Strengthening data quality to support safety monitoring of medicinal products used during pregnancy and breastfeeding

Opening and welcome	**R. Gaspar - Director Regulation and Prequalification**
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Spontaneous reporting: data quality aspects of retrieving pregnancy cases from VigiBase, the WHO global database of adverse event reports for medicines and vaccines.	**B. Raemaekers & L. Sandberg - WHO CC for International drug monitoring, UMC**
Real world data: types of pregnancy exposure registries in low- and middle-income countries. How quality data can contribute to support safety monitoring.	**N. Bhat - PATH**
Electronic records: Experience of Hong Kong with use of electronic clinical records for pharmacovigilance activities	**I.C.K. Wong - University of Hong Kong and Aston University UK**
Panel questions that all presenters will address	**P. Lundquist - WHO CC for International drug monitoring, UMC** **S. Pal - WHO PVG**
Wrap-up and action points	**S. Pal - WHO PVG**

Opening

The Director of Regulation and Prequalification opened the webinar discussing how global pharmacovigilance has been impacted by the decision of regulatory agencies not to share full data with the global WHO database maintained by the WHO Collaborative Center for International drug monitoring - Uppsala Monitoring Centre, or when national regional or sub-regional clusters try to establish standards which are not aligned with the international agreed standards. Lack of the full pharmacovigilance information diminishes capacity of prompt response to protect human life.

This webinar highlights the technical work that needs to be done to integrate systems of Member States for universal health coverage and for response in emergencies. One of the main critical issues in the area is the limited data quality for health outcomes monitoring. This is due to lack of harmonization of standardized data and methods to collect evidence. During COVID-19 and today during mpox empirical decisions were made because of lack of standardized tools and methods. WHO is working to create a global digital health framework, with new and adequate data standards.

Need for harmonization of standardized data sets for monitoring maternal, fetal and newborn outcomes

The work on harmonization of data sets for monitoring maternal and newborn outcomes started in 2017 when representatives from different WHO entities found that poor data quality in terms of maternal and newborn health was due to diversity in terminology, definitions and methods used, which prevented data comparability and meta-analysis between studies. To address these challenges, a harmonized set of standardized health indicators and data elements for collection across all who regions and Member States needed to be defined.

Therefore, the pharmacovigilance team initiated the WHO interdepartmental task force that gathers representatives from 12 different entities of WHO headquarters with different areas of work, with the aim to define standardized WHO minimum maternal newborn health data set (MNHDS). Based on 60 documents published across these areas of work, 1001 indicators were identified. Following mapping and deduplication, 211 different indicators were classified across the continuum of care. The two-stage consensus activity, which is a modified Delphi method was used to develop a candidate minimum data set and to sought input from the members of the WHO Interdepartmental task force as well as external experts, colleagues from WHO regional and country offices. Stakeholders gave their input based on whether these indicators were action focused, important, simple and valued, operational and feasible (**Figure 1**).

Criteria for selecting the core WHO MNHDS

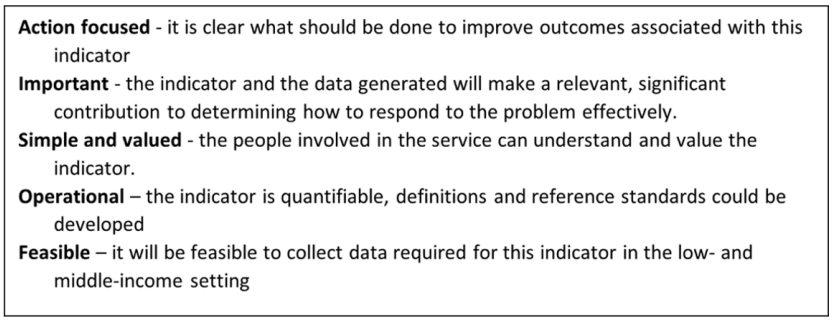

Figure 1. Criteria for selecting the core WHO maternal and newborn health data set

The resulting core data set included 15 indicators, for which consensus was obtained, to be universally collected across WHO entities, regions and countries. This core data set is accompanied by a catalogue data set not obtained by consensus, but it's specific for each area of work and, for the moment, contains 62 indicators. That means that working in safety requires monitoring core data set and selected catalogue indicators pertaining to safety. Similarly, for colleagues working in nutrition they need to monitor the core data set and the specific indicators for nutrition of the catalogue data set. All WHO MNHDS have definitions, computations and other aspects of data element measurements. To facilitate monitoring, the 15 core indicators are classified in five different groups: mortality, maternal, newborn, vaccination exposure, maternal newborn, drug exposure and inverse events, maternal, fetal and newborn outcomes, maternal risk factors and screening (**Figure 2**). WHO minimum MNHDS (mMNHDS) were compared to data set from WHO programmes and global initiatives to strengthen global harmonization and collaboration. When indicators were comprised to WHO programmes and global initiatives, we found an alignment with those.

