Participants in person: Linda Nesbitt (LN), Viska Indriani Iskandar (VII), Katharina Hartmann (KH), Alexander Precioso (AP), Narendra Arora (NA), Madhava Ram Balakrishnan (MRB), Alioune Badara Sall (ABS), Aminata Diagne (AD), Ana Paula Loch (APL), Awa Ly (AL), Chetanraj Bhamare (CB), Eliana Nogueira Castro (ENC), Mandar Kshirsagar (MK), Paulo Takey (PT), Sumit Tandon (ST), Vanessa Infante (VI), Rajinder Suri (RS), Sonia Villaseñor (SV).

Online participants: Beverly Cooper (BC), Beatriz Lucchesi (BL), Chien Luu Anh (CLA), Fita Noer Puspita (FNP), Fitriani Dewi (FD), Hoa Phan (HP), Hongde Xie (HX), Huong Nguyen Thuy (HNT), Huong Giang Thi Le (HGTL), Shifalee Magazine (SM), Jie Zhou (JZ), Bernadette Hendrickx (BH), Lillis Setyaningsih (LS), Melisa Sitepu (MS), Min Ji (MJ), Shuyan Zuo (SZ), Thang Ngo (TN), Tuyet Le Thi Tanh (TLTT), iphone not identified participant.

LN chaired the meeting and welcomed the attendees, going first through a round of introductions of the participants in person and online.

LN introduced the topic, in terms of AVSS, with the development of COVID-19 vaccines the focus has increased in safety surveillance. Many manufacturers from LMICs do not have the experience or capacity for AVSS. The introduction of new vaccines without extensive pre-licensure experience is coming more common and poses unique challenges. A survey conducted within the members of the WG showed that members in their region have expressed varying levels of experience with the implementation of AVSS. NRA involvement in AVSS is a challenge for the majority of the member companies s due to lack of transparency or communication. Public health information/background data is not always reliable due to under-reporting and issues with data quality.

LN showed the results from the survey on the status of AVSS in each of the countries/regions where the PV WG member companies reside.

- In Brazil the main issues are within the electronic PV system and turnoer and training of vaccinators. ANVISA allows MAH to perform AVSS in Brazil. AP added that the lack of communication among different safety databases is a challenge still to overcome. Sometimes AVSS is an independent initiative from the manufacturer. CB asked if there are any fixed guidelines under which situations in which the NRA asks to conduct an AVSS, and if the NRA supports the manufacturer while preparing the AVSS protocol or conducting the study. VI said that it is usually an initiative from the manufacturer, but in cases of emergency release, the NRA can request the AVSS.
- In India, NRA does not deem AVSS necessary if clinical trials have been conducted with 3000+ participants. However, the NRA can request the manufacturer to conduct the AVSS study, which has been the case for few new vaccines Serum Institute India has developed. The expertise and help from NRA are limited. Spontaneous reporting is very low. AEFIs are not sent to EPI, which affects the reliability of publications. For COVID vaccines, the government is publishing the assessed AEFIs on their website.
- Vietnam. AVSS is initiated by the NRA not by the manufacturer. When the AVSS studies are developed by CDC/NRA, there will be a communication to the manufacturer providing safety data of the product. There is no internal reliance on published safety data. CDC publications are used to monitor background incidence.
- China. AVSS is conducted on new vaccines with sample sizes of minimum 3000 participants. NRA and CDC run the AVSS, there is communication and expertise support to the manufacturer. Information on the background incidence is a challenge.
- Indonesia. New regulations from NRA require the RMP to be submitted in the dossier for

new vaccines, including the protocol of AVSS study. Indonesian NRA has great expertise and gives good feedback.

- Africa. In South Africa, manufacturers need to submit the RMP and decide whether or not AVSS is needed. This delays approval of emergency vaccines. In the past the studies were done in parallel. NRA does not have great expertise but is improving. AD said in Senegal the NRA is working with WHO to put AVSS in place. Before COVID there was no need for AVSS as no vaccine was developed in Senegal. Since COVID they started performing studies to observe the effectiveness of the vaccine in the hospitals. A new electronic database is being put in place. The maturity level is expected to be reached by April so that reporting is made quickly. LN suggested to approach the AU-3S safety system to be included in an electronic regional database.

AP said background rates are important for the RMP and in many LMIC that kind of data is not available. CB said in many cases on adverse events literature is available. It is very dependent on the literature available.

