and expectations of PDVAC, as it relates to the work under the COVAX manufacturing task force (MTF) (workstream 3);
- Define the process for engaging PDVAC in future COVAX MTF-related activities, with respect to lead time, deliverables, communication;
- Discuss how PDVAC could support and partner with regional initiatives to identify priority vaccine targets for the mRNA platform and hubs; what role can PDVAC play?

PDVAC conclusions and recommendations:

- A subgroup of PDVAC members with the requisite expertise will be formed to review proposals related to the WHO mRNA and other platform technology manufacturing hubs, but proposals will be available to all members.
- PDVAC will develop a framework/white paper for identifying priority antigens for mRNA vaccine development.
- A dedicated PDVAC session will be set up to review the mRNA vaccine framework and recommendations in 2022, with a view to helping to inform mRNA vaccine manufacturing priorities for LMICs.

Meeting summary:

1) Welcome and Introduction of new members (*David Kaslow, PATH*)

The meeting was opened by David Kaslow followed by a round of introductions as this was the first PDVAC meeting including five new members: Sophie Biernaux, Raman Rao, Gustavo Santos, Kavita Singh and Gerd Zettlmeissl (bios of members).

2) Overview of the WHO mRNA hub strategy (*Martin Friede, WHO*)

The COVAX manufacturing taskforce hub (MTF) strategy aims to expand the capacity of LMICs to produce mRNA vaccines of regional priority. There are multiple mRNA vaccines in development from several developers/manufacturers, ranging from preclinical stages to licensed COVID-19 vaccines. In addition, there are multiple technologies including simple coding mRNA, self-amplifying mRNA as well as variations in the lipids used to deliver the mRNA. These factors can affect the immunogenicity, efficacy, reactogenicity, thermostability and costs of mRNA vaccines. While there are many promising technologies, to date, the only proven technologies are those from Moderna and BioNTech. Intellectual property barriers, including patents filed in some countries and access to know-how, need to be considered when adopting these technologies.

Following requests to WHO from several regions to receive access to know-how and manufacturing capacity for mRNA vaccines, the COVAX Manufacturing task force was created. It is structured around three worksteams:

- **Workstream 1 – Immediate COVAX response** - is focused on input of supplies (glass vials, reagents etc), creating partnerships and accelerating the export permits/customs clearance for supplies. [Post meeting note: As of March 2022, this workstream has been sunsetted]

- **Workstream 2 – Short and Mid-Term COVAX response** - is focused on: expanding fill and finish mechanisms/partnerships; creating an overview of global manufacturing capacities; better utilizing existing capacities; and developing regulatory and manufacturing workforces. [Post meeting note: As of March 2022, this workstream has been sunsetted]

- **Workstream 3 – New & expanded capabilities of existing manufacturers in LMICs** - is focused on: expanding the capabilities of existing manufacturers in LMICs; establishing sustainable capacity in regions with no significant capacity; and creating normative policy frameworks and stimulating manufacturing innovations and investments. PDVAC supports this workstream (see below).

There are two approaches for increasing vaccine manufacturing capacity and supply in LMICs:

- Bilateral technology transfer from one manufacturer to another.
- Multilateral technology transfer through a hub and spoke model where several manufacturers (spokes) can receive technology through training at a central hub. The first step in the process is to establish the hub by bringing requisite expertise together: developers, researchers, experts, IP holders and in some cases Member States to establish the manufacturing process, before training and technology transfer to recipient manufacturers (the spokes). This is the model selected by the COVAX manufacturing taskforce.

The establishment of the central technology transfer hubs is structured around six working groups:

1) Technology innovation, selection and IP (negotiating licenses to technologies etc.)
2) Product development, manufacturing, and plants (ensuring process and facilities are suitable)
3) Regulatory and clinical development
4) Business model and financing to ensure sustainability
5) Funding and governance
6) Workforce development (identifying workforce training needs for both hubs and recipients such as training in GMP and generic operational processes/documentation etc). [Post meeting note: As of March 2022, this is now being supported through a global biomanufacturing training hub in Republic of Korea.]