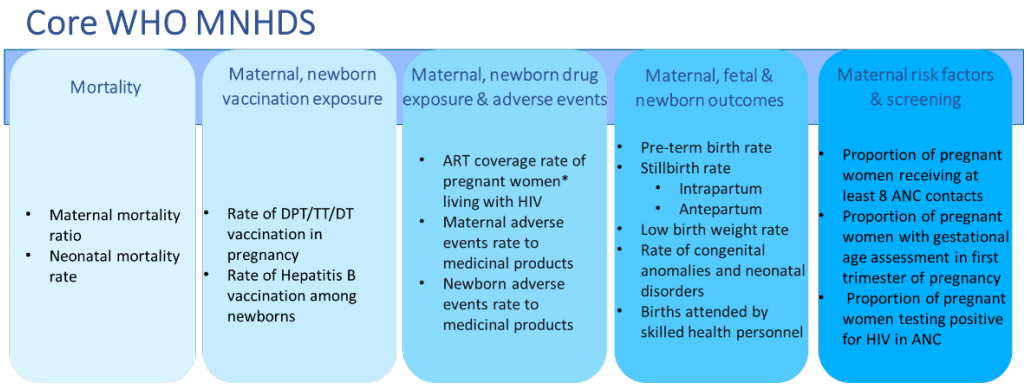

Figure 2. Core (minimum) WHO maternal and newborn health data set

Next step included assessment of whether different health settings were able to collect WHO mMNHDS. For this reason, a pilot study was initiated in healthcare facilities with primary objective to determine the capacity of nominated hospitals to prospectively collect the required elements. Moreover, secondary objectives included: identification of elements posing challenges in the settings, identification of elements already captured in the routine health systems, support future implementation strategy of this data set and subsequent revisions. The data collection period was of consecutive 28 days, including holidays and vacation. Prospective data collection was chosen to facilitate data collection. Countries from African, Southeastern Asia and Eastern Mediterranean regions were interested in participating in the study. Referral hospitals were nominated from the ministries of health of seven countries (Bangladesh, Ethiopia, Gambia, Nepal, Nigeria, Pakistan, Uganda) from these regions.

The pilot study started with the preparatory phase consisting of meeting study teams and drafting the tools and the study protocol. The introductory phase included submission of the protocol for ethical clearance in the WHO ethical review committee and in the local instances, as well as training and capacity exchange. Data collection phase comprised data collection, data cleaning as well as a quality study that consisted of having interviews with the study teams about challenges, gaps and strengths during the entire study. On 12 and 13 September 2024 a meeting was hosted in WHO HQ, in which the lessons learnt from the pilot study were discussed.

The preliminary results obtained from 6 of seven referral hospitals, showed that data that are routinely used in the hospitals were more complete. Identified similarities and differences between countries are due to the differences of the health systems and programmes. Collection of data elements to inform adverse events following medicines and drugs for women and newborns was challenging for all hospitals. Study limitations included the 28-day collection period, lack of follow up following a hospital discharge and lack of data on history of referred patients. Routine data sources include gaps in terms of multiple documents in multiple locations (hospital wards). Other gaps included duplication of documentation, limited funding for team data systems and low leadership focus on data. Nevertheless, an opportunity to work for strengthening routine systems to improve quality care of maternal and newborn health, track global health disruption (i.e., pandemics) and introduce novel interventions (e.g., rollout of new vaccines) without starting from scratch was identified.

Spontaneous reporting: data quality aspects of retrieving pregnancy cases from VigiBase, the WHO global database of adverse event reports for medicines and vaccines.

VigiBase is the WHO global database of adverse event reports for medicines and vaccines. These reports are received from member countries and territories of the WHO Programme for International Drug Monitoring (PIDM). So far, over 39 million Individual Case Safety Reports have been collected, making this the world's largest repository of its kind. VigiBase is currently built around the E2B(R2) data elements. It is important to note that VigiBase is not a pregnancy-specific database, however, pregnancy cases are present among those 39 million reports.

Considering data quality of reports in VigiBase, the "completeness" aspect often comes to mind. Both structured data can be missing, such as the drug start date, and free text, such as the case narrative. The completeness of a report can be quantified using the completeness score. However, missing data is just one of several data quality aspects. Quality data needs to be accurate; there are several reports in VigiBase that have a patient age in the designated field, but the number entered is 999 years. Consistency within the report is another parameter for quality. For example, reports with a different patient age in the structured data than in the free text. Granularity shows the level of detail in a report. A report with "Death" as the only reported event is not very informative as to what exactly happened. When it comes to pregnancy cases in VigiBase, the first obstacle is selecting the relevant reports, which is difficult for a total of 39 million reports. There is not one specific data element that indicates whether this is a pregnancy case yes or no. Still, many different data elements have the potential to hold pregnancy information. An algorithm, therefore, can take multiple data elements into account to find pregnancy cases. The VigiBase pregnancy algorithm has been available to WHO Programme members since November 2022, and the in-depth scientific evaluation has been ongoing since then. This was an opportunity for PIDM members to access a new method rather quickly, and for UMC to receive feedback for further improvement.

