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Enhancing global vaccine pharmacovigilance: Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination

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ABSTRACT

New vaccines designed to prevent diseases endemic in low and middle-income countries (LMICs) are now being introduced without prior record of utilization in countries with robust pharmacovigilance systems. To address this deficit, our objective was to demonstrate feasibility of an international hospital-based network for the assessment of potential epidemiological associations between serious and rare

Abbreviations: AEFI, adverse events following immunization; AM, aseptic meningitis; CI, Confidence Interval; CSF, cerebrospinal fluid; EMC, Erasmus Medical Center; FDA, Food and Drug Administration; GVSI, Global Vaccine Safety Initiative; ITP, immune thrombocytopenic purpura; IRR, incidence rate ratio; LMICs, low and middle-income countries; MMR, measles, mumps, rubella vaccines; PMNs, polymorphonuclear leukocytes; OR, odds ratio; SCCS, self-controlled case series; SCRI, self-controlled risk interval; WHO, World Health Organization.

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adverse events and vaccines in any setting. This was done through a proof-of-concept evaluation of the risk of immune thrombocytopenic purpura (ITP) and aseptic meningitis (AM) following administration of the first dose of measles-mumps-containing vaccines using the self-controlled risk interval method in the primary analysis. The World Health Organization (WHO) selected 26 sentinel sites (49 hospitals) distributed in 16 countries of the six WHO regions. Incidence rate ratios (IRR) of 5.0 (95% CI: 2.5–9.7) for ITP following first dose of measles-containing vaccinations, and of 10.9 (95% CI: 4.2–27.8) for AM following mumps-containing vaccinations were found. The strain-specific analyses showed significantly elevated ITP risk for measles vaccines containing Schwarz (IRR: 20.7; 95% CI: 2.7–157.6), Edmonston-Zagreb (IRR: 11.1; 95% CI: 1.4–90.3), and Enders'Edmonston (IRR: 8.5; 95% CI: 1.9–38.1) strains. A significantly elevated AM risk for vaccines containing the Leningrad-Zagreb mumps strain (IRR: 10.8; 95% CI: 1.3–87.4) was also found. This proof-of-concept study has shown, for the first time, that an international hospital-based network for the investigation of rare vaccine adverse events, using common standardized procedures and with high participation of LMICs, is feasible, can produce reliable results, and has the potential to characterize differences in risk between vaccine strains. The completion of this network by adding large reference hospitals, particularly from tropical countries, and the systematic WHO-led implementation of this approach, should permit the rapid post-marketing evaluation of safety signals for serious and rare adverse events for new and existing vaccines in all settings, including LMICs.

1. Introduction

With increasing number of vaccine products available, expansion of vaccine manufacturing capabilities, and availability of new vaccines targeted against diseases highly prevalent in low and middle-income countries (LMICs) [1], there is a need to enhance vaccine pharmacovigilance infrastructures globally [2]. Many countries do not have technical capacity and/or large enough populations to permit the evaluation of rare adverse events following immunization (AEFI) [2,3]. Enhancement of vaccine pharmacovigilance capabilities is a key activity for the World Health Organization (WHO) Global Vaccine Safety Initiative (GVSI) [4–6]. A previous international pilot study sponsored by WHO and the Food and Drug Administration (FDA), to evaluate the safety of the 2009–10 pandemic influenza vaccine, demonstrated that multinational hospital-based vaccine safety studies were feasible and could provide a useful framework for the evaluation of safety concerns [7]. Optimization of operational models, centralization of case adjudication, improvements in data quality control, closer supervision of data abstraction, and demonstration of the feasibility of such international collaborations, with high participation from LMICs, were identified by WHO as issues to be resolved [7]. Thus, for a subsequent demonstration project, it was important to reach higher participation from LMICs, select a vaccine widely used, and an AEFI that, at least in severe cases, would require hospitalization [2]. It was also essential to select an AEFI known to be associated with some of the vaccine strains being used.

Measles-containing vaccines are live-attenuated, often given in combination with mumps and rubella vaccines. The first dose is usually given at one year of age, although it is administered at nine months of age in countries with ongoing measles transmission [8]. The second dose is either given at 15–18 months of age, at 4–6 years of age, or in campaigns. Our objective was to demonstrate feasibility of an international hospital-based network for assessing epidemiological associations between serious and rare adverse events and vaccines in any setting, including LMICs. Two well-established associations were chosen: risk of aseptic meningitis (AM) following first dose of mumps-containing vaccines [9–11], and risk of immune thrombocytopenic purpura (ITP) following first dose of measles-containing vaccines [8,12–14].

2. Methods

International hospital-based retrospective observational study conducted as proof-of-concept for the investigation of rare AEFI using two analytical case-only methods: self-controlled risk interval (SCRI) and case-crossover [15,16]. For this purpose, WHO selected 26 sentinel sites (49 hospitals) distributed in 16 countries of the six WHO regions (Fig. 1). Selection criteria and capability assessments are described elsewhere (Bravo-Alcántara P, Perez-Vilar S, Molina-León HF et al. (accepted for publication in Vaccine [45])).

2.1. Study population

The study population included children ages 9–23 months admitted to a network-participating hospital during January 2010-March 2014, with a discharge diagnosis of either AM or ITP. Only individuals living in the pre-defined catchment area of the hospital, or, for those hospitals without a pre-specified catchment area, in the same city in which the hospital was located, were eligible.

2.2. Case ascertainment and classification

Participating hospitals identified potential cases through hospital discharge databases using pre-specified ICD-9/ICD-10 codes (Supplementary material; Table S-1) whereas hospitals not using a discharge codification system or not having electronic databases used free text. A trained physician or nurse blinded to vaccination status reviewed medical records of potential cases according to established case definitions (Supplementary material; Tables S-2 and S-3). Potential cases for which medical records were not available were excluded. Only first episodes of AM or ITP were considered.

Potential AM cases were excluded if they met criteria for encephalitis [17] (Supplementary material; Table S-4), the medical records showed that a physician ruled out a diagnosis of AM, a meningitis pathogen other than mumps virus was identified in cerebrospinal fluid (CSF), CSF protein concentration (in absence of traumatic lumbar puncture or intracerebral event) was $\geq$50 mg/dL with $\geq$10 leukocytes/mm^3 and glucose $\leq$40 mg/dL in CSF, or if polymorphonuclear leukocytes (PMNs) in the CSF were >1000/mm^3 with glucose $\leq$40 mg/dL (modified from Lussiana et al.) [18].

Potential ITP cases were excluded if classified as chronic (defined as lasting >6 months) [12,14], with onset of symptoms occurring >42 days prior to hospital admission, or if a physician diagnosis in the medical records ruled out the diagnosis of ITP or thrombocytopenia. ITP cases with medical conditions associated

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