With regards to progress so far:

- Following a call for expressions of interest to become an mRNA training and technology transfer hub in April 2021, a consortium of South African entities was selected (Afrigen as the hub, Biovac as the spoke with involvement from several South Africa Universities). This was announced publicly in June 2021.
- In September applications from PAHO countries were reviewed and mRNA manufacturing spokes announced in Argentina and Brazil.

- Additional spokes will be included through open calls (see: November call) as well as a call to establish a biomanufacturing training hub. There may also be a call for other technology hubs with different manufacturing technologies such as viral vector vaccines. [Post meeting note: As of March 2022, several spokes have been nominated across all WHO regions and WHO is in discussion with potential additional spokes, see: www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub]

It should be noted that separately, Pfizer/BioNtech announced a fill/finish partnership with Biovac and both BioNtech and Moderna have since announced plans to set up production facilities in Africa.

The technology currently being evaluated at the South Africa hub is based on the published Moderna composition. Negotiations are ongoing to license second-generation technologies with improvements.

There are several challenges and opportunities:

- There are bilateral plans from some manufacturers to establish mRNA vaccine production facilities in Africa.
- There is a clear need for manufacturing capacity in all regions, and this needs to be included in the global strategy;
- Next generation products will need to be thermostable and have a reduced cost of goods in order to be suitable for LMICs;
- mRNA clearly has advantages due to its speed from concept to the clinic and it elicits antibodies as well as CD4 and CD8, and can probably be used repeatedly (while viral vectors may lead to anti-vector immunogenicity with potential impact on repeated use); however the immune response induced by mRNA is not fundamentally different to heterologous prime boost regimens with viral vectors.
- Beyond COVID-19, what other vaccines could the facilities produce?
    - From the LMIC perspective there is a clear need for TB, HIV and malaria vaccines but mRNA is not likely to solve the biological problems with antigen selection in vaccine development.
    - Other potential vaccines could include RSV, Dengue, CMV, pandemic and seasonal influenza and others.

With regards to the role of PDVAC, the committee will be expected to advise the WHO secretariat as follows:

- Provide technical evaluation of proposals/expressions of interest for:
    - The hubs (e.g. a biomanufacturing training hub as well as hubs with other technologies such as viral vector vaccines).
    - Recipients of technology transfer (spokes), PDVAC will be expected to review the proposals in terms of:
        - Technical/infrastructure/HR capacity to receive the technology.
        - Likelihood of bringing vaccines to approval.
        - National regulatory agency maturity (will they reach maturity level 3 in the time needed to develop their vaccines).
        - Addressing inequity: what is capacity in region/subregion/country.
- Advise the WHO secretariat on whether a technology is appropriate.

Discussion:

- WHO has been in discussions with several funders to ensure alignment on establishing regional manufacturing strategy and minimize overlap and resource wastage.
- All spokes will receive the training on one technology, but this will not obligate or limit them to that specific technology; they can diversify.
- Beyond COVID-19 vaccines, in the long term this initiative will establish capacity and knowledge acquisition for other vaccines and related technologies, in the regions, and the potential for response to future outbreaks or pandemic. Regions and countries will be positioned to undertake research and development in line with their context specific priorities.

- The PAHO project has developed a business model where, through the PAHO revolving fund, mRNA vaccines produced in Brazil and Argentina will be available to all countries in the region.
- A critical element to consider is access to raw materials for producing mRNA vaccines as they are expensive with limited suppliers. More capacity to produce raw materials is needed.
- In order to overcome the thermostability issues of mRNA, several technologies are being assessed based on publications, patents and discussions with biotech companies.
- WHO will provide information on maturity levels of NRAs and what actions are being undertaken by the regulatory systems strengthening unit at WHO and the national regulatory agency to reach maturity level 3 and timelines for doing so (for those not there yet).
- Beyond COVID-19 vaccines, there are IP barriers to producing other vaccines, the freedom to operate is being assessed to identify potential opportunities for use.
- With regards to the role of PDVAC in advising on appropriate technologies, this would be primarily for PDVAC members with the scientific expertise and background to be able provide a technical assessment of different technologies to ensure the most appropriate technologies are selected.