The algorithm has been built into VigiLyze, the signal management tool available to PIDM members, under the filter for patient characteristics. Applied to the complete database of >39 million reports, 1.1% of reports in VigiBase are flagged as a pregnancy cases. "Pregnancy case" in this context means that a medicinal product has been administered to a pregnant person, so a maternal exposure shortly before or during pregnancy or labor with or without an adverse event in the pregnant person or the fetus-prenatally-exposed child. This means that lactation exposures and paternal exposures are out of the scope (**Figure 3**) as they require separate approaches to be addressed properly.

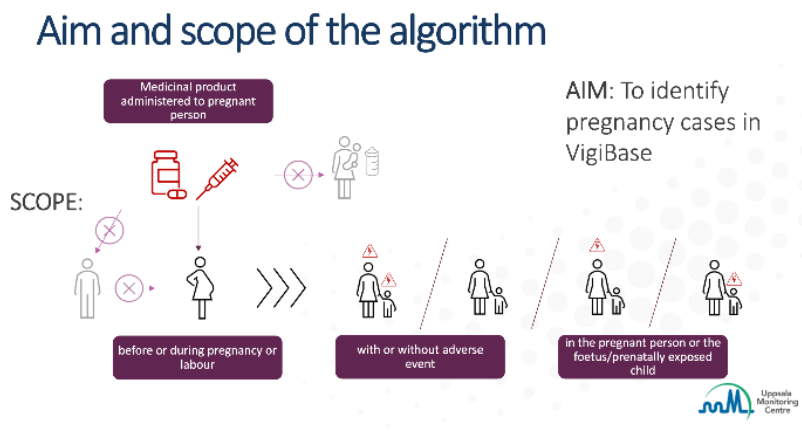

Figure 3. Aim and scope of the VigiBase pregnancy algorithm

The algorithm is totally rule based, meaning that there are certain exclusion and inclusion criteria that decide whether a case is deemed to be a pregnancy case or not. The rules are based on several structured data elements with the potential to hold pregnancy information. Reports that are unlikely to be about the maternal exposure are ruled out based on, for example, the patient age. Reports are then ruled in as pregnancy cases based on, for example, the reported adverse events or the indications being pregnancy-related, or the route of administration being reported as transplacental, or if a gestational age has been reported.

Evaluation of the algorithm included assessing how capable it is of identifying pregnancy cases in VigiBase and how precise the algorithm is when identifying such cases. After a manually assessing more than 8000 reports in VigiBase to create a reference set of reports the algorithm was applied. The output from the algorithm was compared with the output from the manual assessment. When the algorithm was applied to all reports in the reference set, it managed to identify 75% of the cases that were manually assessed as pregnancy cases. When analysis was restricted to only E2B reports which is the current standard format for transmission of case reports, the algorithm identified 91% of the pregnancy cases. The algorithm was quite precise with 92% correctly identified reports when compared to the manual assessment.

Through the evaluation of the algorithm insights of quality of reporting of pregnancy exposures in VigiBase were collected. It was noted that pregnancy exposures are quite inconsistently reported across the database due to differences in coding principles such as whether a pregnancy exposure is reported as an event or not, the use of different terminologies for coding and the different transmission formats used when exchanging reports. In some reports the pregnancy information was only given in free text, for instance in the case narrative, without any information about pregnancy in the structured fields. Also, there were cases where the pregnancy information was not specific and a pregnancy exposure could only be inferred from several pieces of more indirect information from the reports, posing a challenge both, for manual assessors and for the algorithm. Another issue encountered was reports with ambiguous information. This included reports in which the pregnancy information was miscoded as such, or when it was unclear whether the pregnancy event was concurrent or historical, or when it was unclear if the report concerned the pregnant person versus the fetus or child.

The analysis also revealed that most pregnancy cases in the reference set manually assessed referred to the pregnant person. In addition, some reports related both to the pregnant person and the fetus/child in the same report. These latter are quite difficult to handle and to interpret. Equally it was challenging to interpret reports with inconsistent information in which for example, the patient age referred to the pregnant person while the events concerned the fetus or child.

The conclusion from the algorithm evaluation is that the algorithm has potential to facilitate pharmacovigilance related to pregnancy exposures and it can be used as a tool to learn more about the quality of those reports. In addition, the evaluation highlights the importance of harmonized standards for reporting of such exposures. A manuscript is under preparation, describing the algorithm and this evaluation in detail. Additional information can be found in a poster available the website: https://who-umc.org/media/j2cpykuc/pregnancy_poster_digital.pdf.

Next steps include exploring whether the algorithm may be of use, when applied in signal detection, focusing on pregnancy exposures in VigiBase.

Real world data: types of pregnancy exposure registries in low- and middle-income countries. How quality data can contribute to support safety monitoring.

PATH in collaboration with WHO and the University of Washington in Seattle, USA conducted a landscape analysis of pregnancy exposure registries in low- and middle-income countries (LMICs).

Drug and vaccine safety information in pregnancy is usually insufficient in LMICs often due to lack of resources as well as lack of introduction of new products. Pregnancy exposure registries (PERs) and similar systems can be aimed to monitor product safety, but the overall number and nature of these systems in LMICs is unknown. Therefore, better understanding of the landscape of pregnancy exposure registries in LMICs, will support system strengthening and prepare for new vaccine and drug introductions. Landscape analysis identified resources that include formal PERs, but also other surveillance systems and databases that record exposures during pregnancy and collect data on subsequent maternal and perinatal outcomes.

