Participants in person: Patricia Mouta (PM), Viska Indriani Iskandar (VII), Katharina Hartmann (KH), Beatriz Lucchesi (BL), Beauty Moloto (BM), Devang Patel (DP), Reza Bosman (RB), Vanessa Infante (VI), Rajinder Suri (RS), Sonia Villaseñor (SV).

Online participants: Aminata Diagne (AD), Antoine Diatta (AD), Arani Chatterjee (AC), Beverly Cowper (BC), Billo Tall (BT), Chetanraj Bhamare (CB), Fitriani Dewi(FD), Linda Nesbitt (LN), Mandar Kshirsagar (MK), Manish Mahajan (MM), Shuyan Zuo (SZ), Sumit Tandon (ST), Triana Rahmila (TR)

RS welcomed the participants, and invited them to focus on the content and contribute to the delivery objectives of the Workshop. RS invited them to go through a round of introductions. RS emphasized the importance of joining in-person in every meeting in the future, as the quality of interactions is much better face to face than online. RS reminded the participants that he represents the manufacturers in certain highest decision-making bodies like Act A, GAVI, WHO, CEPI, PAVM highlighting what we are doing and what we need, so it is important for members to keep contributing and sharing so that relevant information can be transmitted on such platforms for suitable actions.

How can AVSS help with vaccine safety issues

KH gave some examples from LMICs, and reminded few important points that were discussed in the Workshop in February'23

AVSS is a data collection system that seeks to ascertain certain safety issues. AVSS is not very well established in LMICs.

PM shared the example of the Vaccine Safety Datalink (VSD) that USA implemented to conduct almost real time surveillance on COVID-19 vaccines; linked to the information of health insurance systems and medical records of individuals. This method of real time surveillance could be very useful to be implemented in LMICs, where all collected information is stored in the same place and all stakeholders have access to the data. The participants shared information on the situation in their countries; implementing a similar system would be very challenging. Safety communication is also a challenge. Information on adverse events need to reach the health professionals in a way that they understand the signs and symptoms they need to look for, but that does not create anxiety within the population and vaccine hesitancy. Communication needs to flow very quickly.

As per the contributions of the participants, it was reported that the situation in each country was different during COVID-19 e.g., while in countries like Brazil, the manufacturers did not receive any communication from the NRA about the reports of adverse events received, in India the NRA was in constant communication with the manufacturers.

Collaboration between different stakeholders is essential. It is beneficial to discuss the Risk Management Plan (RMP) upfront with all the stakeholders, including planed AVSS activities together with a timelines and Responsible Centers (RCs).

Such discussions with NRAs should be possible. Lobbying: As a network we could have more strength to come to this discussion with the Ministries of Health.

PM and KH shared some examples of AVSS performed in different LMICs. Details of such examples are in the slides shared with all participants. KH emphasized that it is important also to evaluate the cost-benefit effectiveness as well, not only the benefit-risk effect. This kind of study could represent a high investment.

While analyzing the different examples, the group concluded that signal detection has become the most important part of pharmacovigilance. Causality assessment is very important; most of the time many different factors are involved that lead to the adverse event, such as

immunization errors which need to be considered and analyzed thoroughly. The focus should be on the process of the causality assessment. There is a specific causality scale for vaccines, the WHO AEFI classification A B C, and the WHO classification used for drugs. PM will share with the participants links to available tools and trainings.
Including genetic factors in the analysis may become the future for vaccine risk assessment and personalizing vaccine indication.

4 conclusions were drawn from the first session:

1. The need to have better databases and to link these databases, and there is a need to talk with the stakeholders in the LMICs to move forward in this direction.
2. Epidemiological data should be available. It is important to embrace the methodology with the AVSS studies; it is important s to have regional epidemiological data for considering background incidences.
3. Communication strategies need to be implemented to avoid safety problems that can arise, e.g., specifically during mass vaccination campaigns.
4. Importance of causality assessment; t the manufacture's causality assessment process should be well defined to allow for a standardized assessment and to avoid inconsistencies.