3) An overview of the IA2030 SP7 remit and objectives (*David Kaslow*):

The Immunization Agenda 2030 (IA2030) includes a strategic priority (SP7) on Research and Innovation. IA2030 builds on lessons learned from the Global Action Plan for Vaccines (GVAP) however one key difference is that IA2030 is not a top down approach, it aims to engage with countries to tailor to the national context. SP7 is not only about developing new vaccines but also increasing the reach and impact of immunization to all countries and communities.

The objectives of SP7 are to:

- Establish and strengthen capacity at all levels to identify priorities for innovation, and to create and manage innovations.
- Develop new vaccines and technologies and improve existing products and services for immunization programmes.
- Evaluate promising innovations and scale up innovations, as appropriate, based on the best available evidence.

The key areas of focus are:

- **Needs-based innovation:** Strengthen mechanisms to identify vaccine-related research and priorities for innovation according to community needs, particularly for underserved populations, and ensure that the priorities inform innovations in immunization products, services, and practices.
- **New and improved products, services, and practices:** Accelerate the development of new vaccines, technologies and improved products, services and practices, while ensuring continued progress in the development of vaccines for priority targets, including HIV, TB, malaria and emerging infectious diseases.
- **Evidence for Implementation:** Shorten the path to maximum vaccine impact by implementation and operational research and through evidence-informed decisions on policy and implementation based on sound evidence of needs, benefits and risks.
- **Local innovation:** Build local capacity to address programme challenges and maximize impact by cooperative creation, sourcing, adopting and scaling-up of innovations.

There are 13 technical working groups and 3 functional/cross cutting working groups (WG) for IA2030. The SP7 WG is lead by PATH. The WGs will have a balanced representation of North/South countries, country regional and global levels as well as balanced gender etc.

Each of the working groups will commit to at least one consultative engagement with stakeholders per year. The working groups will drive monitoring and evaluation cycles and provide technical guidance to drive the immunization programmes and learning agendas.

The terms of reference for the SP7 working group have been developed and will be shared with PDVAC. The ToRs identify key connections to make with other initiatives such as GAVI 5.0 (VIPS and VIS), CEPI 2.0, WHO CAPACITI, COVAX, GVIRF, WHO AMR Value Attribution Framework, and the R&D blueprint.

The working group will consist of 18 members. Twelve of those will be independent members with the aim to have two from each of the WHO regions and then six ex officio members from the core IA2030 partners (WHO, GAVI, CEPI, UNICEF, NIH, Wellcome Trust).

The SP7 working group is supposed to organize a series of regional consultations in 2022 to help identify and determine the R&D agenda setting at the national, regional, and global level. If this is able to be achieved, the information would be collected, synthesised and discussed with PDVAC with the goal to bring the outputs to SAGE in October 2022. However, the COVID-19 pandemic has had an impact on operationalizing IA2030 and engagement with countries on a broad immunization R&D agenda has been challenging.

The regional workshops are likely to be held virtually and there needs to be some thinking about how to structure and run these. There is need to engage with regions with respect to the level of R&D agenda setting that is currently in place. There is now a question in the WHO-UNICEF Joint Reporting Form (JRF) where all countries are asked whether they have a R&D/immunization agenda in place.

There are also plans to conduct a broad landscape analysis about what the current priorities are of countries and regions. In addition, WHO has commissioned the development of vaccine value profiles for about 20 different pathogens including some monoclonal antibodies. These would be helpful source documents for discussions around prioritization.

The outcomes of all of these efforts will be triangulated to determine the prioritization list.

The SP WG will also be working to accelerate and expand the COVAX R&D agenda and particularly the COVAX manufacturing taskforce efforts.

Innovation needs to come from the voice of LMICs but PDVAC will play a role in this in terms of proposing guidance with respect to identifying the priority targets for vaccines beyond HIV, TB and malaria and including emerging infectious diseases.

PDVAC's role in this will be to:

- **PDVAC** to review the annual IA2030 M&E report and provide feedback on in-depth assessments of specific topics conducted by the IA2030 SP7 Working Group:
  - **Contribute to assessment of progress** in achieving specific IA2030 SP7 area goals and objectives and highlight areas of concern.
  - **Provide technical feedback** on topics elevated to PDVAC by IA2030 SP7 Working Groups or requested by the Coordination Group on behalf of the IAPC.