The approach adopted was a scoping systematic review, which is a modification of the more formal systematic review in which a broader set of data are collected. The systematic review used electronic literature published between 2000 and 2022. In parallel an online survey was sent out and interviews were conducted with a select number of key informants. The protocol was reviewed by technical advisors as well as a WHO expert committee. The databases used included Medline, Embase and other regional databases that are coordinated by WHO. Search was conducted in June 2022, and the survey was conducted about one month later. The methodology of screening, data extraction and analysis was typical for systematic reviews: title and abstract screening; full text review of those that met predefined inclusion criteria and then data abstraction. Once it was realized that the collected information referred to a variety of different resources, a system to categorize these resources was developed. Then resources were summarized by key features including strengths and weaknesses where available, including where they were located, what organizations might have hosted or coordinated the registry, whether there was any product focus, as well as sources of funding, years of operation, study, design and outcomes captured.

Initial electronic literature search revealed about 7500 records that were narrowed down to about 400 for full text review after screening. Ultimately 47 additional resources from the survey interviews and other sources were identified. This resulted in about 203 records that were deemed relevant for the study. These included publications, websites and other grey literature. From these 203 records 45 pregnancy exposure registries were identified; 36 of them were actually currently in operation and were organized them into six major categories. Systems were in majority located in Africa, in Asia, as well as Latin America. Strengths, limitations and challenges at the group level as well as for selected individual resources were summarized for the report. Of note, systems included concerned both vaccines and drugs. Generally collected systems were prospectively collecting data.

The six different categories (**Figure 4**) included pregnancy exposure registries. These had the specific purpose of collecting data from pregnant women. They included prospective enrollment and had a stated aim to record the exposures and outcomes. The next group were health and demographic surveillance systems, or HDSS, and other observational cohorts. These were generally population-based cohorts with prospective collection of clinical and epidemiological data. The next category

included outcomes-based registries focused on the outcomes specifically, such as birth defects. Maternal condition-based registries collect data on women with specific underlying conditions such as epilepsy or with cardiac disease who are receiving disease-specific medications or treatments.

Resource Categorization

Resource Category	Brief Description	Number of Resources (Currently active)
Pregnancy exposure registries	Self-designated PERs with prospective enrollment and a stated aim to record exposures and outcomes	11 (7)
Health and demographic surveillance systems and other observational cohorts	Population-based cohorts with prospective collection of clinical and epidemiologic data	7 (7)
Outcomes-based registries	Registries that focus on outcomes, such as birth defects	7 (7)
Maternal condition-based registries	Registries that enroll pregnant women with specific underlying health conditions	6 (3)
Manufacturer registries	Registries established by a drug or vaccine manufacturer, often for regulatory purposes	8 (6)
Electronic medical record databases and clinical software platforms	Electronic platforms that prospectively record clinical information within a health care institution or system	6 (6)
Total		45 (36)

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Figure 4. Resource categorization

Manufacturer pregnancy exposure registries typically are based in high income countries and were included if they were international or global in scope and included populations from LMICs. These were registries established by the manufacturer and usually administered by them or by a contract organization, often for regulatory purposes. The last category were electronic medical record databases and clinical software platforms. These were relatively newer where electronic medical platforms would prospectively record clinical information within a healthcare institution or system.

Identified the resources were predominantly in Africa, Asia and Latin America. Some of these identified resources were part of larger networks and therefore there were some commonalities in terms of features and methodology.

Key features by resource type were evaluated and some important aspects of each resource were highlighted. For instance, in most cases they involve prospective enrollment of pregnant women, though this was not universally the case. Another parameter included was whether the resources were able to easily ascertain information on the exposures on the background conditions of the mothers, as well as the outcomes in both the mother and the infant. Inclusion of a comparison group was also examined; whether that was non pregnant women receiving the exposure or pregnant women who did not receive these exposures. Ability to calculate relative risk associated with exposures was included, as well as at their ability to adapt and include new vaccines or drugs of interest. Finally, the complexity and resource requirements were assessed to determine whether they were resource intensive or not.

To access the detailed assessment, the report can be consulted in the WHO PVG webpage. However, key points include that several pregnancy exposure registries are in Africa. Many of them are focused on particular drug classes or product classes such as antiretrovirals and antimalarials. These were all prospective registries and many of them are supported by or funded by donor organizations or the public sector and administered by academic or non-profit research groups. The Health and

demographic surveillance systems category was dominated by several networks, such as the IeDEA network, or the International Epidemiology databases to evaluate AIDS, the INDEPTH network, and the maternal newborn health registry (MNHR). These were longstanding. Most outcomes-based registries are focused on birth defects surveillance with a focus on antiretroviral exposures. Otherwise, there are a number based in middle-income countries that are generically focused on identifying birth defects but without a specific drug or vaccine focus. Of note, several the birth defect surveillance systems in Africa have come together to develop a network themselves to share information and expertise. Maternal health conditions-based registries include those for epilepsy and cardiac disease and are primarily in middle income countries. Manufacturer registries were usually global in coverage. There is a large literature on manufacturer registries, but those studies are mainly focused on high-income countries. Finally, the electronic health records and other clinical software platforms in most cases were not focused on pregnancy, but usually had some module or other programming to study safety in pregnant cases.
In conclusion, resources found were categorized into different groups that have unique features. It's a very diverse set of resources in LMICs, but there a lot of work remains to understand what the global needs are and where, as well as identify the directions that need to be emphasized for the future in terms of strengthening what exists and how can we support data quality, data sharing and sustainability.