Steps to define if AVSS can help

PM mentioned that passive surveillance is the cornerstone of vaccine pharmacovigilance, even if we do AVSS, passive pharmacovigilance is complementary, and it is inexpensive but has its limitations. AVSS can be directed to seek specific information on a specific adverse event. AVSS can complement a passive surveillance system and can help confirm or discard signals that have come in our system. It can help define the relative risks of adverse events.
AVSS studies can help in any of these situations:

1. Introduction of a novel vaccine for which only limited safety data is available from other countries
2. Introduction of a well-established (i.e., in widespread use) vaccine into a new country for the first time
3. Evaluation of special populations or circumstances that could be involved.

It can be proposed as part of the RMP when there are identified gaps; it can also be requested by the NRA; when a new safety issue has been identified in the passive surveillance system, and to study the safety profile of a new vaccine in LMICs.
The design of the AVSS study must be balanced with the budget available, the quality of data that can be collected, the type of system in the country. Sometimes the best design cannot be realized n terms of budget or is not feasible due to several different reasons. It is important to involve the statisticians and the whole multidisciplinary team upfront.
Everything starts with the correct identification of the knowledge gap and thus, defining the correct research question.
Sometimes several protocols are needed to address different questions with different designs.
The steps to follow are:

1. Identify if there is a Significant Knowledge Gap (SKG)
2. Confirm if that gap exists after further research
3. Identify if the knowledge gap can be closed with existing passive surveillance
4. Confirm AVSS is the appropriate tool to close the SKG

5. Moving forward with AVSS: selecting the right type of data collection strategies in AVSS and practical implementation issues.

Furthermore,

- PV team should participate all along the life cycle of the product, not only once the product has been launched, but from the very beginning of the clinical development.
- The Clinical & Development team needs to work in an integrated manner with the PV team so that information is well transmitted between the teams.;
- It is important that PV is involved in all clinical documents containing safety sections.
- All safety data should be included in an integrated safety database that all safety information is retrievable at one single place.
- It is important to hold pre-filing meetings with regulators.

PM and KH also reviewed the data collection strategies and the information needed in AVSS: individual data, health event/outcome data, sources of observational/Real World Data and potential bias and confounders. Most important are the basic questions to be able to define the Research Question. It is important to have discussions with the stakeholders and experts to explore the best way to define the research question.
It is also important to promote a better harmonization of regulations between countries.

Team Activity

The participants were divided into 2 teams; one team worked with a Chikungunya vaccine in development and the other with a new prototype of an oral Rotavirus vaccine to be introduced into an LMIC. Each team was requested to define a research question, and justify the importance of the question, propose a general design of an AVSS study to address that question, and define outcomes expected with that design.
On the second day of the workshop, the teams presented their results and conclusions. RS appreciated the teamwork, which was remarkable, very integrative and participative, including the participants online. After the presentation, each team received feedback on how to improve the presentations. A copy of the final presentations was shared with all participants.

Next steps of the project

Based on the learnings of this workshop, members have learnt how to propose the research question, how to make the study design, and to establish the expected outcomes.

PHASE IV

- Each participant member company will decide a product of their company for which they would like to prepare an AVSS synopsis protocol. It is important that each Member company creates a multidisciplinary team including Clinical team, Clinical Operations, Regulatory, Epidemiologists, Statisticians, to participate in the project. It is important to ensure feasibility. Consider the data available, the data that will be needed. This phase will be carried out in Q4 2023 - Q1 2024.
  Members could take advantage of this project also to show within their companies the importance of integrating all areas of the collaboration.

PHASE V

- The protocol summaries prepared by the members will be submitted for review by expert consultants by the ***end of February***. Working Group online meetings will be held to solve

questions and receive guidance. One-to-one calls with KH can also be held to address confidential issues.

