Establishing Vaccine Pregnancy Registries and Active Surveillance Studies in Low-and Middle-Income Countries: Experience from an Observational Cohort Surveillance Project in The Gambia

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Despite significant advances in child survival, infectious diseases continue to be among the leading causes of neonatal deaths.[1] Maternal immunization is a well-recognized public health intervention to reduce vaccine-preventable disease-related morbidity and mortality in the pregnant woman, her foetus, and infant from tetanus, pertussis, seasonal influenza, and COVID-19.[2] The development of new maternal vaccines against respiratory syncytial virus (RSV) and group B streptococcus (GBS) may significantly decrease the morbidity and mortality from these diseases in neonates and infants, [2] with the FDA approval for licensure of an RSV vaccine to be administered in pregnancy occurring in August 2023.[3] .

Ongoing safety assessment of novel vaccines administered during pregnancy requires well-functioning passive and active surveillance systems to collect and assess adverse maternal and neonatal outcomes.[4] In high-income countries (HICs), regulatory authorities, such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), require extensive post-authorization safety monitoring activities for products used during

pregnancy, including active surveillance for safety-related events through pregnancy registries and observational cohort studies. [4,5,6] However, safety surveillance for vaccines used in pregnancy in many low- and middle-income countries (LMICs) currently relies on passive surveillance systems whose output cannot be interpreted appropriately due to lack of information on background rates of adverse events in pregnancy in general and lack of data on the number of pregnant women vaccinated as the relevant specific comparator.[4,5,6]

Pregnancy registries routinely collect important outcome information for pregnant women (PW) and infants and are highly relevant to maternal vaccine safety surveillance. Like observational cohort studies, such registries also actively collect detailed vaccine or drug exposures during pregnancy. By allowing the comparison of PW exposed to a vaccine or drug and unexposed PW in the comparator cohort, data from pregnancy registries can help identify and estimate the risk of multiple maternal and neonatal outcomes associated with an exposure.[,5] PW and their infants are to be followed to the end of pregnancy, or longer, to collect specific pregnancy and neonatal outcome data.[,5,6] Although known to be important for improving vaccine and drug safety monitoring during pregnancy, pregnancy registries are limited or absent in most LMICs.

Data from pregnancy registries from high-income countries have shown that there is no evidence of risk to the foetus from vaccinating PW with currently recommended vaccines for PW (e.g., tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap), and seasonal influenza) or certain populations of PW (e.g., quadrivalent conjugate meningococcal vaccine (MenACWY), hepatitis A vaccine).[7]

Most recently, COVID-19 vaccines have also been recommended for PW. Despite the absence of clinical trial data in this population, available evidence shows that COVID-19 vaccines are

effective and safe during pregnancy.[8] Pregnancy registries played a vital role in gathering these reassuring data, though most were implemented in HICs and predominantly relate to mRNA - based COVID-19 vaccines.[7,8] Additional safety data from COVID-19 vaccines used in pregnancy stem from voluntary smartphone-based active-surveillance systems and active surveillance through telephone interviews. [8,9] Further data from LMICs and for other COVID-19 vaccines not implemented in HICs are needed to establish that the reassuring safety records also apply across different geographical regions and relating to different vaccines.
Availability of comprehensive safety datasets will assist to mitigate major drivers of vaccine hesitancy among PW globally.[2]

To address the evidence gap and increase awareness of the benefits of vaccines during pregnancy, an ongoing observational cohort-based surveillance program was established in 2022 in three selected high-volume antenatal clinics in The Gambia. These include the Bundung Maternal and Child Health Hospital, Fajikunda Major Health Centre and Brikama District Hospital. These public health facilities each serve an annual birth cohort of up to 5,000 and have antenatal and obstetric facilities EPI clinics and offer COVID-19 vaccines. Additionally, surveillance program staff have access to relevant medical records from these facilities or referral hospitals for admitted PW.

To generate high-quality data for comparability, pooling, and sharing across settings, standardised measurements (e.g., gestational age (GA) assessment) and standardised case definitions (CDs) for key outcomes are needed.[2,4,10] Through the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, 26 novel maternal and neonatal standardised CDs were developed to classify adverse events into levels of diagnostic certainty, which include guidelines for data collection and maps of disease codes across

terminologies (e.g., MedDRA and ICD).[2,10,11,12] A selection of these standardized CDs for the key maternal and neonatal outcomes (i.e., maternal death, stillbirth, neonatal death, preterm birth, low birth weight, and congenital anomalies) is being utilized for the observational cohort surveillance program in The Gambia. The project outcomes were selected according to important pregnancy outcomes and in line with WHO interest and GAIA guidance.[2,13]