Electronic records: Experience of Hong Kong with use of electronic clinical records for pharmacovigilance activities

This discussion will focus on the use of electronic medical record to monitor psychotropic drug during pregnancy.
Use of attention-deficit /hyperactivity disorder (ADHD) medication significantly increase over the last 10 years. Two papers Chan et al., in 2023 (https://pubmed.ncbi.nlm.nih.gov/37181411/) and Raman et al., in 2018 (https://pubmed.ncbi.nlm.nih.gov/30220514/) demonstrated the increase of ADHD diagnosis and use of pharmacological treatment. The question was whether this was due to an increase in the prevalence of the condition. This also led to monitoring of risk factors and try to reduce the number of children with ADHD or at least the treatment of ADHD.
A few years ago quite a lot of reports discussed the association between antidepressant use in pregnancy with the increase of ADHD in the children later. Evaluation of this association was quite challenging because quite a lot of report came out, but with different limitations; small sample size preventing statistical significance as well as other confounding factors that are not taken into consideration such as maternal illness or genetic factors. In addition, as ADHD is highly heritable an additional problem was under-diagnosis of adult ADHD. This latter is comorbid with other mental problems including anxiety and depression. This is a case of a mother has ADHD that is not diagnosed but has other mental problems and passed down the genes to the children.
All these were important incentives to further investigate the association between the use of antidepressant during the pregnancy and the risk of ADHD in children. To do so Hong Kong electronic medical records were used.

Electronic medical record in Hong Kong is unusual compared to other countries. In Hong Kong, all publicly-funded hospital data are linked up. So, there is one unique ID number, no matter which hospital the patient goes to. This means that health care professionals can see the same record.

Records include diagnosis, procedures, drug prescribing and dispensing history, admission and discharge details, as well as laboratory and pathology results. Importantly, there is a mother-baby link that is provided in delivery, so that health professionals know precisely which baby comes from which mother and the link is permanent. For this study, population included comprised all children born in the public hospital in Hong Kong between the 1st of January 2001 and 31st of December 2009. Patients coming abroad, for which no mother-baby link, and thereby an ID number, was available were excluded. Non-Hong Kong resident were also excluded. Few cases were also excluded for which birth episode details were missing. The exposed group (treatment group) comprised mothers on antidepressant during pregnancy. Two different control groups were used: one without treatment of antidepressant and another (negative control) comprising mothers that had antidepressant before pregnancy, but they stopped the treatment during the pregnancy.

Cox regression was used, and covariates included several elements including psychiatric disorders, hypertension epilepsy and other conditions and status. Population studied included 1616 mothers with antidepressant or antipsychotic drug during pregnancy and 189 000 mothers without using antidepressants or antipsychotics.

As expected, the use of antidepressant and SSRI during pregnancy increase of ADHD in the offspring. Interestingly, the risk of ADHD was increased for babies born to mothers that were not under SSRI. That means that the negative control group who stopped the treatment before pregnancy have an increased risk for their babies to develop ADHD. However, these mothers did not take any antidepressants, so there is no exposure to the fetus. That means antidepressants do not increase the risk of ADHD, but something else; the causes may be genetic, maybe environmental, but it doesn't look like the antidepressants causing it. These results were reassuring to mothers who need antidepressants to treat clinical depression.

Following publication of this work (Man et al 2017 https://www.bmj.com/content/357/bmj.j2350), and since then, the same methodology was used, for studies looking into different type of psychotropic drugs to see whether there are effects. It became a sort of like a standard methodology to use the negative control and the sibling control. The negative control and the user control produce similar results no matter which study people do.

In summary, in the past it was thought that antidepressant use was causing ADHD in children (**Figure 5**). Then, if the mother has an undiagnosed ADHD manifested as a depression or anxiety (because in older generation they didn't have the diagnosis of ADHD), she was put on antidepressant and the ADHD was diagnosed in children. This is the red line. However, it seems that the blue line is true, as there is a genetic side or an environmental side of it that is transmitted to the child.

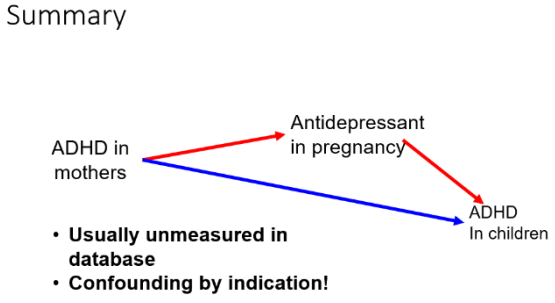

Figure 5. ADHD transmission to offspring

If in the database other important factors are captured, such as other psychotropic drug use, like the psychiatric illness before the event might be captured. However, if this information is not included, then wrong conclusions might be made, what is called confounding by indication. This is one of the classical problems in pharmacovigilance and pharmacoepidemiology.

