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Operational lessons learned in conducting a multi-country collaboration for vaccine safety signal verification and hypothesis testing: The global vaccine safety multi country collaboration initiative

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ABSTRACT

Timely and effective evaluation of vaccine safety signals for newly developed vaccines introduced in low and middle- income countries (LMICs) is essential. The study tested the development of a global network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing. Twenty-six sentinel sites in sixteen countries across all WHO regions participated, and 65% of the sites were from LMIC. We describe the process for the establishment and operationalization of such a network and the

Abbreviations: AEFI, adverse events following immunization; AM, aseptic meningitis; CRF, case report form; GVSI, Global Vaccine Safety Initiative; ITP, immune thrombocytopenic purpura; ERC, Ethical Review Committee; GBS, Guillain-Barre Syndrome; IRB, Institutional Review Board; LMICs, low and middle-income countries; PPV, positive predictive value; QAC, quality assurance committee; SCCS, self-controlled case series; WHO, World Health Organization.

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lessons learned in conducting a multi-country collaborative initiative. 24 out of the 26 sites successfully contributed data for the global analysis using standardised tools and procedures. Our study successfully confirmed the well-known risk estimates for the outcomes of interest. The main challenges faced by investigators were lack of adequate information in the medical records for case ascertainment and classification, and access to immunization data. The results suggest that sentinel hospitals intending to participate in vaccine safety studies strengthen their systems for discharge diagnosis coding, medical records and linkage to vaccination data. Our study confirms that a multi-country hospital-based network initiative for vaccine safety monitoring is feasible and demonstrates the validity and utility of large collaborative international studies to monitor the safety of new vaccines introduced in LMICs.

1. Background

The number of vaccine doses administered worldwide is increasing as new vaccines are developed and made more widely available for larger numbers of people. The safety of vaccines is assessed in pre-licensure studies which typically allow for the identification of untoward events that would occur as rarely as one per 1000 doses of vaccine. After licensure when the number of people receiving the vaccines is usually in the range of millions, rarer safety events may occur and can be identified. Vaccine reactions are usually mild and time-limited but can, rarely, be serious. Conversely, unsubstantiated vaccine safety scares can adversely affect successful vaccine programs. There is, therefore, an increasing need to include reliable vaccine safety assessment in immunization programs globally [1,2].

Timely and effective evaluation of safety signals is essential and may prompt the conduct of epidemiological risk assessment studies involving countries where the vaccine is used. The need for large sample sizes to investigate hypotheses related to rare vaccine adverse events calls for multi-country collaborative approaches [3]. A first multi-center international proof of concept study investigating the association between Guillain-Barre Syndrome (GBS) and the 2009 H1N1 pandemic influenza vaccine successfully demonstrated the political and scientific feasibility of such global collaboration [4].

As several newly developed vaccines address diseases such as malaria, dengue, typhoid, or cholera which are mostly prevalent in low and middle- income countries (LMICs), it is now critical that those countries develop vaccine safety monitoring capacity beyond passive surveillance, including the ability to conduct risk assessment studies.

In an effort to address WHO's Global Vaccine Safety Blueprint [5] strategic goal of enhanced pharmacovigilance capacity, the Global Vaccine Safety Initiative [6], through its WHO secretariat, tested the development of a global network of hospital-based sentinel sites for vaccine safety signal verification and hypothesis testing incorporating a number of LMICs across the WHO regions. The aim of the project was to identify optimal models and processes for establishing and operationalization of such a network. Because serious and rare adverse events often require complex diagnostic capabilities and easy data access, and lack of denominators is a frequent shortcoming in LMICs, a hospital-based approach using case-only methods was chosen for a subsequent pilot study.

The primary objective of this project was to assess the feasibility of an international hospital-based active surveillance system, including a significant proportion of LMICs, for the evaluation of vaccine safety. It more specifically aimed at: (a) identifying and prioritising the steps required to initiate and conceptualize such network; (b) assessing the capacity of participating hospitals and the collaborative network as a whole to verify well-established risks between a vaccine and an adverse event following it using a common protocol and case abstraction forms; (c) comparing the use of self-controlled case series (SCCS) and case crossover epidemiological designs; and (d) estimating the positive predictive value (PPV) of the hospital discharge codes used at the participating hospitals. This publication is reporting on the steps taken to establish and assess the network, and is sharing lessons learnt.

2. Design

The proof of concept study used case only designs: the self-controlled-case series [7,8] and the case crossover [9]. These are efficient designs that can be used without population denominators but require linkage to the patients' vaccination records. Details are described elsewhere [10].

3. Methods

3.1. Sentinel hospitals selection

Epidemiologic evaluation of possible vaccine associated adverse events using hospital outcome data requires first the ability to identify clinical cases that present the outcome of interest from hospital discharge databases. Subsequently (i.e., to ensure blinding towards exposure), the vaccination history of all cases needs to be ascertained. In view of these data needs, potential sentinel hospitals were selected based on criteria listed in table 1.

Initial expression of interest was sought from hospitals through WHO regional offices; interested hospitals participated in a survey for assessment of compliance with the criteria. To evaluate the actual hospitals capacity for the identification of cases of an outcome of interest from their medical records and their ability to subsequently determine the vaccination history of such cases, hospitals were asked to identify hospitalized cases of a given outcome and provide vaccination history for these children. Only hospitals that successfully obtained complete and verifiable data were finally selected.

Representatives from national regulatory authorities (NRA)/national pharmacovigilance (PV) centre and/or national immunisation programme were engaged from the project inception. An international meeting was organised to discuss the necessary management principles for a WHO-facilitated collaboration with governmental focal persons and at least one clinician from each of selected hospitals. The framework for a memorandum of understanding was discussed, covering the areas of collaboration, confidentiality aspects, publication policy, promotion and ownership of products, responsibility and relationships of the parties. All interested hospitals were subsequently invited to have a dialogue with the Ministry of health (MoH), NRA, institution management and clarified the mechanism for institution/national clearance.

3.2. Proof of concept study

For this international proof of concept study, it was important to select: (a) a vaccine recommended in all participating countries, (b) one or more adverse events known to be associated with, at least, some of the vaccine strains in current use in those countries,

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