- Expert consultants will review the protocols to give feedback.
- In ***May 2024*** the project will be closed, and the different Member teams could present their results on the final wrap up meeting (removing confidential information).
- Based on the report's findings, the conclusions that could be helpful for other companies/countries will be published in ***Q2 2024***. These could include the identification of some issues faced in LMICs and what can be done together as a network to address them.

Based on the conclusions of this project, it is important to publish a publication.

SWOT OF PV ACTIVITIES IN DCVMN

The Working group participants created and analyzed the SWOT of PV activities in DCVMN.

Strengths	**Weakness**
1-Analytical skills and knowledge of regulation, Regulatory expectations 2- Some have experience in AVSS studies 3- New perspectives, Enhanced learning through sharing 4- Diverse Regulatory experience from different countries	1- Members don't have experience in all the methodologies 2- Sample size calculation 3- Limited budget 4- Need to improve interaction and communication between cross-functional teams (PV, Reg, CD) 5- Most DC do not have centralized databases
Opportunities	**Threats**
1- COVID pandemic opened some doors for collaboration in PV activities 2- All LMICs are sensitive to the importance of PV activities 3- AI can help us perform certain opportunities (data mining) 4- AVSS is more cost effective than clinical trials. LMICs have Advantage of cost effectiveness in conducting studies. 5- AVSS can help improve hospital information system 6- Regional AVSS studies can help save resources 7- Development of data security using block chain technology	1- Not easy to receive guidance from the NRA on NIP 2- We still need training on PV in order to teach AI to function properly 3- We need to start regulating AI 4- Most NRAs in DC do not share information with the manufacturers 5- Background information is sometimes not linked to vaccination information, AE, deaths, hospitalizations, etc. 6- Information of DC does not flow to WHO Digibase 7- Poor communication of safety data of vaccines increases vaccination hesitancy 8- Data security can lead to competitive disadvantage 9- Poor National PV system makes difficult to do PV

Based on the SWOT analysis, the group proposed several actions to mitigate the manufactures' challenges.

1- DCVMN could advocate with WHO, UNICEF, PAHO and NRAs that manufacturers need to have access to full data locally regarding their products *(PV WG to create slides with scenario for RS to make this presentation- evaluate pros and cons on why they are not giving this data- Challenges, issues, and how it is impacting the industry, mention what is available, what is the tap and how to bridge)*

2- Explore the possibility of receiving the signal detection analysis by WHO/NRA on a periodic basis for own products
3- Create a Teams group for knowledge sharing and crisis management (no confidential information) and seeking advice from PV colleagues
4- Create a combined (PV, Reg, Clinical data) WG meeting for Feb- March next year for improving intra functional communication

Principal difficulties pointed out by companies regarding AVSS execution:

- Regarding data access and quality – need more robust data and linkage of databases (NIP, NRA, etc) to allow MAH to access the safety information available in the countries. It is important to real time surveillance and to allow AVSS protocols execution.
- Need to have access to local epidemiological / background data to allow AVSS study design to be more robust.
- Communication – companies pointed out the need for stakeholders to collaborate and communicate more closely allowing more effective actions regarding PV.
- Stakeholders – important to talk with NRA/NIP previous to vaccine launch in order to align the possible safety surveillance requests, allowing MAH to be able to prepare and plan;
- Companies establish standardized process of safety issues evaluation, that will help to establish AVSS needs;
- Clinical development teams and PV teams need to be aligned
- PV needs to be involved in the clinical development starting from Phase I
- The PV Database must include all SAEs, AESIs, Pregnancy reports (and other safety data as defined in the protocol to be specifically collected) occurring during the entire clinical development. For filing, all safety data from a vaccine compound in clinical development included in the Clinical database and PV database should be integrated an Integrated Safety Database.

RS thanked the Chair and Co-Chair as well as other participants for their contribution, and PM wrapped up the meeting.

Patricia Mouta
Chair - DCVMN PV WG