Panel questions

1. Define the complementarity, strengths and limitations of each system in supporting pharmacovigilance activities

- **Spontaneous reporting :**

Spontaneous reporting data is typically used for generating hypotheses, which can then be confirmed or refuted using other data sources, including pregnancy registries and electronic health records. VigiBase can also be used to get a quick glimpse of whether a specific medicine or vaccine is used in pregnancy at all, which is especially useful with new medicines and vaccines. As for the strengths of VigiBase, it is a large data set and it gives a worldwide overview. Limitation would be the level of detail; for instance especially for pregnancy exposures, it is important to know the gestational age during which the exposure took place and it is more likely to find that level of detail in the other data sources.

- **Registries (different types) as data repositories:**

The group of registries described are very diverse and so have their own individual sets of strengths and weaknesses. I think in terms of formally defined pregnancy exposure registries, strengths include that they are focused on pregnancy and the pregnant population. So, the methodology, the data collection, the analysis can be focused on specific pregnancy related questions, hypotheses, etc. Another strength is that they are usually more rigorous, and can answer epidemiological questions, such as defining risk, especially if they are population based. They can investigate and examine safety signals in terms of complementarity. For instance, the spontaneous reporting can identify safety signals, but then they can be examined more intensively through a registry. A weakness in that might be lack of specificity. Also, they may not be able to adapt their methodology to take in new questions or approaches. In addition, they are more resource intensive because of the focus on structuring the data quality.

- **Electronic clinical records**

The biggest advantage of electronic clinical records is routine data collection. The cost of setting up is expensive, but it helps your clinical management to start and supports pharmacovigilance continuously, collecting data as long as the patient use the medication and remains within the system. Also, the quantity of data collected to be used for analysis is another advantage. However, the major downside is they do not monitor malformation and stillbirth. The reason is because it's based on the patient identification number. The mother already has a record. But the problem is if the mother decided to abort, let's say, because the fetus has a major malformation, then the aborted fetus does not have the ID number of the system, so it is not possible to identify this malformation. Unlike the registry, medical records do not collect extra information like sociological history. In addition, other country like in the UK they use the probabilistic approach which is based on area where the person lives or on the household number, and then they link up if there is a child. However, this does not allow to know whether it's a mother, or a young grandmother with a grandchild, or really the mother with the daughter or the son. So, people need to interpret data carefully. In terms of the complementarity of the different systems: Spontaneous reporting system is throughout the life span, it's a hypothesis generation and then that allow the registry and the electronic medical record to test the hypothesis. It is almost impossible to use the electronic medical record for the purpose of hypothesis generation. So, the three systems are complementary specifically for the developing countries, the registry is the best solution to prospectively collect all the information required for monitoring safety of drugs.

Do you give this information back to the healthcare system, especially patient safety, policy making?

I. Wong - Yes, studies on electronic medical data are funded by the Research Grants Council from the Hong Kong Government. So, findings are reported back to the government and are also presented in different conferences, in meetings, to also reach healthcare professionals and patient groups. In terms of the ADHD study, the message was that if a woman needs the antidepressant or the antipsychotic drugs, they should have it because the damage from not having them could be far greater than the damage of having it. There's diversity in which different groups use the data for the scientific community. For instance, signal detected of neural tube defects with use of antiretrovirals during pregnancy such as Dolutegravir and other integrase inhibitors. And so, these birth defect surveillance systems had been set up expressly for monitoring that. The results of that were then fed back to the scientific community as well as to policy makers, and then finally to the communities where, you know, they were eventually reassured of the lack of a safety risk.
In other situations a HDSS or a demographic surveillance system is very engaged with their community with a lot of discussions with the community about their findings.

2. The second question focuses on how we can improve data quality in each system, specifically in terms of resources and education, including capacity exchange and sharing experiences.

S. Lamprianou - From the discussions with countries and referral hospitals it seems that the next step to support data quality should be focused in streamlining and standardizing the existing data. This is important and requires a lot of work in terms of funding, time investment from the healthcare professionals, collaboration, commitment from the management. Importantly, it was mentioned health professionals and health settings should acquire “the culture of data” and colleagues were saying that in their settings they were lacking this culture of data, when frontline healthcare worker do not spend some time to collect the data feeling they need to choose where to invest their time; in providing health services or collecting data. This requires training to understand what the use of the data collected would be, and how this would serve ultimately the patient and the health system.

B. Raemaekers - There is room for improvement on both, the data capture side of spontaneous reporting and on the analysis side. However, if building capacity refers to the data capture side, this would tie back to the need for harmonization of standards and adherence to existing standards for reporting pregnancy exposures. While developing the algorithm, it was noted that if all countries reported in the same way, an algorithm would not be needed because then one could just use, for example, the Maternal exposure “during pregnancy” term to find all the relevant cases. So, there's a lot to be gained there from coding. In addition, it is required to ensure the relevant information is in the in the relevant fields and on the analysis side, we could see refining the algorithm further. This could improve data quality as well as help distinguish between the maternal cases and the child / foetus cases.