In this currently ongoing program, the selected key maternal and neonatal outcomes are recorded prospectively among PW vaccinated and unvaccinated with a COVID-19 vaccine, seeking routine antenatal care at the clinics to generate background data on the pre-specified outcomes, and evaluate whether outcomes of special interest differed between the groups.Eligible women in the surveillance program are those aged 18 years and older, in alignment with the COVID-19 guidelines in The Gambia, with access to a mobile telephone who consent to participate, including allowing medical record review, if applicable. PW in the vaccinated group must have documentation of receipt of at least one dose of a COVID-19 vaccine during the periconceptional period of 30 days before their LMP. The surveillance program seeks to strengthen maternal vaccination programs and demand by informing immunization advisory groups' recommendations to vaccinate PW, supporting clinical guidance around vaccination during pregnancy, and encouraging vaccine uptake by generating local vaccine safety data and therewith increasing community trust. In the absence of a functioning pregnancy register, the program aims to manually link maternal and neonatal outcome data from maternal and child health programs with the pharmacovigilance system. The cohort platform established through this surveillance program also lays the foundations for a future electronic pregnancy registry that is functional for pharmacovigilance and therefore able to monitor the safety of already recommended and future maternal vaccines (e.g., RSV and GBS) in The Gambia, if and when available. The results of the observational cohort-based

surveillance program will be published on its completion, anticipated in Q1 2024. Here, we report critical observations during the launch of the cohort program.

Establishing observational cohort studies in PW and pregnancy registries in LMICs requires standardization of information collected and specialized trainings for implementation staff. In the selected antenatal clinics in The Gambia, antenatal care and maternal medical records are paper-based, often incomplete and poorly maintained. Maternal vaccination is often not documented. Paper-based records are notoriously difficult to access systematically or link within health facilities or across systems, including the pharmacovigilance system. The key outcomes such as births, deaths, and other adverse events of special interest often occur outside of medical facilities and come to attention due to the regular follow-up with the pregnant women participating in the cohort study by the surveillance program staff. Collaboration between the immunization program and regulatory authorities in the country is required to interpret and utilize the findings. [4,5,6] To consistently evaluate outcomes in regular practice requires additional human and financial resources, in addition to routine antenatal care.

In most LMICs, standardised CDs and measurement of GA are not used routinely to classify maternal and neonatal outcomes GA is an important variable, given that some maternal vaccines can be administered only during specific trimesters. However, GA is often not reliably recorded on paper-based antenatal cards being used in the selected facilities in The Gambia cohort program. To determine the GA, the last menstrual period (LMP), fundal height, physical examination of the mother or ultrasound information can be used with varying degrees of diagnostic certainty.[14] Although in the Gambian facilities LMP and fundal height are most commonly used, [11] in many cases, PW do not know the exact date of their LMP; therefore, surveillance program staff need to refer to the ultrasound scan for GA estimates, if available. To address limitations of inconsistent GA documentation, facilities participating in the

surveillance program are asked to proactively document GA on the antenatal cards to the best of their ability to strengthen the process and information collected.

Healthcare worker (HCW) training on medical data abstraction and application of the tools are critical to ensure the reliability and consistency of data. These trainings include information on the rationale for the selected CDs, clinical presentation, causes, diagnosis, levels of diagnostic certainty for the condition of interest, use of the data abstraction tools, and case scenarios for hands-on practice. Additional trainings may be required for adverse events following immunization (AEFI) investigation and adjudication. To strengthen these capacities, trainings were provided for HCWs, the AEFI Investigation Committee, the National Causality Assessment Committee, and members of the immunization and regulatory agencies in The Gambia in December 2022.

In order to manually link maternal and neonatal outcome data from maternal and child health programs with the pharmacovigilance systems, stakeholder discussions on the data flow are critical at the conception of pregnancy registries to ensure data sharing in compatible formats via appropriate channels. These discussions ensure any safety signals can be immediately investigated and adjudicated with timely communication to mitigate any adverse consequences for the mother-infant pair, as well as to the vaccination program.[15] In The Gambia, it was decided that the health facility would use the routine AEFI reporting form and the relevant maternal or neonatal outcome data collection forms, for reporting the outcomes of interest to the pharmacovigilance system. The National Regulatory Authority would follow its predefined system to share the information with the local vaccine marketing authorisation holders.

The shortage of healthcare workers in LMICs and the absence of digital health records impedes data collection for pregnancy surveillance via routine staff due to existing work pressure. In The Gambia, field staff from the Medical Research Council (MRC) Unit The Gambia are working closely with designated governmental data collectors on identifying and registering PW and collecting outcome data via maternal interviews and medical chart abstraction, using an electronic data collection tool. While starting with a limited electronic database developed specifically for this project, The Gambia Ministry of Health plans to transition to electronic medical records nationally, including a nationwide pregnancy registry, that would address these challenges. To ensure the sustainability of pregnancy registries, electronic tools are needed that can be incorporated into routine antenatal care. Such tools should be developed and tailored to fulfil the needs of national governments and programs. Lessons learnt from implementing a cancer registry in the country will be useful.

In summary, monitoring the safety of vaccines during pregnancy is critical for a successful maternal immunization program. Long-term investments are required to develop sustainable systems that systematically collect and link pregnancy and infant outcomes and vaccination data within the routine surveillance and pharmacovigilance systems. Other LMICs could consider the model used in The Gambia, involving an initial smaller-scale observational cohort surveillance project in select facilities while exploring mechanisms to implement a pregnancy registry nationally.

Close collaboration between immunization, maternal/child health, and regulatory authorities is required to address the needs and challenges in implementing pregnancy registries to strengthen the safety monitoring of drugs and vaccines used in PW globally. The need for such monitoring tools is urgent as new vaccines for use in pregnancy are entering the market.

Declaration of interests

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