MRB offered the participants to approach him for any question they may have as he is a WHO PV expert. He explained WHO has set 25 core variables for AEFI reporting, and now there is a unique solution which gives feedback for AVSS also. WHO provides systems called VigiFlow (for secure and controlled data sharing) and VigiBase (WHO's global database). There are 3 important datasets that you need to collect when you look at surveillance for AEFI: Place of vaccination, reporter and patient. In passive surveillance these 3 datasets are used, and WHO tries to pinpoint where events are happening. With a mobile phone one can scan barcodes and directly report into your country up to the district level. The manufacturers asked why they can't access this data. MRB said it has sensitive data and when it has been made available to the public, misinterpretations have occurred even resulting in cases going to court. Therefore, it is being given only on a case-by-case basis. LN expressed that in South Africa they are not even being able to access data related to their own product (only those for COVID vaccines but not the others). MRB said unfortunately they have no control over what each NRA can share with the manufacturers, but he encouraged the manufacturers keep on reporting.

AP added that it is very important for the companies to get access to the data for PV activities. Even CEPI is trying to find ways with partners to improve this access to the data.

LN raised the concern that if they need the information due to an emergency, they need to pay around €45,000. MRB said that VigiBase needs to be maintained, so when it has been given to the countries it is based on the country GDP. WHO is being forced to slowly give it free of cost. Therefore, somebody needs to pay for it, which most likely is the manufacturers.

Active Vaccine Safety Surveillance – AVSS (Module I- Introduction) by KH

The difference between passive vaccine safety surveillance (spontaneous reporting of AEFIs during the whole life cycle of the vaccine) and Active vaccine safety surveillance (data collection system seeking to ascertain the number or AEFIs in a given population by a continuous organized process). AVSS does not replace Passive surveillance, it complements it, and it could be expensive. AVSS is a fundamental tool in PV. It provides the most accurate and timely information, but it is an expensive strategy.

AVSS studies could be Post- Authorization Safety Studies- PASS (EMA GVP VIII) or Post-Authorization Efficacy Studies – PAES (EMA PAES Guidance). If the manufacturer plans to do any of these, it needs to be included in the RMP including the protocols, for approval by the NRA before implementation (in most countries). If not, the reason why it is not done must be

indicated in the RMP.
MRB asked if there is any difference in the ethical clearances within the Phase I, II and II studies. KH said it can depend on the country, but you can also have ethical questions in the observational study. She suggested that within a company it is always good to have the opinion of an ethical committee although it may not be required for specific observational studies. AP added every investigational study involving human beings requires ethical approval. KH said the investigator is the one who needs to get the ethical approval, but the company should make sure the investigator gets it. MRB added that ethical committees are much more stringent in phase I studies and as it gets to late phase studies, they get less stringent. But there are many differences from country to country.
PAES are very important mainly for COVID vaccines. MRB pointed It is very important to consider there are large scale falsified vaccines.

MRB mentioned the IDSP (Integrated Disease Surveillance Programs), especially in LMIC is one of the existing systems that could provide post-authorization data from a non-interventional setting.

AVSS is an important tool for proactive, timely and rigorous safety surveillance to address knowledge gaps, e.g., when introducing new vaccines with limited safety data package at the time of deployment (e.g EUA) or when introducing an established vaccine into a new market. Knowledge gaps should ideally be addressed in the RMP.

BC asked if a manufacturer wishes to introduce a new vaccine for a disease for which the government already has a safety surveillance system running (e.g., new rotavirus vaccine), could they take it into that program and use it as its safety study. KH said that if you get the data in real time, it could be fine. MRB said that from a WHO perspective it is preferrable to keep the programs independent. In terms of clearances, it is very important to clarify and get the audience's consent before starting. If the programs are merged the possibility of immunization errors may occur which could affect the study.
KH confirmed that the post authorization effectiveness studies need also to be communicated to the NRA through the RMP. BL asked if the manufacturer should include a safety objective in the post-authorization effectiveness study. KH said in any kind of study safety data needs to be collected and reported, so it is up to the company to put it as a primary or secondary outcome. BH also pointed out that it will affect the budget; the benefit of such a study needs to be assessed, compared to the timelines and budget.

KH said AVSS can be implemented any time for the post-authorization lifecycle of the product, not only after approval is granted, but also if a safety issue comes up or if the vaccine target population is extended, and in any case if requested by a regulator

MODULE II Principles and Methodology
While selecting the study design, it is very important to ask the right research question, what evidence do we want to get out of the study and from there which research design is most appropriate to answer the research question. This needs to be done by a multidisciplinary team (including medical doctors, epidemiologists, pharmacists, QA, etc). NA added that the 3 components need to be considered: clinical, epidemiological and programmatic. AP emphasized

PV is not only a post-licensure activity and shall be involved from the early stage of the development.

LN asked if a DSMB (Data Safety Monitoring Board) (or DMC-Data Monitoring Committee) is needed to be involved. KH said that a DSMB is typically involved when studying a new compound, new platform, new adjuvant. The difference between the Ethics Committee and a DSMB is that the first one is mandatory and has decisive power, the DSMB is voluntary safeguard set up by the sponsor and makes recommendations. The DSMB meeting minutes with the recommendations must be included in the regulatory filing dossier, so it is advisable for the company to follow them. The set up and payment of a DSMB is the sponsor's responsibility; the sponsor is also responsible for the study participants insurance.

