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Workshop on Assessing Consequences of Maternal Immunization on Foetal Outcomes

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Title: How to tackle causality assessment of adverse events following immunization (AEFI) and maternal immunization (AEFMI)

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Assessing individual reports of adverse events following immunization (AEFI) is challenging. As part of the Centers for Disease Control and Prevention-funded Clinical Immunization Safety Assessment (CISA) Network, an algorithm was developed to assess causation after complex AEFI in individual subjects. Key questions asked during the implementation of this algorithm included: Is the diagnosis of the AEFI correct? Does clinical or laboratory evidence exist that supports possible causes for the AEFI other than the vaccine in the affected individual? Is there a known causal association between the AEFI and the vaccine? Is there strong evidence against a causal association? Is there a specific laboratory test implicating the vaccine in the pathogenesis? Using this standardized algorithm, causation for the AEFI was grouped into three categories, consistent with causal association with vaccine, indeterminate, and inconsistent with causal association with vaccine. Using this algorithm, 119 cases of AEFI were assessed in CISA; 23% were determined to be consistent with causation, 15% inconsistent with causation, 57% indeterminant, and 5% non-unanimous determination. The high percentage of indeterminant cases was largely the result of incomplete data collection surrounding the event, supporting the need for a more comprehensive field collected database to assess causality.

Assessment of adverse events following maternal immunization (AEFMI) is even more complex, as maternal, fetal, neonatal and pregnancy-related outcomes must be considered. Events such as miscarriage, preterm birth and other adverse pregnancy outcomes may occur coincidentally during pregnancy. As recommendations for maternal vaccination expand and new maternal vaccines are introduced, standardized methods are needed to distinguish coincidental outcomes from those potentially causally related to vaccination.

In 2013, using the CISA framework WHO developed a standardized causality assessment methodology , algorithm and software for individual AEFI , which was subsequently adapted for AEFMI. The adapted method builds on existing WHO causality assessment frameworks while addressing the specific features of maternal, fetal, neonatal and pregnancy-related outcomes. A key feature is its emphasis on case investigation, with approximately 70% of the method based on field data collection, followed by expert review and classification using validated case definitions, including those developed through the GAIA/Brighton Collaboration process.

Following WHO ethical approval, the AEFMI method and software, which support systematic data collection, expert notification, case assessment, classification and automated report generation, were pilot tested in Egypt. Ongoing work with experts in Argentina, Australia, Canada, Germany, India and other global experts has demonstrated the value of the approach in improving standardization, transparency and safety monitoring of vaccines administered during pregnancy, particularly in low- and middle-income countries. Areas identified for refinement include software usability and security, flexibility in estimating gestational age, manual data review, and contextualization of findings in settings with high background rates of adverse pregnancy outcomes.

The method has been reviewed by the GACVS and is informing development of the WHO manual for reporting, investigating and assessing the cause of AEFMI. It highlights the importance of clear documentation, rigorous training, accurate diagnosis, confirmation of pregnancy and pregnancy onset, timing of exposure during gestation, and streamlined evaluation of AEFI and AEFMI. Effective public communication, particularly for inconclusive findings, is essential to avoid misinterpretation and maintain public trust. A standardized, trackable and reassessable approach can advance vaccine safety science after maternal immunization and support national programmes as newer maternal vaccines are introduced globally.

i. https://doi.org/10.1016/j.vaccine.2013.08.087
ii. https://www.who.int/publications/i/item/9789241516990
iii. https://gvsi-aefi-tools.org/
iv. https://iris.who.int/server/api/core/bitstreams/64b8d2ba-84b3-4b78-b501-2dfc6837d399/content