N. Bhat -Following landscape analysis of pregnancy exposure registries, several examples of networks were found within the different resource types. For instance, network of HDSS sites called INDEPTH or the network of HIV based research groups. In those, there is an opportunity or a motivation to improve data quality across the different members because they must standardize their terminology and their methods.

I. Wong - Depending on the type of electronic medical record another approach is required to improve data quality. The one in Hong Kong or the one in the UK are used literally for the patient clinical management. In such circumstances, the healthcare professionals understand the value and do not really need extra training beyond their clinical practice. However, education is far more important to the general public. There is a lot of mistrust in different countries about using the electronic medical record for safety monitoring for research. So, the education is required for the general public for them to understand that their information is protected, but at the same time they contribute to the society. The other side of it is about the education on how to use the data. Often, people who decided to study using the electronic medical records, they didn't quite understand how the record worked, for example that some of the data based on the insurance record have very different purposes compared to the electronic medical record. It happened that people use the data wrongly in designing the study, the result is completely wrong, but no one realized it not even the editor and the reviewers subsequently found that people used the wrong methodology. So, researcher must be educated to understand how and when the data can be used and when they cannot be used.

Provide an example where systems have improved through capacity exchange.

N. Bhat - Networks such as the one created between birth defects surveillance registries in sub-Saharan Africa were able to share resources and they helped each other in terms of developing approaches for health service provision and follow up on children with birth defects that were identified. In addition, they share educational or training videos on how to conduct birth defect examination and other methods.

3. Define stakeholders and their role in improving these systems in all levels: local, national, regional and global.

B. Raemaekers - Locally you would have the healthcare professionals and the consumers and other primary stakeholders nationally, regionally the collaborations such as EMA and then globally, UMC and WHO as stakeholders. Ideally, there is a cycle between the primary stakeholder providing data which will reach the global level. From the global level insights and education can be provided to the primary stakeholder. It is a system that thrives on feedback in both directions.

N. Bhat - The underlying motivation for the landscape analysis of pregnancy exposure registries was that most data on maternal pharmacovigilance comes from high income countries. There are specific characteristics of low- and middle-income populations, where it would be important to get safety information from pregnant population there. In addition, there are differences in terms of their underlying conditions: HIV, malaria, malnutrition, different other contextual aspects, such as other

concurrent diseases that may be encountered. Should also be mentioned the limitations in terms of the health system and the ability to access healthcare. Therefore, the stakeholders are going to be somewhat different. It isn't going to be necessarily or as much focused on the manufacturers gaining information on the safety for the overall general public, but perhaps public health and multilateral agencies like WHO. Other specific communities that have specific questions on antiretrovirals, antimalarials or other products. And this this is a very important aspect for reassurance and trust in health systems.

S. Lamprianou - Locally there is a need to involve the frontline healthcare workers. It is important to provide feedback to people collecting data or involved in data to improve the quality of data collected, but also to encourage them to invest their time to collect data of quality. In a national level, involvement of different disease programmes will facilitate adherence and harmonization. Importantly, the WHO minimum maternal and newborn data sets are a fruit of collaboration between colleagues with different areas of work, monitoring maternal and newborn health. In a similar way, collaboration between different disease programs between the NRA, pharmacovigilance centers (when they exist) and NPI will be very fruitful and will impact the quality of the national vigilance system.

I. Wong - From the regulatory point of view the data belong to the hospitals or the healthcare providers. Of course, the regulators would like to use the data to do the monitoring, so it is important to have closer relationship. The pandemic broke down a lot of barriers; the healthcare providers and the regulators worked very closely to monitor the COVID-19 vaccine safety. So locally, it is important to make sure that the care providers have the data and work with the regulators, so that the regulators can address the safety concerns and take the decisions. Researchers will be able to become the bridge between the two sides to allow the methodological development and to run the study. In terms of regional level, quite a few Asian countries have electronic medical records. Not the same, but not too far away from each other. Members of the Asian Pharmacoepidemiology Network collaborate to run study together to address safety issues (https://pubmed.ncbi.nlm.nih.gov/25907076/), whether this is COVID-19 vaccine or any other issues. There is a room for improvement to involve more the regulators, but different regulators have their own agenda and deal with things differently. From the academic side there are a lot of successes from collaboration not only within one region, but globally.

4. How the safety information collected will be used, either from a national or a global perspective. In the context of introducing a new product, such as a new vaccine.

N. Bhat - One of the most likely cases that are coming up is the RSV maternal vaccine. That has already been introduced in many countries in the high-income world and hopefully will be coming to the low- and middle-income world relative within a few years. That vaccine, for instance, from the phase three studies have a safety signal of preterm birth, and so that will have to be investigated as the use increases over time. The large electronic surveillance and spontaneous reporting is going to be helpful to analyze or test a hypothesis to see if there is a real epidemiological risk.