Case-Control Study Design: Basic study design is always from the outcome/ disease/ AEFI to exposure, so it is always retrospective. Case control studies does not work in a highly vaccinated population.
LN asked for clarification of confounding factors: Confounding occurs when the apparent effect of an exposure on risk (e.g., vaccine studied) can be distorted by another factor that influences the outcome (e.g., diabetes). Uncontrolled confounding factors in the study may cause or contribute to the patient's outcome (e.g., getting the disease) besides the vaccine being studied, e.g., diabetes., Other vaccines being applied at the same time can also be confounding factors. ST clarified that the co-administered vaccine will only be considered as confounder if the other vaccine is known to cause the same AEFI (e.g., intussusception).
Dr. Arora mentioned the Nested Case Control Study design: This is a case control study within a cohort from the same population where events (cases) occurred. Controls without the event (up to 5) are selected from the remaining population and the same analysis is performed. This method provides the opportunity to look into different variables within the universal cohort. In addition, overmatching is a danger because it can introduce bias.
Self-Controlled Case Series (SCCS) is a strategy originally developed to estimate the relative incidence of an acute transient adverse event in a very predefined risk period following vaccination and would be paired with other times of the same individual. So, the individual is its own control. This study needs much less subjects.
BC commented that sometimes having all these types of studies can create more confusion mostly if data does not tie with what was seen before. KH said that not every situation has to be an AVSS exercise because in many situations you can do it with targeted passive surveillance, sometimes a cohort event monitoring design could be very helpful. But it is important that when a risk is spotted, either by the company or the NRA, it might be good to do an AVSS. AP said that in the process of having a new vaccine licensed, as it happened during the pandemic period, much of the information could not be obtained in the pre-licensure, so post-licensure surveillance became important. Therefore, PV needs to be considered very early in the development process to define the commitments in terms of safety while designing the type of study that will need to be made.

KH explained that the background rate is the rate of health events occurring in a cohort that has not been exposed to the vaccine. She shared a link to a free toolbox of background rates (see slides). Background studies are very useful when introducing a new vaccine for which the target population is critical for accepting the vaccine.

The basic questions when conducting an AVSS studies are the funding, who is responsible for the study/who runs the study/ what approvals are needed? The sponsors are in the end responsible for the study. The procedures need to be in place. Then KH reviewed the company functions involved in AVSS study and the project documentation needed.

KH reviewed the structures and processes to follow (6 basic steps). Start with the research question, to reach the outcome you want to study. And gave some examples of protocols. The study registration is sometimes mandatory and in other countries or situations only recommended, but it needs to be done before the study starts. It is important to note that some journals will only publish your results if you have your study registered. Depending on the country where the study is being performed, it could be registered in EMA, NIH, or in the International Clinical Trials Platform. Ethical approval should be received before implementing the study.
The role of the statistician is very important for the sample size estimation. The rule of three was explained without consideration of background incidence and then with consideration of background incidence.
The final report is ultimately the responsibility of the sponsor or the MAH. The principal investigator collects and enters the data in the system but may not have the tools to prepare the report.
The group discussed situations in which the data is not properly collected, results not appropriate or other kind of fraud being made by the CRO, investigator etc. KH suggested that such situations must be foreseen and addressed in the contract. BH suggested having a crisis management team. VI said that it is better to stop and wait until the CRO fixes the problem before continuing. CB added that if the fraud is being detected after the study is over, the sponsor can decide whether to include or not the particular site data in the analysis. CB mentioned that fraud is clearly a no go.
The group discussed regulatory reporting; interim reporting, the timing of the safety report of the study results must be predefined. The results need to be submitted to the national regulators generally within 6-12 months of ending the data collection. Time could be extended, but beware that it could generate some kind of mistrust.
KH showed about the AVSS studies on View Hub, supported by John Hopkins University where they collect all the effectiveness data, and it also has safety studies. Cf. https://view-hub.org
The final message is that during the lifecycle data from continuous safety monitoring strategies provide complementary insights to the vaccine safety profile; safety surveillance does not stop, even with very well-established vaccines. PV is being watchful from the “cradle to the grave” of a vaccine.

LN mentioned that there was originally a project involved submitting our own study protocol for evaluation and review by individual consultants, but certain circumstances have changed but we will investigate that. Then she adjourned the meeting. RS thanked the chair and co-chair, as well as the consultant and special guests. AP and MRB offered their continuous support to DCVMN.

Linda Nesbitt

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Chair of the DCVMN PV WG