- PDVAC findings could be included in the feedback to:
    - **IA2030 SP7 Working Group** to highlight specific areas of importance and areas of focus for consultative engagements
    - **Regional and National Immunization Technical Advisory Groups** to align on priority areas and R&D agendas
    - **SAGE** reporting from IA2030 SP7 WG on IA2030 implementation progress
    - **IA2030 Coordination Group** on potential areas for process improvement

4) AFRO vaccine R&D strategic priorities and how the mRNA hub may shape these (*Lindiwe Makubalo/Moredreck Chibi*)

The African Regional Office (AFRO) has a new Science and Innovation Office. The strategy of the Science and Innovation Office is still being defined but one of the first steps will be coordinating within the region and setting up mechanisms to ensure coordination between different groups. This will also include supporting the development of R&D agendas in countries as well as to provide a marketplace/platform for exchange between countries. The regional committee will be working closely with member states to support investments.

In terms of the mRNA hub project, the Office will help to coordinate this and to work with countries to ensure support and sustainability. The Office will also work to support regulatory strengthening.

Beyond COVID the Office will also be looking at other key research and innovation priorities, such as NTDs, HIV, TB etc and the Office will be looking forward to PDVAC support in this area.

AFRO is focusing on three workstreams to promote access to quality assured vaccines for sustainable impact in Africa:

1) Foster and strengthen quality and sustainable local production of vaccines.
2) Market shaping: procurement, supply management and vaccine delivery.
3) Support strengthening of country and regional regulatory systems.

AFRO is taking a value chain approach to support everything from R&D, clinical development, regulatory systems, manufacturing, supply chain, to market.

Among other activities, this includes conducting assessment of the burden of vaccine preventable disease to inform targeted R&D efforts. In addition to supporting the establishment up of the mRNA hub in South Africa, AFRO plans to support local production of raw materials and reagents.

The AFRO Science and Innovation office also plan to develop a regional database and knowledge hub for emerging products, technologies and platforms.

The AFRO innovation marketplace focuses on emerging technologies and innovations. The platform already has 2.5 million subscribers from research institutions, university and innovations hubs and serves as an exchange forum for research activities in Africa.

With regards to countries wishing to establish local vaccine production, AFRO will support economic feasibility assessments and will support negotiations to technologies and capacity building.

With respect to market consolidation and market shaping, AFRO can engage with countries for pollical commitment and regional alignment on the procurement of vaccines and other medical products in the in the context of regional health security.

5) Discussion

What principles can we formalize for engagement with PDVAC on COVAX MTF/WHO hub & spoke-related issues?

- The first call for recipient manufacturers (spokes) will be an expression of interest along with a letter of support from their Governments.
- This will be followed with a questionnaire sent to eligible manufacturers to gather additional information about current capacities. The questionnaire will be shared with PDVAC for input before it is sent to manufacturers.
- A subgroup of PDVAC members with requisite expertise in this area will be set up to review proposals and provide their recommendations to the Secretariat, but the proposals will be sent to all members to weigh in if they wish to.
- PDVAC will be informed when expressions of interest will open and close so that members can plan ahead of time when proposals will need to be reviewed.

What are the opportunities and potential mechanisms for improving engagement and partnership with regions on developing national, regional, and global R&D priorities?

The needs to be coordinated through WHO regional office to bring in the regional and country voices to this process. The SP7 regional engagement process will facilitate this approach.

Is there a need to develop a priority pathogen list for WHO-supported mRNA hubs? If yes, what would be the process for that?

Beyond COVID-19, there's is a desire to use this technology for a variety of other pathogens, therefore it would be worthwhile to develop a prioritized list of pathogens for consideration for using the mRNA technology. A starting point could be to look at the list of diseases to see where vaccines are not optimal, unsuitable, or unavailable. The PDVAC priority pathogen list should be revisited as a staring point. An assessment of which pathogens have been evaluated in the past using mRNA vaccine technology should be undertaken to assess if there were specific failures or negative results. Biological and scientific feasibility should be taken into consideration as well as clarity on regulatory pathways.