I. Wong - During COVID-19 pandemic, there were barriers for monitoring safety on the pregnant population because without the precise day of the vaccination and the precise day of the delivery, it would be extremely difficult to figure out whether it is before the pregnancy or after the pregnancy. Data providers have difficulty to understand why this was so important. This highlights the need for regulators and data providers to work closely to understand the data quality needs.
In addition, in Hong Kong there is also private system. However, the two systems do not exchange data between them for research or pharmacovigilance. COVID 19 vaccines were fully funded by the Government, so data are fully available. However, for other vaccines such as flu vaccines that can be paid by patients and administered in private system, it is difficult to identify whether a patient was vaccinated in another system. In addition, lack of data from the private system created a lot of uncertainty. So, regulators, health professionals and researchers work together to improve the data in long term. A lot of development work needs to be done with mainland China datasets as the health systems are quite different between China and Hong Kong.

S. Lamprianou - The need to define the standardize and normalize definitions reposed to the lack of comparability of the data. Serious adverse events from vaccines or drugs are rare. Sometimes are not even defined. Pregnant women are not always included in the clinical trials except if the if the product is specific for pregnancy. To determine rare events, a large population is needed but data are not comparable as they measure different outputs. During the COVID pandemic, there was not information on TTS because people used different definitions with different data, different timelines. In addition, data came more from high income settings and thus, the guidance for TTS might not be applicable to settings with limited resources. Standardized and harmonized case definition will also allow application of regulatory reliance. So, if Hong Kong has good data for a new product, then another country can use these data and then adapt them to their own population without using their scarce resources reproduce the same data. Safety data of quality can be therefore used in different levels to support national and global vigilance.

B. Raemaekers - When a new vaccine or medicine is launched, there is typically no data on the safety and pregnancy already, so that experience needs to be built up over time. Usually at first, it's accidental exposures. People are not aware that they are pregnant, and they take a vaccine and it's important that this experience is documented somewhere. Whether it is through spontaneous reporting or a pregnancy exposure registry, at least one of these systems should be used to capture all the information possible. It is important on the national level to emphasize that. So then other pregnant women can, for example, intentionally use that vaccine because they know there is experience and they know if there are any risks associated with it.
As for the algorithm, there was a lot of thought was put into this even before the pandemic. However, with COVID-19, the cases series became larger, so manual selection of the pregnancy cases was particularly difficult. Therefore, an algorithm could help identify the relevant cases.

5. What information each system helps put together or collect, and how would this be useful, either from the national perspective or global perspective in identifying an event or managing it, or characterizing it ?

N. Bhat - This relates to whether a safety signal can be identified through sporadic reporting or even media reports, but then needs to be examined in a more thoughtful and structured way. Preterm birth has a variety of definitions. It can be different in different systems and similarly, gestational dating may not be evenly practiced across different populations. Having a registry to approach this systematically and with a common standardized procedures can help to support more intensive evaluations of a specific adverse event. Like with TTS or myocarditis associated with some COVID-19 vaccines again the sporadic reporting will have a variety of definitions, but with a registry there is opportunity to use more standardized approaches.

I. Wong - The spontaneous reporting system, probably for the new drug stay good in a sense that it gives time to collate the data. It will take a long time to collect all the data required to one study, so it's important to have the spontaneous reporting system continuously look into it. In the case of thalidomide, nobody even knew about this situation until case series were published in BMJ journal. So, a spontaneous system in place to help identify the potential signal and then the registry and the electronic medical record, to have some data in 1-2 years to confirm or to refuse the hypothesis. This will give time to have some information holistically, using different data sources. Then, clinicians and patients can make an informed decision at that point when clinically indicated, for starting or continue a treatment.

B. Raemaekers - The spontaneous reporting data would generate a hypothesis. If there is an adverse outcome of the pregnancy, people will consider if there was anything that could have prevented this, scrutinizing the events leading up to that outcome. The adverse outcome will be reported as a potential side effect, but it always needs to be confirmed in another data set, as it could be just the background risk. Therefore, it is important to not only go by the spontaneous data in pregnancy cases. In addition, on the national level, once there is an adverse event identified and confirmed, risk minimization measures such as the pregnancy prevention programmes in valproate can be developed.

S. Lamprianou - Once this combination of systems is used, data quality is fair and clinical management decision is taken. To illustrate this importance, one can remember the contaminated syrup cases detected and then reported in the WHO global database, which allowed reaction in a global level to follow up to see whether we had in other countries that had the same problem, but also in the national level.

Key take aways

Following the pandemic, new ways of thinking and approaches need to be embraced. Some of that work was and is triggered by the previous and current events. Therefore, the standards, the systems, the applications and machine learning algorithms and longitudinal data sets like electronic records. Improving them collaboratively, collectively will allow embracing them and applying them into a sub population that has remained largely off the radar due to various reasons.

But it is now possible to be more optimistic and address the needs of pregnant women and their newborns and see how these efforts can be used to improve the standard care and best practices within this population about interventions.

This is the beginning of a long-term dialogue and work in this area.